ORIGINAL ARTICLE

Dorsolateral Prefrontal Cortex Activation During Emotional Anticipation and Neuropsychological Performance in Posttraumatic Stress Disorder

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Context: Posttraumatic stress disorder (PTSD) has been associated with executive or attentional dysfunction and problems in emotion processing. However, it is unclear whether these two domains of dysfunction are related to common or distinct neurophysiological substrates.

Objective: To examine the hypothesis that greater neuropsychological impairment in PTSD relates to greater disruption in prefrontal-subcortical networks during emotional anticipation.

Design: Case-control, cross-sectional study.

Setting: General community and hospital and community psychiatric clinics.

Participants: Volunteer sample of 37 women with PTSD related to intimate partner violence and 34 age-comparable healthy control women.

Main Outcome Measures: We used functional magnetic resonance imaging (fMRI) to examine neural responses during anticipation of negative and positive emotional images. The Clinician-Administered PTSD Scale was used to characterize PTSD symptom severity. The Wechsler Adult Intelligence Scale, Third Edition, Digit Symbol Test, Delis-Kaplan Executive Function System Color-Word Interference Test, and Wisconsin Card Sorting Test were used to characterize neuropsychological performance.

Results: Women with PTSD performed worse on complex visuomotor processing speed (Digit Symbol Test) and executive function (Color-Word Interference Inhibition/Switching subtest) measures compared with control subjects. Posttraumatic stress disorder was associated with greater anterior insula and attenuated lateral prefrontal cortex (PFC) activation during emotional anticipation. Greater dorsolateral PFC activation (anticipation of negative images minus anticipation of positive images) was associated with lower PTSD symptom severity and better visuomotor processing speed and executive functioning. Greater medial PFC and amygdala activation related to slower visuomotor processing speed.

Conclusions: During emotional anticipation, women with PTSD show exaggerated activation in the anterior insula, a region important for monitoring internal bodily state. Greater dorsolateral PFC response in PTSD patients during emotional anticipation may reflect engagement of cognitive control networks that are beneficial for emotional and cognitive functioning. Novel treatments could be aimed at strengthening the balance between cognitive control (dorsolateral PFC) and affective processing (medial PFC and amygdala) networks to improve overall functioning for PTSD patients.

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An estimated 50% to 80% of people will experience a significant traumatic event during their lifetime.[1-3] One of the most common traumatic events is intimate partner violence (IPV), experienced by 16% to 30% of people in the United States.[2,4,5] Intimate partner violence has been reported as the leading cause of injury among women,[4] and an estimated 25% to 65% of female IPV victims subsequently develop posttraumatic stress disorder (PTSD).[6-8] Posttraumatic stress disorder can be a debilitating disorder involving, among other symptoms, reexperiencing of the traumatic events through nightmares, flashbacks, and unwanted memories; emotional distress and physiological arousal in response to reminders of the traumatic events; avoidance of triggering stimuli; decreased interest or pleasure in life activities; difficulty sleeping; anger and irritability; and difficulty concentrating.[9]

In relation to concentration difficulties, PTSD patients often report problems in a variety of cognitive domains, including attention, learning, and memory.[10,11] The

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most robust findings in neuropsychological studies investigating objective cognitive function of PTSD patients have been in the domains of executive function,[12-19] processing speed,[17,20] and verbal learning.[13-26] In healthy control subjects, tasks involving executive functions, such as working memory, inhibition, or attentional switching, typically activate prefrontal regions that overlap with those involved in processing and regulating emotion, including the medial prefrontal cortex (PFC) and orbitofrontal cortex, anterior cingulate cortex (ACC), and dorsolateral PFC (dlPFC).[27-31] Thus, evidence supports the idea that these brain structures could underlie the emotional and cognitive dysregulation associated with PTSD. Identification of common neural substrates for cognitive and emotional symptoms of PTSD could lead to the development of novel treatments beneficial to both dimensions.

Neuroimaging studies (using positron emission tomography or functional magnetic resonance imaging [fMRI]) in PTSD have primarily focused on symptom provocation or responses to trauma-related or emotional stimuli. In general, results from these studies suggest increased activation within the amygdala and insula and hypoactivation of prefrontal regions, including the ACC, medial PFC, and lateral PFC,[32-36] although there have been some inconsistencies regarding the directionality of these effects.[36] The few studies investigating neural activations of PTSD patients during cognitive inhibition and working memory tasks have reported reduced activation in the inferior frontal gyrus, dlPFC, ACC, and medial orbitofrontal cortex.[12,37] In a study by Falconer and colleagues,[12] activation in prefrontal regions during an inhibition task correlated negatively with the rate of commission errors and PTSD symptom severity, suggesting that attenuated PFC activations relate to observed cognitive and emotional symptoms. Studies involving the presentation of emotional distracters during working memory tasks have suggested that PTSD is associated with increased activation in ventral PFC regions (eg, ventromedial PFC) during processing of emotional distracters but decreased activation in dorsal PFC regions (eg, dorsal ACC and dlPFC) and the parietal cortex[38-40] during the working memory task itself. By generalizing across findings from studies involving symptom provocation and/or cognitive tasks, one could speculate that an imbalance between an overactive ventral/limbic emotional processing stream and an underactive dorsal prefrontal cognitive processing stream (eg, dlPFC and dorsal ACC) could underlie cognitive impairments observed in PTSD.[24,39,40]

This study examined the relationship between cognitive and emotional functioning in individuals with IPV-related PTSD. In particular, we hypothesized that greater impairment in measures related to the executive functions of cognitive inhibition and attentional switching (Delis-Kaplan Executive Function System [D-KEFS] Color-Word Interference Inhibition and Inhibition/Switching subtests) and complex processing speed (Wechsler Adult Intelligence Scale, Third Edition, Digit Symbol Test) would relate to less activation within dorsal prefrontal regions considered important for cognitive control and working memory (eg, ACC and dlPFC) and greater activation within regions considered important for processing of emotional stimuli (ie, amygdala and insula). To that end, we (1) investigated the neural responses of women with IPV-related PTSD to a task combining anticipation of emotional images with a simple attentional task (continuous performance task [CPT]) and (2) examined the relationship between these neural responses and performance on neuropsychological tests.

METHODS

Forty-one women with IPV-related PTSD and 34 healthy control women with no history of trauma or PTSD completed diagnostic, clinical, and neuropsychological assessments and the anticipation paradigm during fMRI. Subjects were recruited specifically for this study, and there was no overlap between the present cohort and those in previous studies conducted by the same laboratory.[41] Four PTSD subjects were excluded owing to excessive movement (>4 mm in roll, pitch, or yaw directions) during scanning that resulted in poor image quality. Thus, a total of 37 PTSD subjects (mean [SD] age, 38.32 [9.13] years) and 34 healthy controls (mean [SD] age, 37.76 [11.13] years) were included in the analysis. Although groups did not significantly differ by age ($F_{1,69}$=0.07 [P=.79]), the PTSD group had significantly fewer years of education than the control group (mean [SD], 14.15 [1.84] vs 15.51 [1.54] years; $F_{1,69}$=11.37 [P=.001]). Therefore, educational level was used as a covariate in all analyses involving group comparisons.

Intimate partner violence trauma was defined as physical and/or sexual abuse committed by a romantic partner and occurring within 5 years of but having ended at least 1 month before enrollment in the study. All women in the PTSD group were seeking treatment for PTSD symptoms and met full (n=31) or partial (n=6) *DSM-IV* criteria for PTSD, verified through the Clinician-Administered PTSD Scale (CAPS)[42] (see the eAppendix for definitions of full and partial PTSD [http://www.archgenpsychiatry.com]). Controls had never experienced a traumatic event that met criterion A for *DSM-IV* PTSD nor had they met criteria for any mental health disorder. Exclusionary criteria for both groups included substance abuse in the past year; history of longer than 5 years of substance abuse; use of psychotropic medications within 4 weeks before the study; history of bipolar disorder, schizophrenia, attention-deficit disorder, or any learning disability; loss of consciousness longer than 10 minutes; any neurological illness; irremovable ferromagnetic bodily material; pregnancy; or claustrophobia. The study protocol was approved by the University of California, San Diego, Human Research Protections Program and the Veterans Affairs San Diego Healthcare System Research and Development Office. Written informed consent was obtained from all participants.

In addition to the CAPS, subjects completed the Beck Depression Inventory II[43] on the day of fMRI scanning. Subjects also completed neuropsychological testing in advance of the scanning session, including (1) the D-KEFS[44] Color-Word Interference Test, with color and word reading conditions serving as measures of attention and processing speed and color-word inhibition and inhibition/switching conditions serving as measures of inhibition and attentional switching; (2) the Wisconsin Card Sorting Test[45] as a measure of abstract reasoning and cognitive flexibility; (3) the Wechsler Adult Intelligence Scale, Third Edition, Digit Symbol Test[46] as a measure of visuomotor processing speed; and (4) revised National Adult Reading Test (NART-R)[47] as an estimate of IQ.

fMRI DATA ACQUISITION

During scanning, subjects performed an anticipation task, which was conducted as previously described[41,48] and as shown in

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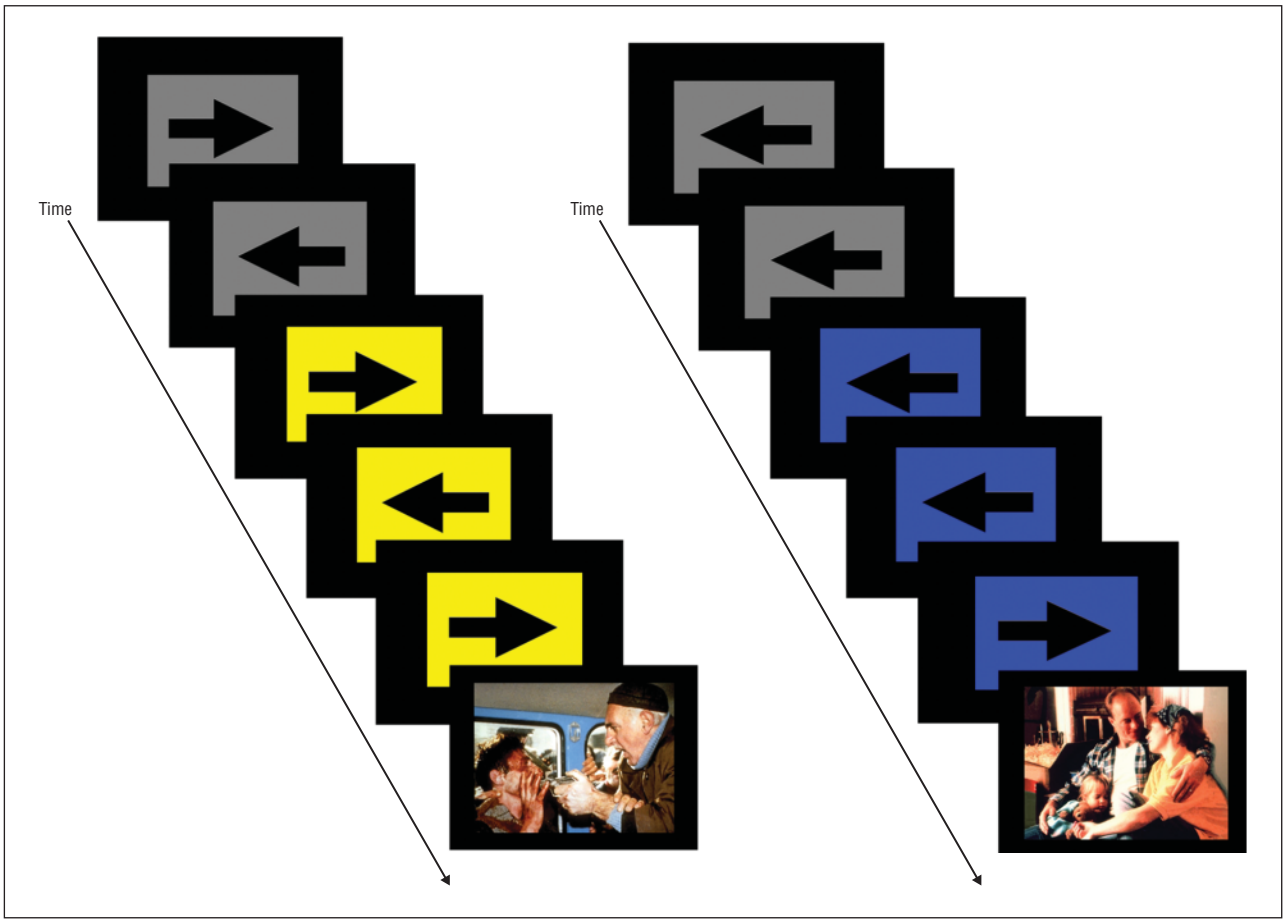

Figure 1. Functional magnetic resonance imaging anticipation task. This task combines a continuous performance task with the interspersed presentation of affective stimuli. Subjects are asked to press a left or right button based on the direction of the arrow. Subjects are instructed before the task that a blue square accompanied by a low tone indicates that a positive image is going to appear. In contrast, a switch to a yellow square accompanied by a high tone signals an impending negative image. Images used in this paradigm were taken from the International Affective Picture System.[49]

Figure 1 (see the eAppendix for a full description of the task). Briefly, this task combined a CPT with the interspersed presentation of affective visual stimuli from the International Affective Picture System.[49] Subjects were instructed (1) to press a button corresponding to the direction of an arrow on the screen and (2) that when the background screen turned blue, accompanied by a 250-Hz tone, a positive image would soon appear, whereas when the background turned yellow, accompanied by a 1000-Hz tone, a negative image would appear. The trials in which the background was blue or yellow represented the anticipation periods of positive and negative images (API and ANI), respectively. Anticipation periods lasted 6 seconds, image presentation lasted 2 seconds, and the baseline CPT task was interspersed for variable duration averaging 8 seconds. Total task duration was 580 seconds. Response accuracy and reaction times were obtained for the CPT during the baseline and anticipation periods.

The anticipation task was conducted during a single fMRI scan sensitive to blood oxygenation level–dependent (BOLD) contrast using a 3.0-T scanner (Signa Excite; GE Healthcare) (T2*-weighted echoplanar imaging; repetition time, 2000 milliseconds; echo time, 32 milliseconds; 64 × 64 matrix; thirty 2.6-mm axial sections with a 1.4-mm gap; 290 scans). During the same experimental session, a high-resolution T1-weighted image (spoiled gradient recalled; repetition time, 8 milliseconds; echo time, 3 milliseconds; 172 sections; field of view, 25 cm; approximately 1-mm^3 voxels) was obtained for anatomical reference.

DATA ANALYSIS

Clinical, Neuropsychological, and Behavioral Data

Clinical and neuropsychological measures were compared between groups using analysis of covariance (ANCOVA) with educational level as the covariate, using commercially available statistical software (SPSS Inc). Scaled scores for the D-KEFS measures and the Digit Symbol Test and the raw number of total correct items on the Wisconsin Card Sorting Test and NART-R were used for analyses. Correlation analyses were conducted using the Spearman rank correlation coefficient (ρ value) to examine relationships among clinical, self-report, and neuropsychological measures. Behavioral data collected during the fMRI anticipation paradigm (CPT reaction time and accuracy) were subjected to repeated-measures analyses of variance to examine main and interaction effects of task condition (ANI vs API) and group (PTSD vs control). Clinical, neuropsychological, and behavioral results were considered significant at $P < .05$.

fMRI BOLD Data

Data were preprocessed and analyzed using the Analysis of Functional NeuroImages, or AFNI, software package[50] and the R statistical package (http://www.r-project.org/). All echoplanar images were aligned to high-resolution anatomical images. Voxel data points representing outliers relative to surrounding data points were eliminated and interpolated. Data were spatially

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Table 1. Clinical and Neuropsychological Measures: Descriptive Data and Group Differences

Measure	No. of Subjects, PTSD/Control	Group, Mean (SD) Score		*F* Value[a]	*P* Value
		PTSD	Control		
CAPS intake					
Total	37/0	70.57 (17.58)	NA		
Cluster B		20.00 (6.25)	NA		
Cluster C		27.49 (9.98)	NA		
Cluster D		23.08 (6.75)	NA		
BDI-II	36/32	20.00 (8.54)	2.72 (4.13)	91.08	<.001
D-KEFS Color-Word Interference Test	37/33				
Color Reading scaled		8.78 (2.72)	9.06 (2.81)	0.15	.70
Word Reading scaled		9.81 (2.69)	9.91 (2.94)	0.01	.92
Inhibition scaled		9.97 (2.64)	11.24 (2.65)	1.35	.25
Inhibition/Switching scaled		9.59 (3.17)	11.39 (2.30)	5.29	.03
WCST total correct raw score	32/28	48.37 (8.47)	49.93 (6.28)	0.36	.55
WAIS-III Digit Symbol Test scaled	37/31	9.11 (2.63)	11.71 (2.56)	10.97	.002
NART-R raw score	36/32	32.94 (8.97)	38.25 (10.62)	0.86	.36

Abbreviations: BDI-II, Beck Depression Inventory-II; CAPS, Clinician-Administered PTSD Scale; D-KEFS, Delis-Kaplan Executive Function System; NART-R, revised National Adult Reading Test; NA, not applicable or collected; PTSD, posttraumatic stress disorder; WAIS-III, Wechsler Adult Intelligence Scale, Third Edition; WCST, Wisconsin Card Sorting Test.

[a] Calculated from analysis of covariance examining group differences while covarying for educational level.

blurred with a 4-mm full-width at half maximum spatial filter and normalized to Talairach space. Preprocessed individual time-series data were analyzed using a multiple regression model and a BOLD hemodynamic response function with a 4- to 6-second peak. Regressors of interest included 2 orthogonal regressors used to quantify neural activation during the API and ANI conditions. The following 7 regressors of no interest were entered into the linear regression model: 3 motion-related regressors roll, pitch, and yaw; a white-matter mask to control for physiological noise; linear trend used to eliminate slow signal drifts; and positive and negative image presentation periods.

Percent signal change (PSC) was calculated by dividing the regressor of interest by the control regressor. To identify group and task effects on BOLD activation, PSC for API and ANI were subjected to linear mixed-effects analysis using the R statistical package. A linear mixed-effects analysis was first conducted within the control and PTSD groups separately, with task valence (ANI and API) as fixed effects and subject as random effects, to identify task main effects. Second, a linear mixed-effects analysis was conducted to examine the group × valence interaction effect on BOLD activation, with subject treated as random effects, group (PTSD and control) and task valence (API and ANI) as fixed effects, and years of education as the covariate.

Huber robust regression analyses,[51] which provide a more conservative estimate of correlational associations by minimizing the effect of outliers, were conducted within the PTSD group to examine the relationship between differential BOLD activation during anticipation (ANI – API) and *z*-transformed scores on the following: (1) CAPS severity score, (2) Digit Symbol Test scaled score, and (3) Color-Word Interference Inhibition/Switching scaled score. These specific neuropsychological tests were chosen for analysis because they showed the most robust performance differences between PTSD subjects and controls.

All fMRI analyses were conducted voxelwise across the whole brain. A threshold adjustment method based on Monte Carlo simulations (conducted via the AFNI program Alpha Sim) was used to guard against identifying false-positive areas of activation. This resulted in a minimum volume of 13 voxels (832 μL) for a cluster to be considered significant. While the cluster significance of $P < .05$ (2 tailed) was used for all analyses, corrected voxelwise probability was $P < .00001$. All reported coordinates are center-of-mass Talairach coordinates (x, y, z) labeled on the basis of visual observation and Talairach Daemon software.[52] For identified activation clusters, average *F* and *P* values (for linear mixed-effects analyses) or regression coefficients and *t* statistics (for regression analyses) are reported. To enable further characterization of effects observed from regression analyses with differential PSC (ANI – API), post hoc Huber robust regression analyses were conducted with the independent variable of interest and extracted PSC for ANI and API separately, and the corresponding *t* statistics were reported.

RESULTS

SELF-REPORT AND BEHAVIORAL RESULTS

Clinical and neuropsychological data for the PTSD and control groups are displayed in **Table 1**. Results of the ANCOVA analysis (covarying for educational level) revealed that individuals with PTSD reported greater levels of depression (Beck Depression Inventory II) and performed worse on the Digit Symbol Test and Color-Word Interference Inhibition/Switching subtests compared with controls. There were no significant differences in performance on the Wisconsin Card Sorting Test, NART-R, or the Color-Word Interference Color Reading, Word Reading, or Inhibition subtests. The CAPS and Beck Depression Inventory II scores did not correlate significantly with neuropsychological measures (eTable 1).

Behavioral data from the CPT conducted during fMRI was available for all but 2 subjects (1 control and 1 PTSD subject). Repeated-measures ANCOVA analyses conducted with CPT accuracy and reaction time revealed no significant differences between groups or task conditions (reaction time, $F_{2,65}=0.38$ [$P=.69$]; accuracy, $F_{2,65}=0.22$ [$P=.81$]).

fMRI RESULTS

Task Valence Effects

For the control and PTSD groups, ANI was associated with greater activation than API in regions that have been

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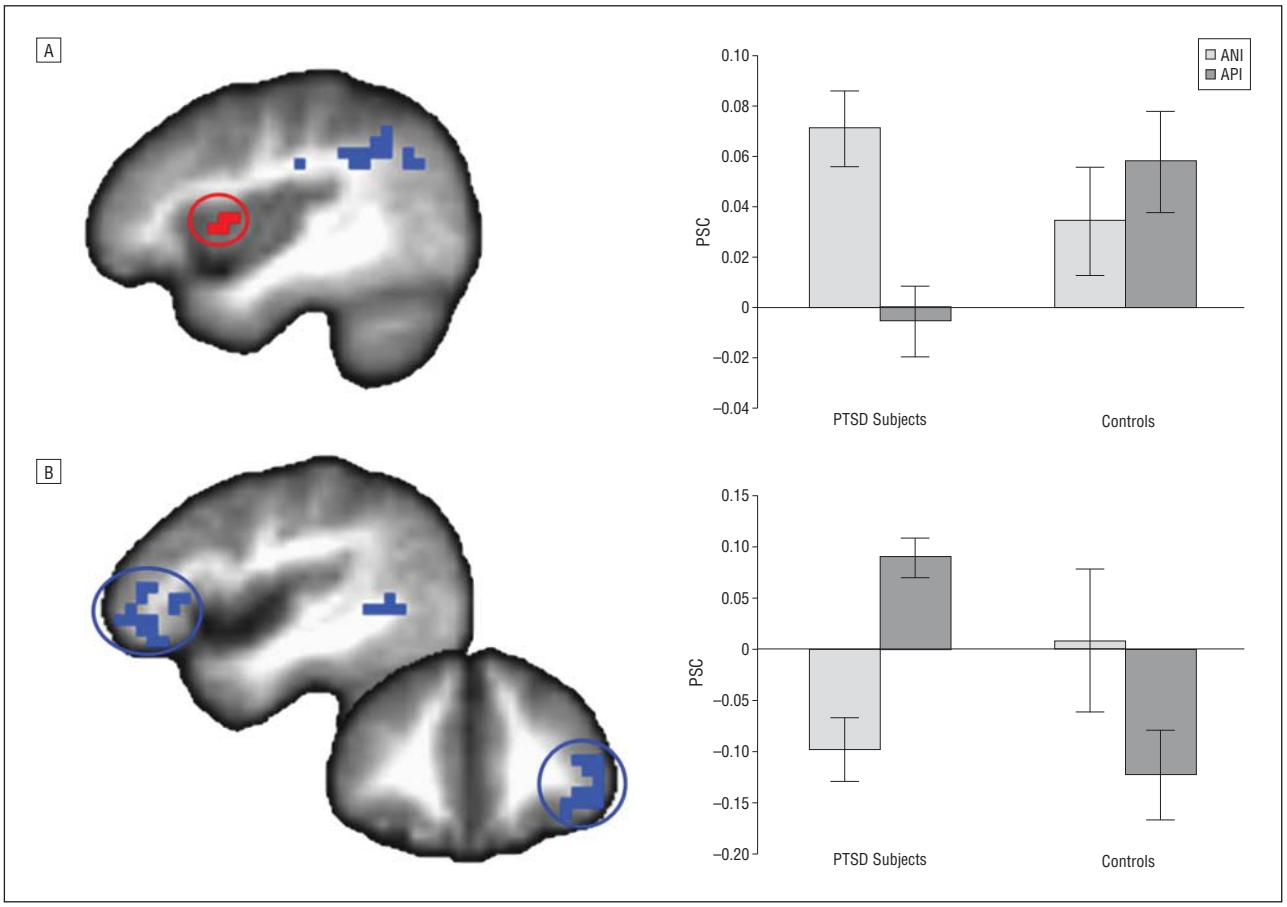

Figure 2. Group × valence interaction effect on functional magnetic resonance imaging blood oxygenation level–dependent activation for anticipation of negative (ANI) vs positive (API) images. Posttraumatic stress disorder (PTSD) was associated with greater differential activation (ANI – API) within the right middle/anterior insula and claustrum (A) (Brodmann area [BA] 13; x, y, z center-of-mass coordinates, 33.8, 6.5, 7.2; image shown at x = 40) and reduced differential activation (ANI – API) within the left ventrolateral and dorsolateral prefrontal cortex (B) (BAs 46 and 47; x, y, z center-of-mass coordinates, –42.0, 36.1, 2.3; images shown at x = –42 and y = 38). Graphs depicted for each image represent average percent signal change (PSC) for each condition. Other regions identified in the group × valence interaction effect analyses are listed in Table 2. Error bars represent 1 SE.

previously implicated in emotional anticipation, including the bilateral anterior insula (Brodmann area [BA] 13), inferior frontal gyrus, lateral (including BAs 6, 9, 45, and 46) and dorsal medial (BA 8) PFC, and regions of the inferior/superior parietal (BAs 39 and 40) and middle/superior temporal (BA 39) cortices (see eTables 2 and 3 for full lists of task effects for each group).

Group × Valence Interaction

Linear mixed-models analysis of the group × valence interaction effect was conducted while covarying for educational level. The PTSD group exhibited greater differential activation (ANI – API) than did the control group within the right middle/anterior insula (BA 13), inferior frontal gyrus, and middle temporal cortex (BAs 21 and 22), the left precentral gyrus (BAs 6 and 44), and precuneus (BAs 4, 7, and 19). The PTSD group exhibited less differential activation within the left dorsolateral and ventrolateral PFC (BAs 46 and 47), caudate tail and parahippocampal gyrus, medial posterior cingulate (BAs 29 and 30), and left inferior parietal cortex (BA 40) (**Figure 2** and **Table 2**).

Anticipatory Brain Activation and Psychiatric Symptoms

Results from Huber robust multiple regression within the PTSD group indicated that a greater CAPS score was related to greater differential activation (ANI – API) within the left posterior cingulate (BAs 23 and 30) and right precuneus (BAs 5 and 7) and less differential activation within the right dlPFC (BAs 9 and 46), left dlPFC (BA 9), and right precentral gyrus (BA 6) (**Table 3** and **Figure 3**).

Anticipatory Brain Activation and Neuropsychological Function

Results from Huber robust multiple regression conducted within the PTSD group indicated that better performance on the Digit Symbol Test related to greater differential anticipatory activation (ANI – API) within the right dlPFC (BA 9), left ventrolateral PFC and ACC (BAs 10 and 32), inferior parietal cortex (BA 40), and precentral gyrus (BAs 6 and 7). In comparison, better performance was related to less differential activation within an extensive area of the medial PFC (BAs 9, 10, and 32), right precentral gyrus (BA 6), and left parahippocampal/

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Table 2. Interaction Effects of Group × Valence on Brain Activation During Anticipation of Emotional Images[a]

Side	Region	BA	Cluster Size, Voxels	Center-of-Mass Coordinates x, y, z	Mean *F* Value	PSC[b]
			PTSD > Control Group (for ANI > API)			
Right	IFG, precentral	44, 6	960	53.8, 2.0, 18.4	5.56	Both
Left	Precentral, parietal cortex	4	1152	−52.5, −5.7, 17.1	6.08	Negative
Left	Precuneus, parietal cortex	7, 19	896	−15.0, −80.1, 38.1	6.53	Both
Right	Middle temporal	21, 22	1152	62.2, 0.8, −8.9	6.30	Both
Right	Middle insula to claustrum	13	1280	33.8, 6.5, 7.2	6.00	Positive
Left	PHG		1152	−27.5, −28.1, −15.3	5.19	Positive
			Control > PTSD Group (for ANI > API)			
Left	dlPFC and vlPFC	46, 47	2496	−42.0, 36.1, 2.3	5.58	Both
Medial	Posterior cingulate	29, 30	960	−2.7, −43.7, 16.8	6.69	Negative
Right	Supramarginal gyrus, inferior parietal	40	3008	36.7, −47.3, 31.4	6.45	Negative
Left	Caudate tail and PHG		1088	−37.3, −47.1, 4.8	6.89	Negative

Abbreviations: ANI, anticipation of negative images; API, anticipation of positive images; BA, Brodmann area; dlPFC, dorsolateral prefrontal cortex (PFC); IFG, inferior frontal gyrus; PHG, parahippocampal gyrus; PSC, percent signal change; PTSD, posttraumatic stress disorder; vlPFC, ventrolateral PFC.

[a] Results are shown from analyses of group (PTSD vs healthy control women) by valence (ANI vs API) interaction effect on the PSC ($P<.05$), Monte Carlo adjusted for whole-brain volume (832 μL) multiple comparisons. All coordinates are Talairach coordinates (x, y, z) based on Talairach Daemon software.

[b] Negative indicates PSC from baseline was negative for both groups and conditions; positive, PSC from baseline was positive for both groups and conditions; both, PSC was positive for some group/condition combinations and negative for others.

Table 3. Results of Regression Analysis Examining Relationship Between Brain Activation During Emotional Anticipation (ANI–API) and CAPS Score Within the PTSD Group

Side	Region	BA	Cluster size, Voxels[a]	Center-of-Mass Coordinates x, y, z[b]	ANI–API Huber Regression Mean Statistics[c]		Post hoc Regression *t* Statistics[d]	
					Coefficient	*t* Statistic	ANI Only	API Only
				Positive Relationship With ANI–API				
Left	Posterior cingulate	23, 30	1792	−2.8, −49.2, 15.1	0.15	2.47	2.17	−1.59
Right	Precuneus, postcentral gyrus	7, 5	1216	7.3, −54.3, 58.5	0.10	2.69	2.34	−3.18
				Negative Relationship With ANI–API				
Right	dlPFC	9, 46	1664	37.9, 24.6, 26.8	−0.08	−3.05	−3.46	2.27
Right	Lateral frontal, precentral	6	1152	30.9, −5.5, 37.3	−0.04	−2.70	−2.62	−0.39
Left	dlPFC	9	1088	−35.7, 2.9, 25.1	−0.06	−2.81	−3.17	0.00

Abbreviations: ANI, anticipation of negative images; API, anticipation of positive images; BA, Brodmann area; CAPS, Clinician-Administered PTSD Scale; dlPFC, dorsolateral prefrontal cortex (PFC); PTSD, posttraumatic stress disorder.

[a] Clusters were identified using Huber robust multiple regression implemented using the R statistical package and including *z*-transformed CAPS score as the regressor and differential blood oxygenation level–dependent activation during anticipation (ANI–API) as the dependent variable. Results were considered significant at a threshold of $P<.05$, Monte Carlo adjusted for whole-brain volume (832 μL) multiple comparisons.

[b] All coordinates are Talairach coordinates (x, y, z) based on Talairach Daemon software.

[c] Unstandardized regression coefficients and *t* statistics are shown for the initial Huber regression analyses with ANI–API.

[d] To further characterize results, *t* statistics are shown from post hoc linear regression analyses conducted with each measure as the independent variable and ANI only and API only as the dependent variables.

amygdalar region. Similarly, better performance on the Color-Word Interference Inhibition/Switching subtest related to greater differential activation within the right dlPFC (BA 9) and precuneus (BA 19) and less differential activation in the bilateral lateral superior frontal cortex (BAs 6 and 8) and posterior cingulate (BA 23) (**Table 4** and **Figure 4**). The extracted average PSC within each of these regions did not significantly relate to the NART-R score or educational level ($\rho<0.30$ for all). Post hoc correlation analyses were conducted with the extracted PSC for the activated clusters identified in the Huber regression analyses to determine whether individuals who exhibited greater activation in dlPFC regions also exhibited less activation in more ventral PFC and limbic regions. The dlPFC cluster was negatively related to the medial PFC ($\rho=-0.54$ [$P=.001$]) and parahippocampal gyrus/amygdala ($\rho=-0.44$ [$P=.007$]) PSC and positively related to the ventrolateral PFC/ACC ($\rho=0.46$ [$P=.005$]) and the inferior parietal ($\rho=0.54$ [$P=.001$]) and precentral gyrus ($\rho=0.43$ [$P=.007$]) PSC from the Digit Symbol Test regression analyses. With regard to the Color-Word Interference Inhibition/Switching analysis, extracted PSC for the dlPFC cluster showed a negative correlation with the extracted PSC for the posterior cingulate ($\rho=-0.39$ [$P=.01$]) and precentral gyrus ($\rho=-0.40$ [$P=.02$]) clusters.

The relationship between performance on the Digit Symbol Test and Color-Word Interference Inhibition/Switching subtest was also investigated using Huber robust regression within the healthy control group (eTable 4). For the control group, there were no consistent findings across results from the 2 tests as was found for the

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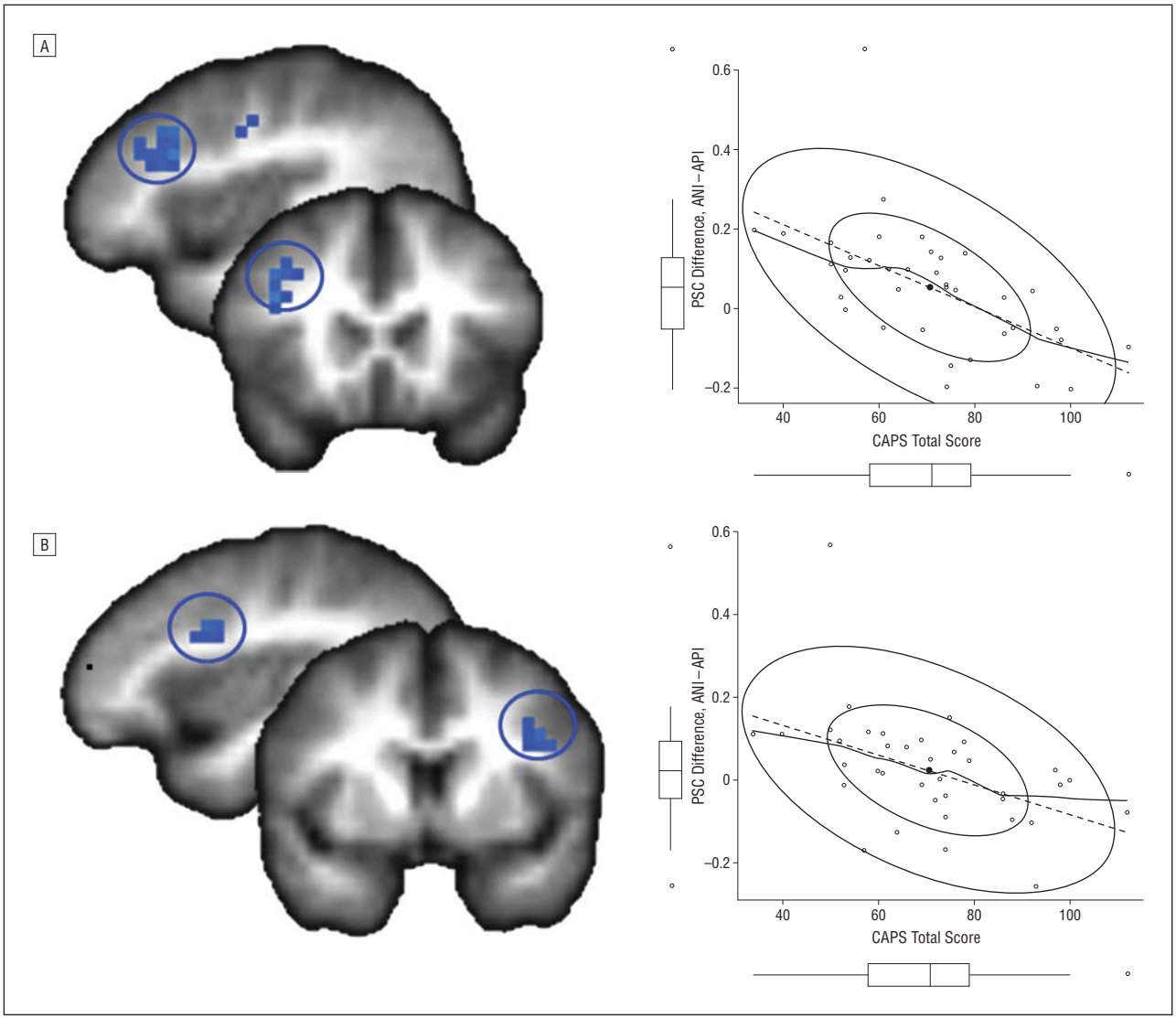

Figure 3. Greater posttraumatic stress disorder (PTSD) symptom severity related to less differential activation for anticipation of negative (ANI) – positive (API) images in the bilateral dorsolateral prefrontal cortex (dlPFC). Huber robust regression analyses were implemented in the R statistical package to identify brain regions in which differential activation to ANI – API related to symptom severity as measured via the Clinician-Administered PTSD Scale (CAPS). Greater CAPS severity score was related to less differential activation (ANI – API) within the right (A) (Brodmann area [BA] 9; x, y, z center-of-mass coordinates, 37.9, 24.6, 26.8; images shown at x = 40 and y = 18) and left dlPFC (B) (BA, 9; x, y, z center-of-mass coordinates, –35.7, 2.9, 25.1; images shown at x = –36 and y = 6). Other regions in which differential activation exhibited a relationship to the CAPS score are listed in Table 3. PSC indicates percent signal change. The box-and-whisker elements to the left of each y-axis and below each x-axis show the medians (lines in the middle of the boxes); upper and lower quartiles (upper and lower part of boxes); minimum and maximum values or, in the case of outliers, 1.5 times the upper and lower quartile (whiskers); and outliers (open circles beyond the whiskers).

PTSD group. For the controls, Digit Symbol Test performance was positively related to activation within the right subgenual ACC (BAs 24 and 25) and caudate and left posterior cingulate (BA 30) and negatively related to activation within the medial (BA 10) and right lateral PFC (BAs 6 and 9), bilateral posterior insula (BA 13), and bilateral temporal and parietal cortices. Color-Word Interference Inhibition/Switching subtest performance was positively related to superior/middle temporal cortex (BAs 20 and 21) and negatively related to left caudate activation.

COMMENT

The present study examined the relationship between neural responses during an emotional anticipation task and neuropsychological function in PTSD. Results suggest that (1) IPV-related PTSD is associated with hyperactivation of insula regions and hypoactivation of lateral prefrontal regions during anticipation of negative emotional images, (2) greater dlPFC response during anticipation of negative emotional images relates to lower levels of PTSD symptoms, and (3) greater dlPFC response during anticipation of negative emotional images relates to better performance on measures of complex visuomotor processing speed (Digit Symbol Test) and inhibition and attentional switching (Color-Word Interference Inhibition/Switching subtest) for women with IPV-related PTSD. Taken together, increased activation of the amygdala and insula regions and attenuated activation of the dlPFC may reflect an imbalance in PTSD between internally focused affective networks and externally focused cognitive control networks.

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Table 4. Results From Regression Analyses Examining Relationship Between Brain Activation During Emotional Anticipation (ANI–API) and WAIS-III Digit Symbol Test or D-KEFS Color-Word Interference Inhibition/Switching Subtest Scores Within the PTSD Group

Side/Region	BA	Cluster Size, Voxels[a]	Center-of-Mass Coordinates x, y, z[b]	ANI–API Huber Regression Mean Statistics[c]		Post hoc Regression *t* Statistics[d]	
				Coefficient	*t* Statistics	ANI Only	API Only
WAIS-III Digit Symbol Test							
Positive relationship with ANI–API activation							
Right/dlPFC	9	960	47.3, 8.0, 28.9	0.11	3.10	2.84	–1.09
Left/ACC spreading to vlPFC	32, 10	1664	–13.6, 39.2, –1.9	0.12	2.57	1.85	–2.98
Left/inferior parietal, supramarginal	40	1344	–36.4, –50.0, 41.8	0.06	2.76	2.58	–2.47
Left/precentral, middle frontal	6, 7	1024	–19.3, –18.4, 60.5	0.06	2.72	2.22	–0.76
Negative relationship with ANI–API activation							
Right/precentral, middle frontal	6	832	33.3, –7.4, 47.3	0.07	2.99	1.86	–1.46
Bilateral/medial, superior frontal and ACC	9, 10, 32	11 456	–1.0, 49.9, 16.9	–0.13	–2.71	–3.75	3.30
Left/PHG, uncus, amygdala		1024	–25.0, –5.7, –22.0	–0.12	–2.91	–3.65	2.45
D-KEFS Color-Word Interference Inhibition/Switching Subtest							
Positive relationship between ANI–API activation and WAIS-III Digit Symbol Test							
Right/dlPFC	9	896	32.1, 9.7, 26.0	0.06	2.95	1.61	–1.37
Right/precuneus	19	896	28.7, –67.4, 26.7	0.06	2.97	3.10	0.88
Negative relationship between ANI–API activation and WAIS-III Digit Symbol Test							
Left/lateral superior frontal	8	1024	–31.8, 20.3, 49.8	–0.13	–2.62	–2.97	4.70
Right/lateral superior frontal	6, 8	832	34.6, 13.6, 46.7	–0.09	–2.60	–1.70	3.06
Left/posterior cingulate	23	896	–9.2, –29.5, 31.9	–0.06	–2.46	–2.44	4.92

Abbreviations: ACC, anterior cingulate cortex; ANI, anticipation of negative images; API, anticipation of positive images; BA, Brodmann area; D-KEFS, Delis-Kaplan Executive Function System; dlPFC, dorsolateral prefrontal cortex (PFC); PHG, parahippocampal gyrus; PTSD, posttraumatic stress disorder; vlPFC, ventrolateral PFC; WAIS-III, Wechsler Adult Intelligence Scale, Third Edition.

[a] Clusters were identified using Huber robust regression analyses implemented using the R statistical package and including the Digit Symbol Test or the Color-Word Interference Inhibition/Switching subtest scaled score as regressor and differential blood oxygenation level–dependent activation during anticipation (ANI–API) as the dependent variable. Results were considered significant at a threshold of $P < .05$, Monte Carlo adjusted for whole-brain volume (832 μL) multiple comparisons.

[b] All coordinates are Talairach coordinates (x, y, z) based on Talairach Daemon software.

[c] Unstandardized regression coefficients and *t* statistics are shown for the initial Huber regression analyses with ANI–API.

[d] To further characterize results, *t* statistics are shown from post hoc linear regression analyses conducted with the Digit Symbol Test as the independent variable and ANI only and API only as the dependent variables.

The finding of insula hyperactivation during anticipation of negative emotional images is consistent with previous results from our group and others revealing that PTSD patients exhibit exaggerated activation during anticipation and processing of emotional stimuli.[33,36,41,53-56] The insula is considered important for monitoring interoceptive (ie, internal bodily) state and predicting interoceptive changes in response to future events.[57-59] Insula dysfunction may therefore underlie a tendency of PTSD patients to focus on or monitor physiological responses (heart and breathing rates, stomach upset, etc) to potential or experienced emotionally triggering events.

The neuropsychological findings in PTSD patients have been complex and at times inconsistent. Numerous studies have reported PTSD to be associated with impairments in cognitive inhibition,[12-16] processing speed,[17,20] and attention and working memory.[15-19] For this study, we therefore hypothesized that PTSD would be associated with decreased performance on the Digit Symbol Test and Color-Word Interference Inhibition and Inhibition/Switching subtests. In partial support of our hypotheses, we found that women with PTSD exhibited decreased performance on the Color-Word Interference Inhibition/Switching subtest and the Digit Symbol Test. Whereas the Color-Word Interference Inhibition/Switching subtest was designed to measure executive functions related to cognitive inhibition and attentional switching,[44] the Digit Symbol Test is considered a sensitive yet less specific measure tapping into visuospatial processing speed, motor speed, attention, and incidental learning.[60-62] It may thus best be described as a complex processing speed measure. Our findings suggest that the identified impairments were not due to specific circumscribed problems in simpler processing speed, cognitive inhibition, or abstract reasoning because performance on other measures related to these constructs (the Color-Word Interference Color Reading, Word Reading, and Inhibition subtests and Wisconsin Card Sorting Test) did not differ between groups. It is possible that PTSD related to domestic violence specifically influences attentional switching or processing speed in a way that leads to decreased performance uniquely for the Color-Word Interference Inhibition/Switching subtest and the Digit Symbol Test. However, it is more likely that these tasks were sensitive to subtle cognitive impairments owing to being more difficult measures requiring involvement from a combination of several basic processes (eg, cognitive inhibition plus attentional switching for the Color-

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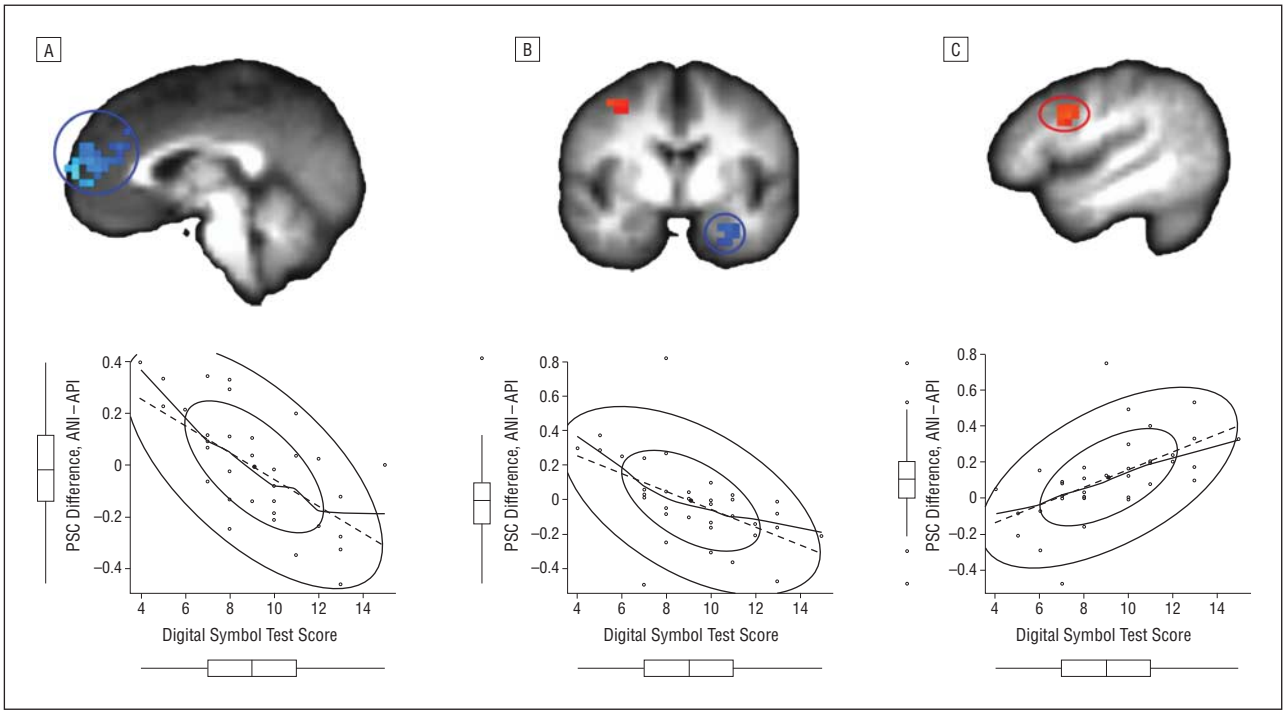

Figure 4. Brain regions in which differential activation to negative–positive anticipation was related to performance on the Wechsler Adult Intelligence Scale, Third Edition, Digit Symbol Test. Huber robust regression analyses were implemented in the R statistical package to identify brain regions in which differential activation to anticipation of negative (ANI)–positive (API) images related to performance on the Digit Symbol Test.[46] Better performance on the Digit Symbol Test related to less differential activation (ANI–API) with the medial prefrontal cortex (PFC) (A) (Brodmann areas [BAs], 10 and 32; x, y, z center-of-mass coordinates, =–1.0, 49.9, 16.9; image shown at x=0) and left parahippocampal gyrus/amygdala (B) (x, y, z center-of-mass coordinates, –25.0, –5.7, –22.0; image shown at y=–4) and greater differential activation within the right dorsolateral PFC (C) (BA 9; x, y, z center-of-mass coordinates, 47.3, 8.0, 28.9; image shown at x=48). Other regions in which differential activation to ANI–API exhibited a significant relationship to performance on the Digit Symbol Test or the Delis-Kaplan Executive Function System Color-Word Interference Inhibition/Switching subtest[44] are listed in Table 4. PSC indicates percent signal change. The box-and-whisker elements are described in the legend to Figure 3.

Word Interference Inhibition/Switching subtest; processing speed plus attention and learning for the Digit Symbol Test). Although the current results generally support previous research reporting executive function impairments in PTSD,[12-16,63] inconsistencies regarding which exact tests show impairment make it difficult to generalize across studies and pinpoint a specific substrate of cognitive impairment in PTSD.

Some of the most consistent findings regarding cognitive inhibition and processing speed deficits in PTSD are found for tasks involving emotional stimuli (eg, the modified Stroop task).[64-67] It is possible that cognitive problems arise during traditional neuropsychological assessments owing to emotional or contextual factors that are difficult to observe, measure, or control for. If this is the case, current and previous results would suggest that measures involving combinations of attentional, working memory, and/or inhibitory and switching functions may be most influenced by such emotional confounds. Perhaps compounding a situation requiring multiple frontal lobe cognitive functions with the additional need for emotional processing increases the overall load on prefrontal neural circuits. Based on current fMRI findings, we would suggest that observed decreases in cognitive performance in PTSD may be due to disrupted responses within a prefrontal-insula-amygdala circuitry in particular.

The dlPFC has been implicated as playing a role in complex attention, working memory, and top-down cognitive control during emotional processing and anticipation.[27,29,30,68-71] Acute psychological stress during a working memory task has been reported to decrease dlPFC activation for healthy controls.[72] In the present study, the extent of recruitment within dlPFC regions during ANI related negatively to PTSD symptom severity and positively to Digit Symbol Test and Color-Word Interference Inhibition/Switching subtest performance. The anticipation task included a CPT during the baseline and anticipation periods, presumably engaging both attentional and emotional processing networks. The periods involving anticipation of negative images most likely represented the most resource-demanding aspects of the task, particularly for PTSD patients. The ability of PTSD patients to recruit the dlPFC during highly stressful and resource-demanding situations may determine their ability to exert cognitive control and maintain optimal neuropsychological performance. Notably, areas of the dlPFC that were correlated with PTSD symptom severity and those that were correlated with neuropsychological measures were adjacent to one another but not overlapping (eFigure and eTable 5). Therefore, top-down modulation of symptom-related expression may be subserved by cortical areas different from but related to those that are more directly related to cognitive functioning. Future investigation will need to further disentangle the role of different parts of the PFC in maintaining emotional and cognitive aspects of PTSD.

Performance on the Digit Symbol Test also related negatively to activation in the medial PFC and amygdala. Fur-

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thermore, activation in these regions correlated negatively with dlPFC activation. Medial PFC and amygdala regions have repeatedly been implicated in the pathophysiology of PTSD.[33,35,36,73] The amygdala is considered important for processing emotional salience,[74,75] and activation in this region has been shown to relate to decreased working memory performance in healthy controls.[76] The medial PFC is thought to be involved in the direct inhibition and regulation of amygdala activation and emotional responses.[77,78] We suggest that, in PTSD, medial PFC activation represents greater mental energy being directed toward internally focused emotional coping, whereas dlPFC activation represents increased cognitive control to maintain focus on the external or cognitive task at hand. Thus, greater amygdala activation in response to pending emotional stimuli, coupled with greater recruitment of the medial PFC to focus on and cope with those emotions, may lead to disruption in processing speed and executive functions. Greater dlPFC response may relate to increased cognitive control of emotional processes and less disruption in these cognitive functions. An alternative interpretation is that medial PFC and amygdala responses relate to emotional processing, whereas dlPFC response relates more generally to inhibitory control regardless of whether the context is emotional or cognitive.

Given the observed inverse relationship between dlPFC and medial PFC/amygdala activation, it is likely that interventions that affect dlPFC response would influence activation in the medial PFC and amygdala and vice versa. Influencing the pattern of activation within this network could influence cognitive performance and PTSD symptoms. Surprisingly, very few fMRI studies conducted thus far have investigated changes in neural response patterns after PTSD treatment. Exposure therapy for PTSD was reported to decrease activation within the amygdala, subcallosal gyrus, and lateral PFC and to increase deactivations of ACC during the emotional Stroop task.[79] Other studies have reported increased activation in the inferior frontal gyrus and/or the ACC during emotional processing paradigms after treatment with cognitive behavioral therapy,[80] paroxetine, or even placebo.[81] Although the specific direction of effects within specific subregions is somewhat inconsistent, these few studies suggest that treatment influences prefrontal-amygdala response patterns. Results from a recent pilot study suggest that psychotherapy for PTSD may have subtle beneficial effects on executive functioning.[82] Perhaps by influencing prefrontal response patterns through cognitive behavioral therapy or medication, the imbalance between emotional processing or regulation networks (eg, medial PFC, amygdala) and cognitive control networks (eg, lateral PFC) can be at least partially ameliorated and help to optimize neuropsychological performance. Further research is needed to identify how current PTSD treatments influence neuropsychological function and prefrontal-amygdala activation patterns.

Another potential treatment strategy for PTSD could be to target dlPFC function directly via attentional or executive function training. Attention bias modification programs have been beneficial for social and generalized anxiety disorder.[83-85] Attention bias training has also been shown to influence dorsolateral PFC recruitment during emotional processing,[86] and cognitive training for patients with schizophrenia has been shown to influence dlPFC response during working memory tasks.[87] Research investigating the effects of computer-based training—whether focused on attentional bias away from threat or on attention and working memory functions more generally—on the neural response patterns and clinical symptoms of PTSD is warranted. We propose that attentional or executive function training could enhance dlPFC function, improve the balance between cognitive and emotional processing networks, and have a beneficial effect on cognitive performance and clinical symptoms in PTSD.

There are several limitations of this study. First, the study population included only female participants and patients with IPV-related PTSD. Therefore, the generalizability to male populations or to populations who developed PTSD subsequent to other types of trauma (eg, combat and non-IPV sexual assault) is unknown. Also, the cross-sectional nature of this study precludes determination of causality, that is, whether decreased executive function and aberrant prefrontal-insula-amygdala response represent vulnerabilities to developing PTSD or whether they are caused by the development of PTSD. The present study did not include a trauma-exposed group without PTSD. Therefore, it cannot be determined whether the group differences (PTSD vs control) resulted from trauma exposure or the PTSD diagnosis. Notably, several studies have reported significant differences in brain responses during emotional or cognitive processing[12,88-90] between trauma-exposed individuals with and without PTSD. Future studies including resilient trauma-exposed individuals could help clarify whether high levels of cognitive functioning or prefrontal engagement could represent a protective factor against the development of PTSD symptoms.

CONCLUSIONS

For PTSD patients, greater propensity to engage the medial PFC and amygdala rather than the dlPFC regions during anticipation of emotional stimuli may relate to impairments in processing speed and executive function. Results suggest that cognitive impairment in PTSD may result from an overactive affective processing and regulation network and an underactive cognitive control network. Interventions aimed at enhancing dlPFC function may have beneficial effects for both cognitive and affective symptoms associated with PTSD.

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