Neural Correlates of Reexperiencing, Avoidance, and Dissociation in PTSD: Symptom Dimensions and Emotion Dysregulation in Responses to Script-Driven Trauma Imagery

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Research suggests that responses to script-driven trauma imagery in posttraumatic stress disorder (PTSD) include reexperiencing and dissociative symptom subtypes. This functional magnetic resonance imaging (fMRI) study employed a dimensional approach to characterizing script-driven imagery responses, using the Responses to Script-Driven Imagery Scale and correlational analyses of relationships between severity of state posttraumatic symptoms and neural activation. As predicted, state reexperiencing severity was associated positively with right anterior insula activity and negatively with right rostral anterior cingulate cortex (rACC). Avoidance correlated negatively with rACC and subcallosal anterior cingulate activity. In addition, as predicted, dissociation correlated positively with activity in the left medial prefrontal and right superior temporal cortices, and negatively with the left superior temporal cortex. Theoretical and clinical implications are discussed, particularly with respect to an emotion-dysregulation account of PTSD.

Several studies have assessed functional neural correlates of symptom provocation in individuals with posttraumatic stress disorder (PTSD) using a script-driven imagery paradigm (Pitman, Orr, Forgue, de Jong, & Clairborn,

1987). Consistent with an emphasis on unitary accounts of PTSD pathophysiology, these studies have principally focused on neural correlates of script-driven imagery in PTSD versus non-PTSD groups. The most replicated findings include diminished activation in anterior cingulate cortex (ACC) subregions and anterior and ventral subregions of medial prefrontal cortex (mPFC) in PTSD participants relative to healthy controls matched for trauma exposure (recently reviewed in Lanius, Bluhm, Lanius, & Pain, 2005). Based on preclinical fear conditioning and extinction literature, these results have been interpreted as evidence of PTSD pathophysiology, specifically as failures of midline prefrontal regions to inhibit subcortical limbic, especially amygdala, reactivity (e.g., Milad, Rauch, Pitman, & Quirk, 2006). However, recent work suggests that psychobiological responses to trauma-related stimuli in PTSD are characterized by subtypes that may have distinct functional significances. Lanius and colleagues (Lanius et al., 2002; Lanius, Williamson, et al., 2005) have found different patterns of activation during dissociative responses than during hyperaroused reexperiencing. Increased activations in ACC (Brodmann Areas [BAs] 32 and 24) and mPFC (BAs 9 and 10) during dissociative responses suggest that, consistent with the phenomenology of dissociation, including disconnection from emotions and derealization, this state may involve ACC and/or mPFC inhibition of limbic activity.

To understand the neural correlates of script-driven imagery responses in PTSD, not only response subtypes but several other issues must be addressed, conceptually and empirically. First, homologies between human and rodent brain regions implicated in fear conditioning and extinction are not firmly established. Regions of human ACC known as subcallosal (SC) and rostral anterior cingulate cortex (rACC) have been thought to be homologous, respectively, to rodent infralimbic and prelimbic cortices implicated in conditioned fear extinction and amygdala inhibition (Milad et al., 2006). Human SC and rACC constitute the ACC affective division (Vogt, 1993), which is activated by emotional tasks and deactivated by cognitive tasks (Steele & Lawrie, 2004). A recent human fMRI study found that only a subgenual/rACC region correlated neg-

atively with amygdala activation during extinction trials (Phelps, Delgado, Nearing, & LeDoux, 2004).

However, another medial prefrontal region, the ventromedial orbitofrontal cortex, which has an even greater homology to the rat infralimbic cortex (Ongur, Ferry, & Price, 2003), has also been associated with extinction memory in healthy humans, in terms of both size (Milad et al., 2005) and activity (Gottfried & Dolàn, 2004). Furthermore, mPFC regions anterior to rACC and dorsal to OFC have been implicated in PTSD pathophysiology and extinction failure (hereafter, these regions are referred to as mPFC). Shin and colleagues (2004) found PTSD to be associated with decreased regional cerebral blood flow (rCBF) during trauma imagery in BA 10 (Montreal Neurological Institute [MNI] peak activation coordinates 10, 52, 2), and with negative correlations between rCBF changes in this region and the amygdala. Based on this mPFC region's anatomical connectivity in nonhuman primates, this was interpreted as consistent with failed amygdala inhibition by mPFC. Also, an mPFC region (BA 9/10 [peak MNI 4, 54, 12]) adjacent to the cluster identified by Shin and colleagues, exhibited increased mPFC activation to trauma imagery in a dissociative PTSD subgroup (Lanius et al., 2002). Drawing on the corticolimbic disconnection model of depersonalization (Sierra & Berrios, 1998), Lanius and colleagues interpreted this as consistent with "successful" mPFC inhibition of amygdala and other limbic activity.

A second key issue is that insular and prefrontal cortices are far more developed in humans than rodents. Functionally, this confers substantial capacities to monitor and respond—including with conscious awareness and intention—to perceptions, memories, and emotions; autonomic arousal; cognitive and behavioral response options, intentions, and impulses; and conflicts within and across these domains (Botvinick, Braver, Barch, Carter, & Cohen, 2001; Craig, 2002; Critchley, Wiens, Rotshtein, Öhman, & Dolàn, 2004; Miller & Cohen, 2001). While giving humans vastly greater self-regulatory potential than other mammals, these capacities can be impaired in PTSD (Frewen & Lanius, 2006), and may require targeted treatment before interventions designed to extinguish conditioned fear responses will succeed (Cloitre, Cohen, &

Koenen, 2006). Thus biological research on PTSD should be expected to implicate structures and functions involved in human self-regulation, but these are beyond the purview of preclinical research.

For example, the dorsal ACC (dACC) or ACC cognitive division (Vogt, 1993), typically activated by cognitive tasks and deactivated by emotional tasks (Steele & Lawrie, 2004), has repeatedly been implicated in conflict monitoring (Botvinick et al., 2001). That dACC monitors emotional processes is suggested by the finding that rCBF in this region during induced emotion positively correlated with scores on an emotional awareness measure (Lane et al., 1998). Also, Lanius and colleagues (2002) found dACC activation during dissociative script responses. Thus dACC, although not homologous with regions implicated in the preclinical fear conditioning–extinction literature, and conventionally viewed as uninvolved in emotion, may play a role in monitoring emotional conflicts or in dissociative responses to trauma-related stimuli.

Finally, a third key issue is that individual differences in PTSD participants' psychobiological responses to script-driven imagery can be conceptualized categorically, as qualitatively different response subtypes, or dimensionally, for example as involving different symptom severities and associated neural activation patterns. Methodologically too, script responses can be characterized dimensionally, which, importantly, allows for wide ranges of co-occurring reexperiencing, dissociative, and other state symptoms. To date, only the categorical approach has been employed. Foundational work is needed on the dimensionality of symptomatic and neural responses to trauma-related stimuli in PTSD.

This study was designed to contribute to that foundation. We developed the Responses to Script-Driven Imagery Scale (RSDI) to enable assessment of state reexperiencing, avoidance, and dissociative symptom responses to script-driven imagery (Hopper, Frewen, Sack, Lanius, & van der Kolk, 2007). Here we report on the neural correlates of severities of these responses in a PTSD group that, categorically speaking, primarily exhibited reexperiencing responses, but also had significant variability in state dissociation severity.

In a block-design fMRI study of 27 individuals with PTSD, RSDI scores were correlated with blood-oxygenation-level-dependent (BOLD) signal levels to identify neural correlates of variability in reexperiencing, avoidance, and dissociative symptoms provoked by script-driven trauma imagery. Based on the extant literature and an emotion-dysregulation view of PTSD, a priori regions were specified, as were, where warranted, hypotheses about correlation directions. For severity of reexperiencing symptoms, negative correlations were predicted with activity in rACC and mPFC, and a positive correlation was predicted for the right anterior insular cortex, an area involved in interoceptive awareness of psychophysiological and emotional states (Craig, 2002; Critchley et al., 2004). For dissociation severity, positive correlations were hypothesized with activation of mPFC and dACC; in addition, positive and negative correlations were predicted with activation in right and left superior temporal lobe structures, respectively, based on previous results (Lanius et al., 2002; Lanius, Williamson et al., 2005). For avoidance severity, associations with activation in the ACC (rACC, SC, and dACC), mPFC, and inferior frontal cortex (IFC) were of particular interest, given prior findings with reexperiencing and dissociative PTSD response subtypes.

METHOD

Participants

The sample was 27 individuals with PTSD (20 women, 26 White), recruited from local therapists and advertisements posted in the community and a medical center. Table 1 presents demographics and psychometrics. Twenty-four were participants in a randomized trial of sertraline for PTSD and a motor vehicle accident (MVA) was their primary trauma; the remaining three experienced childhood sexual or physical assault or adult physical assault. Mean time since primary trauma was 5.0 years ($SD = 8.0$). On 0–100 visual analog scales, MVAs were characterized by extreme levels of fear ($M = 86.7$, $SD = 21.3$), helplessness ($M = 92.6$, $SD = 21.1$), horror ($M = 81.3$, $SD = 25.8$), and sense of danger ($M = 89.3$, $SD = 23.5$); two involved

Table 1. Demographics and Psychometrics

Characteristic	n	%
Gender		
Women	20	74
Men	7	26
Ethnicity		
White	26	96
Native American	1	4
Education level		
High school (or equivalent)	6	22
Some college	12	44
College degree	9	33
Relationship status		
Single	13	48
Married/living with partner	11	41
Divorced/separated	3	11
Employment status		
Fulltime	15	54
Part time	3	12
Unemployed student	2	8
Unemployed/looking for work	7	27
	M	SD
Age	35.9	10.5
CAPS	69.0	20.7
BDI-II	30.9	12.6
BAI	21.4	12.7
DES	9.3	7.1
PDEQ	29.5	7.3

Note. CAPS = Clinician Administered PTSD Scale (Blake et al., 1995); BDI-II = Beck Depression Inventory II (Beck, Steer, & Brown, 1996); BAI = Beck Anxiety Inventory (Beck & Steer, 1993); DES = Dissociative Experiences Scale (Carlson & Putnam, 1993); PDEQ = Peritraumatic Dissociative Experiences Questionnaire (Marmar, Weiss, & Metzler, 1997).

death, and five injuries requiring hospital treatment. Those identifying assaults as primary traumas had experienced single-incident (adult physical assault) and repeated trauma (childhood abuse).

Exclusion criteria included alcohol/substance dependence within a year or abuse within 6 months, current or prior psychotic disorder, and any medical condition not stabilized for 6 months. Clinical trial participants had no prior serotonergic reuptake inhibitor treatment. All provided written informed consent, and procedures were approved by the University of Western Ontario Health Sciences Research Ethics Board.

Measures and Procedures

Posttraumatic stress disorder diagnosis was established with the Clinician-Administered PTSD Scale (CAPS; Blake et al., 1995). Mean CAPS score was 69.0 ($SD = 20.7$). Comorbid Axis I diagnoses, assessed with the Structured Clinical Interview for DSM-IV (First, Spitzer, Gibbon, & Williams, 1997), included 16 (60%) with current major depression, three (11%) with current panic disorder, and two (7%) with current generalized anxiety disorder. Two participants had past histories of alcohol dependence, one of past alcohol abuse, and three of past abuse of marijuana or hallucinogens.

Script-driven imagery. The RSDI (Hopper et al., 2007) is an 11-item instrument for assessing severities of state reexperiencing (4 items), avoidance (3 items), and dissociative symptoms (4 items) provoked by script-driven trauma imagery, with items rated from 0 (*not at all*) to 6 (*a great deal*). It has demonstrated excellent psychometric characteristics in two PTSD samples external to this study ($N = 58$, $N = 61$). Subscale alpha coefficients ranged from .76 to .92, and a confirmatory factor analysis combining those samples with this study's supported its hypothesized three-factor structure. Evidence of convergent and discriminant validity was demonstrated in relation to a psychological scale and trauma script-induced heart-rate change. Alpha coefficients in the present study were reexperiencing, $\alpha = .92$; avoidance, $\alpha = .95$; dissociation, $\alpha = .79$.

Script-driven imagery procedures followed those of Pitman and colleagues (1987), with 30-second script listening and imaging periods, adapted for fMRI (e.g., Lanius et al., 2001). In a block design, three consecutive scripts of the same type (neutral or trauma) were presented, each separated by a 2-minute rest period. Immediately after the third repetition, experiences across script listening and imagery periods of each trauma script were assessed with the RSDI, administered as an interview.

Without sufficient variability, correlating RSDI subscale scores with BOLD signal changes would be unwarranted, and inclusion of outliers in statistical parametric mapping (SPM) analyses would undermine the validity of the results.

Thus before conducting analyses on relationships between RSDI scores and BOLD signal intensity, RSDI scores were inspected to assess for variability and outliers (i.e., values more than 1.5 times the interquartile range above the third quartile or below the first quartile).

Functional MRI data acquisition. Imaging data were acquired on a 4-Tesla whole-body MRI system (Varian, Palo Alto, CA; Siemens, Erlangen, Germany), using methods described previously (Lanius et al., 2001). Imaging planes for functional scans were prescribed from a series of T1-weighted sagittal anatomic images. Functional planes were 12 contiguous, 6-mm-thick axial slices oriented in a plane approximately parallel to the anterior commissure–posterior commissure line centered on a plane level with the ACC. Prior to further imaging, a constrained, three-dimensional (3D) phase-shimming procedure (Klassen & Menon, 2004) optimized magnetic field homogeneity over the prescribed functional planes. During each functional task, BOLD images (T2*-weighted) were acquired continuously using an interleaved, four segment, optimized echo-planar-imaging (EPI) protocol (128×128 matrix size, $TR = 1250$ ms, $TE = 15$ ms, flip angle $= 45$ degrees, 24.0 cm field of view [FOV], volume collection time $= 5000$ ms). Each image was corrected for physiologic fluctuations using a navigator echo collected at the beginning of every EPI train. During each experimental session, a T1-weighted anatomic reference volume was acquired along the same orientation as the functional images using a 3D FLASH (fast low angle shot MRI) acquisition sequence ($256 \times 256 \times 64$ matrix size, 3.0 mm reconstructed slice thickness, $TI = 500$ ms, $TR = 10$ ms, $TE = 4.0$ ms).

Data Analyses

Before conducting correlation analyses of RSDI subscale scores and BOLD activity, relationships between RSDI subscale scores were assessed with two-tailed Pearson correlations, because these relationships have implications for interpreting associations between RSDI scores and brain activation.

The fMRI data analyses employed voxel-wise general linear models with design matrices comprised of epoch-related regressors. Baseline activity was calculated from average patterns for the nonspecific (implicit) 60s baseline (i.e., breath monitoring) periods preceding script-driven imagery. Activations from baseline associated with trauma and neutral imagery were calculated from average activation patterns during the 30s postscript imagery periods. Significant differences in BOLD response location and intensity in the trauma relative to the neutral condition were determined via subtraction analyses using SPM99 (Wellcome Department of Neurology, London, UK; http://www.fil.ion.ucl.ac.uk/spm). These linear contrasts yielded statistical parametric maps of the t statistic (contrast images). RSDI reexperiencing, avoidance, and dissociation scores were then correlated with the SPM maps, using simple pairwise correlations in a whole-brain random-effects model with two-tailed $\alpha < .05$, corresponding to a minimum $|r| \geq .30$ (i.e., medium-sized or greater correlation magnitude).

For subtraction and correlation analyses, to determine the statistical significance of each maximal-voxel t value, a small volume correction (SVC), controlling for the false discovery rate within the small volume, was applied to voxels activated within a minimum cluster size of $k \geq 5$ contiguously activated voxels within a 5-mm spherical search volume centered on the maximal voxel. For clusters in regions specified in any subscale-specific hypothesis, the threshold for reporting associations between activation and the RSDI subscale score was a significance level of $\alpha < .05$ (one-tailed). These criteria were employed for three reasons. First, the sample size, although relatively large for fMRI, was relatively small for correlation analyses (where statistical significance highly depends on sample size). Second, subscale-specific hypotheses were based on prior PTSD imaging studies, a relatively limited database, and every subscale-specific a priori region is part of a network of structures implicated in PTSD and/or emotion regulation. Finally, as the first functional imaging study employing dimensional analyses of PTSD symptom responses, avoiding type II errors was important. For clusters within regions not specified a priori, a more stringent level

of $\alpha < .05$ (two-tailed), controlling for whole-brain false discovery rate, was used (no clusters survived this cutoff).

Because correlations are more easily grasped indicators of relationships between BOLD activity and RSDI scores than t statistics, the latter were converted to r statistics, which are reported for each cluster, along with SVC-adjusted significance levels and z scores. However, the direction, magnitude, and statistical significance of a correlation do not indicate whether it involves data points consisting of activation only, deactivation only, or both activation and deactivation. Therefore, summary data on these relative (trauma-minus-neutral) activation distributions, and illustrative scatter plots, are also reported.

RESULTS

Trauma Minus Neutral Script Subtraction Analyses

Two regions exhibited nonsignificantly greater activation in the trauma than the neutral condition: right anterior insula (MNI 36 −2 14, BA 13), $t(25) = 2.23$, $p = .057$, and right superior mPFC (MNI 18 52 4, BA 10), $t(25) = 2.80$, $p = .050$. Importantly, these within-group subtraction results are not directly comparable to between-group subtraction results reported in prior PTSD fMRI studies.

RSDI Subscale Intercorrelations

Only RSDI reexperiencing and avoidance scores were significantly correlated, and positively so, $r(25) = .43$, $p < .05$. The correlation between RSDI avoidance and dissociation was small and nonsignificant, $r(25) = .18$, *ns*, as was that between reexperiencing and dissociation, $r(25) = .07$, *ns*. With regard to relationships between RSDI scores and BOLD activity, due to positive correlations between RSDI subscales, some regions were expected to exhibit positive and negative correlations with both reexperiencing and avoidance, and perhaps avoidance and dissociation.

State Reexperiencing

The mean reexperiencing score was 3.73 which, given the 0–6 response scale, suggests moderate state reexperiencing symptoms. There was considerable variability, $SD = 2.06$, but no outliers. Table 2 and Figure 1 illustrate that, as predicted, reexperiencing severity was correlated positively with right anterior insula activity and negatively with right rACC activity. Reexperiencing was also negatively correlated with right IFC, a region of interest (ROI) in the avoidance analysis. The predicted negative correlation of reexperiencing with mPFC was not found.

State Avoidance

The mean avoidance score of 2.18 was significantly lower than reexperiencing, $t(26) = 3.44$, $p < .01$, and consistent with mild-to-moderately severe avoidance symptoms. There was significant variability, $SD = 2.19$, but no outliers. As noted previously, rACC, SC, mPFC, and IFC were specified a priori as ROIs, but correlation directions were not predicted. Correlations were found for each region. Table 2 and Figure 1 show that RSDI avoidance was negatively correlated with activation in three separate ACC clusters: left rACC and SC, and bilateral dACC (BA 24a′). Self-reported avoidance was also negatively correlated with activation in right IFC, an a priori ROI for this analysis, and positively with activation in right superior temporal cortex, an ROI in the dissociation analysis.

State Dissociation

The mean RSDI dissociation score was 2.12, nearly identical to avoidance, $t < 1$, but considerably lower than reexperiencing, $t(26) = 3.14$, $p < .01$. Again a significant degree of variability was present, $SD = 1.82$, but no outliers. Table 2 and Figure 1 show that, as predicted, dissociation was positively correlated with activation in two clusters within left mPFC, as well as right superior temporal cortex. In addition, as predicted, dissociation was negatively correlated with activity in left superior temporal cortex, as well as right anterior insula and right IFC, ROIs for the

Table 2. Correlations Between Responses to Script-Driven Imagery Scale (RSDI) Subscales and Blood-Oxygenation-Level-Dependent Signal Change (Trauma Minus Neutral) in Regions of Interest ($N = 27$)

RSDI subscale, correlation direction Region (BA)	MNI coordinates			r	z score	Cluster size (voxels)
	x	y	z			
Reexperiencing, positive						
R Anterior insula (13)	38	0	12	.56	3.05**	81
Reexperiencing, negative						
L Rostral anterior cingulate (32)	−12	40	14	−.54	2.90**	58
R Inferior frontal (47)	46	42	0	−.53	3.15**	51
Avoidance, positive						
R Superior temporal (13)	52	−34	14	.52	2.80**	41
Avoidance, negative						
L/R Dorsal anterior cingulate (24a′)	−4	32	12	−.55	2.95**	81
L Rostral anterior cingulate (32)	−8	42	−4	−.47	2.49*	60
L/R Subgenual anterior cingulate (25)	−2	20	−4	−.52	2.80**	40
R Inferior frontal (46)	44	42	2	−.57	3.12**	70
Dissociation, positive						
L Medial frontal (10)	−12	50	4	.53	2.85**	81
L Medial frontal (10)	−2	52	14	.50	2.67**	48
R Superior temporal (42)	56	−30	18	.47	2.49**	80
Dissociation, negative						
R Anterior insula (13)	38	20	0	−.49	2.61**	81
R Inferior frontal (47)	40	34	−4	−.58	3.18***	63
L Superior temporal (41)	−38	−32	16	−.46	2.44**	46

Note. All regions were hypothesized a priori to correlate with scores on one or more RSDI subscales. Significance threshold was set at $p < .05$ (one-tailed), based on a small volume correction (SVC) applied to voxels activated within a minimum cluster size of $k \geq 5$ contiguously activated voxels within a 5-mm spherical search volume centered on the maximal voxel; see Methods section. R = right; L = left; MNI = Montreal Neurological Institute.
*$p = .05$. **$p < .05$. ***$p < .01$.

reexperiencing and avoidance analyses, respectively. The hypothesized positive correlation between dissociation and dACC activation was not found.

Distributions of Relative Activation in the Trauma Versus Neutral Conditions

As noted previously, the reported correlations do not reveal distributions of data points with respect to relative activation in the trauma versus neutral conditions. These distributions were not skewed, and every correlation involved both relative activation and deactivation between the conditions. That is, on the y axis, representing relative activation, the number of values (above zero) corresponding to greater BOLD signal increase (from prescript

baseline to postscript imaging) in the trauma than the neutral condition ranged from 8 of 27 participants (right IFC with reexperiencing) to 16 of 27 (left superior temporal cortex with dissociation). Figure 2 presents illustrative scatter plots.

DISCUSSION

This study documents significant heterogeneity in psychological and neural responses to script-driven trauma imagery within a PTSD sample. Using a dimensional approach to characterizing responses, state symptoms correlated with brain activation, in predicted ways. Below we review the findings and offer an integrative,

emotion-dysregulation account of their overall pattern, as graphically represented in Figure 3.

As predicted, state PTSD reexperiencing severity correlated positively with activity in the right anterior insula, an area activated in prior script-driven imagery studies (e.g., Bremner et al., 1999) and involved in the neural representation of somatic aspects of emotional states, including

acute sympathetic arousal (Craig, 2002; Critchley et al., 2004). In addition, as predicted, reexperiencing correlated negatively with activity in left rACC (BA 32), an ACC affective division subregion thought to be homologous to rodent prelimbic cortex. Although consistent with viewing PTSD as a failure of fear extinction (Milad et al., 2006), this finding is also compatible with an emotion-dysregulation view of PTSD psychobiology because, as discussed above, rACC inhibition of amygdala reactivity is but one of several ways human PFC may modulate regions involved in conditioned emotional responses. The predicted negative correlation between state reexperiencing and activation of mPFC (anterior to rACC) was not found. However, in the PTSD neuroimaging literature, decreased activation or failure to activate ACC and/or mPFC is the common finding with regard to these midline prefrontal structures.

Reexperiencing correlated negatively with activation of right IFC, a region implicated in inhibition of movement (e.g., Aron & Poldrack, 2005) and of emotional experience (e.g., Phan et al., 2005). Importantly, avoidance and
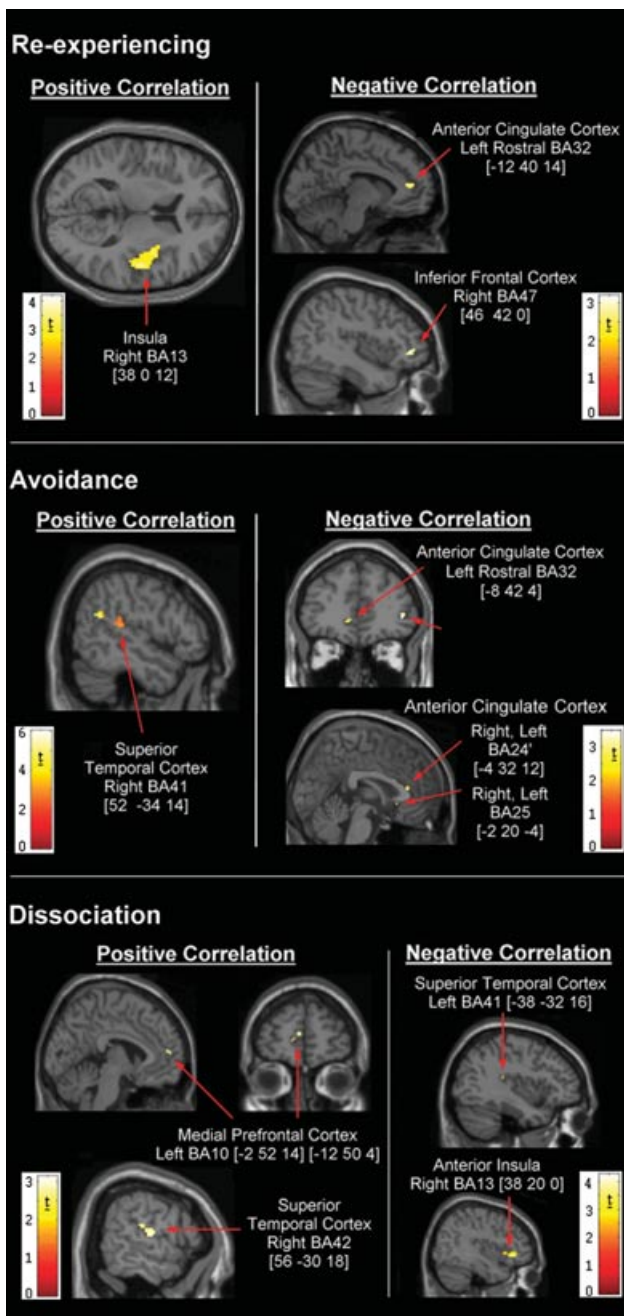
Figure 1. Correlations between state symptoms and neural responses to script-driven trauma imagery ($N = 27$). Activations from baseline associated with trauma and neutral imagery were calculated from average activation patterns during the 30-s postscript imagery periods. Significant differences in blood-oxygenation-level-dependent (BOLD) response location and intensity in the trauma relative to the neutral condition were determined via subtraction analyses using SPM99. The statistical parametric maps of the t statistic (contrast images) yielded by these linear contrasts were then correlated with Responses to Script-Driven Imagery Scale (RSDI) reexperiencing, avoidance, and dissociation scores, using simple pairwise correlations in a whole-brain random-effects model with two-tailed $\alpha < .05$, corresponding to a minimum $|r| \geq .30$ (i.e., medium-sized or greater correlation magnitude). Sample RSDI reexperiencing items: "Did you feel as though the event was reoccurring, like you were reliving it?" "Were you distressed?" Sample RSDI avoidance items: "Did you avoid experiencing images, sounds, or smells connected to the event?" "Did you avoid feelings about the event?" Sample RSDI dissociation items: "Did what you were experiencing seem unreal to you, like you were in a dream or watching a movie or play?" "Did you feel disconnected from your body?"
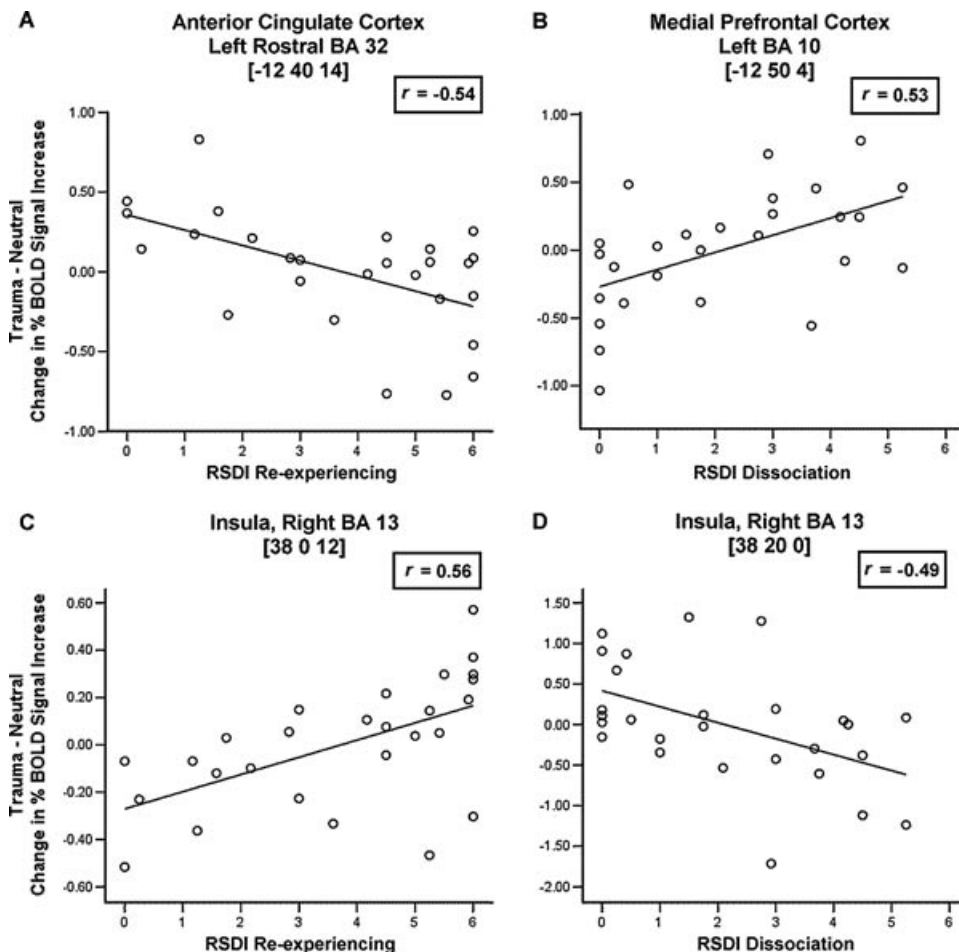
Figure 2. Representative scatter plots of Responses to Script-Driven Imagery Scale (RSDI) subscale scores and neural responses to trauma versus neutral script-driven imagery ($N = 27$). Plots depict relationships between RSDI reexperiencing and dissociation scores and relative blood-oxygenation-level-dependent (BOLD) signal change in prefrontal cortical regions implicated in fear extinction and emotion regulation (A and B), and right anterior insular regions implicated in conscious awareness of emotional states (C and D). Values greater than zero on the y axis correspond to greater BOLD signal increase (i.e., percent signal change from prescript baseline to postscript imaging periods) in the trauma than the neutral script-driven imagery condition, whereas values less than zero correspond to greater BOLD signal change in the neutral than the trauma condition.

dissociation severities were also negatively correlated with right IFC activity. Movement inhibition is a task demand in all fMRI paradigms; perhaps as symptoms become more intense and consume more processing resources, activation decreases in regions that implement movement inhibition.

Severity of self-reported avoidance responses to the trauma script also correlated negatively with activation in three separate ACC subregions: rACC (BA 32), SC (BA 25), and ventral dACC (BA 24a′). The rACC and SC activations were within the affective division, whereas the dACC activation, although strictly within the cognitive division, bordered the affective division. The opposite might have been predicted, with avoidance involving the successful reduction of reexperiencing symptoms via increased inhibitory rACC, SC, and dACC activity. However, we made no directional predictions about avoidance,
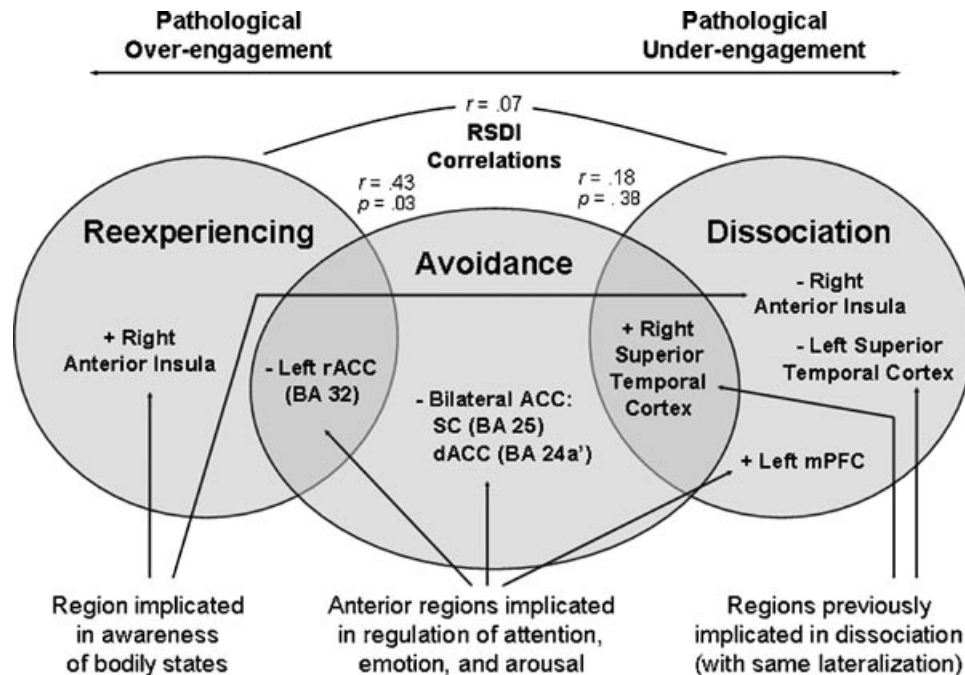
Figure 3. Emotion dysregulation account of responses to script-driven trauma imagery in posttraumatic stress disorder. Signs reflect positive (+) and negative (−) correlations. Brain regions within a circle indicate correlations unique to that specific symptom type; those within areas of overlap indicate correlations common to different symptom types. As indicated, self-reported Responses to Script-Driven Imagery Scale (RSDI) reexperiencing and avoidance scores were positively correlated, but no significant correlations were found between dissociation and reexperiencing or avoidance. ACC = anterior cingulate cortex; rACC = rostral ACC; SC = subcollosal ACC; rACC + SC = ACC affective division; dACC = dorsal ACC or ACC cognitive division; mPFC = medial prefrontal cortex.

for two reasons. No prior PTSD neuroimaging studies have assessed avoidance, and research implicating rACC and dACC in emotion regulation has involved healthy participants implementing avoidance as a prescribed and largely effective cognitive activity (e.g., Phan et al., 2005). In this study, participants were instructed to attend to their imagery "in all of its details," and avoidance correlated positively rather than negatively with reexperiencing. Perhaps participants with severe reexperiencing were also most likely to attempt avoidance and least likely to fully succeed in this regard. Thus increased avoidance may indirectly reflect increased reexperiencing, and common neural correlates may primarily reflect reexperiencing rather than avoidance per se. Assessing perceived successfulness of avoidance could shed light on this issue.

Consistent with previous research (Lanius et al., 2002; Lanius, Williamson et al., 2005) and as predicted, RSDI dissociation correlated positively with left mPFC and right superior temporal cortex activation, and negatively with left superior temporal cortex activation. These findings are noteworthy because the present sample had, on average, trait dissociation levels similar to a previous PTSD sample that displayed predominantly hyperaroused reexperiencing responses (Lanius et al., 2001), and much lower dissociation, both trait and state, than a PTSD group of "dissociative" script responders (Lanius et al., 2002; Lanius, Williamson et al., 2005). The functional significance of superior temporal activations during state dissociative responses, including laterality effects, merits focused investigation.

Perhaps co-occurring increases in mPFC activation and dissociative symptoms reflect passive mental disengagement or detachment from emotional processing, thus a form of emotion dysregulation involving pathological underengagement. Notably, the cluster within left mPFC (MNI −12, 50, 4) correlated positively with RSDI dissociation is, aside from laterality, nearly identical to the right mPFC cluster (MNI 10, 52, 2) previously correlated negatively with amygdala activity during script-driven imagery in veterans with PTSD (Shin et al., 2004).

Although not predicted, the negative correlation between state dissociation and right anterior insula activation may reveal another biological substrate of extreme emotional underengagement. This interpretation is bolstered by the opposite, positive correlation between right anterior insula activity and state reexperiencing. Both findings are consistent with the right anterior insula's putative role in representing physiological conditions of the body and interoception of feeling states (Craig, 2002).

The present findings are consistent with an emotion-dysregulation account of PTSD. More specifically, as summarized in Figure 3, they are consistent with the view that state symptoms assessed by the RSDI may represent underlying dimensions of emotion dysregulation with unique and nonunique neural bases. That is, PTSD may involve multiple (and perhaps simultaneous or rapidly sequentially unfolding) types of psychobiological responses to trauma-related stimuli, all of which may be understood as involving relatively failed or successful attempts to inhibit or modulate aversive emotional experiences. When exposed to trauma-related stimuli, individuals with PTSD may display pathological and nonvolitional emotional overengagement with trauma-related information, typified by extreme reexperiencing and hyperarousal, and/or pathological emotional underengagement with trauma-related information, and "successful" underengagement may involve transient psychological disengagement, including dissociative alterations of perception and consciousness.

Finally, although speculative, the positive correlation between mPFC activation and dissociation may reflect increasingly effective mPFC inhibition of amygdala processing with increasing state dissociation. As in current models of medial prefrontal involvement in fear extinction, this would presumably occur via inputs to inhibitory GABAergic cells that block information flow from the amygdala's lateral to central nucleus (Berretta, Pantazopoulos, Caldera, Pantazopoulos, & Pare, 2005). However, during state dissociation such mPFC activity might impede rather than facilitate extinction of conditioned responses, by preventing sufficient emotional engagement (Jaycox, Foa, & Morral, 1998) via inhibition of amygdala processing and central nucleus output to regions involved in conditioned autonomic, somatosensory, and behavioral responses.

This study has limitations. Participants were predominantly White women with PTSD secondary to MVAs; thus findings may not generalize to other PTSD samples. Low levels of trait and script-provoked dissociation raise the concern that observed relationships between state dissociation and neural activation may not apply to samples with greater dissociative pathology. However, the present findings do suggest the value of a dimensional approach to assessment and analysis of symptomatic responses to script-driven imagery in the relatively low-dissociation samples typical of most PTSD neuroimaging studies. The RSDI does not assess emotional numbing associated with stress-induced analgesia (Pitman, van der Kolk, Orr, & Greenberg, 1990; Nishith, Griffin, & Poth, 2002), for reasons detailed elsewhere (Hopper et al., 2007), but this form of pathological underengagement merits further study. Finally, the findings are correlational in nature, and thus do not support conclusions about causality.

In conclusion, the present findings demonstrate significant levels of within- and between-participant heterogeneity in symptomatic responses to script-driven trauma imagery in a PTSD sample. Using the RSDI, the underlying dimensionality of this heterogeneity was parsed into severities of reexperiencing, avoidance, and dissociative symptoms, and neural correlates of each symptom dimension were probed. These methods and findings provide the beginnings of a foundation for studying the dimensionality of symptomatic and brain responses to trauma-related conditioned stimuli and contexts in PTSD, and support accounts of PTSD as an emotion dysregulation disorder.

REFERENCES

Aron, A. R., & Poldrack, R. A. (2005). The cognitive neuroscience of response inhibition: Relevance for genetic research in attention-deficit/hyperactivity disorder. Biological Psychiatry, 57, 1285–1292.

Beck, A. T., & Steer, R. A. (1993). Beck Anxiety Inventory. San Antonio, TX: Psychological Corporation.

Beck, A.T., Steer, R. A., & Brown, G. E. (1996). Beck Depression Inventory (2nd ed.). San Antonio, TX: Psychological Corp.

Berretta, S., Pantazopoulos, H., Caldera, M., Pantazopoulos, P., & Pare, D. (2005). Infralimbic cortex activation increases c-Fos expression in intercalated neurons of the amygdala. Neuroscience, 132, 943–953.

Blake, D. D., Weathers, F. W., Nagy, L. M., Kaloupek, D. G., Gusman, F. D., Charney, D. S., et al. (1995). The development of a Clinician-Administered PTSD Scale. Journal of Traumatic Stress, 8, 75–90.

Botvinick, M. M., Braver, T. S., Barch, D. M., Carter, C. S., & Cohen, J. D. (2001). Conflict monitoring and cognitive control. Psychological Review, 108, 624–652.

Bremner, J. D., Narayan, M., Staib, L. H., Southwick, S. M., Mc-Glashan, T., & Charney, D. S. (1999). Neural correlates of memories of childhood sexual abuse in women with and without posttraumatic stress disorder. American Journal of Psychiatry, 156, 1787–1795.

Carlson, E. B., & Putnam, F. W. (1993). An update on the Dissociative Experiences Scale. Dissociation, 6, 16–27.

Cloitre, M., Cohen, L. R., & Koenen, K. C. (2006). Treating survivors of childhood abuse: Psychotherapy for the interrupted life. New York: The Guilford Press.

Craig, A. D. (2002). How do you feel? Interoception: The sense of the physiological condition of the body. Nature Reviews Neuroscience, 3, 655–666.

Critchley, H. D., Wiens, S., Rotshtein, P., Öhman, A., & Dolàn, R. J. (2004). Neural systems supporting interoceptive awareness. Nature Neuroscience, 7, 189–195.

First, M. B., Spitzer, R. L., Gibbon, M., & Williams, J. B. W. (1997). Structured Clinical Interview for DSM-IV Axis I Disorders (SCID). New York: New York State Psychiatric Institute, Biometrics Research.

Frewen, P. A., & Lanius, R. A. (2006). Toward a psychobiology of posttraumatic self-dysregulation. Annals of the New York Academy of Sciences, 1071, 110–124.

Gottfried, J. A., & Dolàn, R. J. (2004). Human orbitofrontal cortex mediates extinction learning while accessing conditioned representations of value. Nature Neuroscience, 7, 1144–1152.

Hopper, J. W., Frewen, P. A., Sack, M., Lanius, R. A., & van der Kolk, B. A. (2007). The Responses to Script-Driven Imagery Scale (RSDI): Assessment of state posttraumatic symptoms for psychobiological and treatment research. Journal of Psychopathology and Behavioral Assessment, 29(4).

Jaycox, L. H., Foa, E. B., & Morral, A. R. (1998). Influence of emotional engagement and habituation on exposure therapy for PTSD. Journal of Consulting and Clinical Psychology, 66, 185–192.

Klassen, L. M., & Menon, R. S. (2004). Robust automated shimming technique using arbitrary mapping acquisition parameters (RASTAMAP). Magnetic Resonance in Medicine, 51, 881–887.

Lane, R. D., Reiman, E. M., Axelrod, B., Yun, L. S., Holmes, A., & Schwartz, G. E. (1998). Neural correlates of levels of emotional awareness: Evidence of an interaction between emotion and attention in the anterior cingulate cortex. Journal of Cognitive Neuroscience, 10, 525–535.

Lanius, R. A., Bluhm, R., Lanius, U., & Pain, C. (2005). A review of neuroimaging studies in PTSD: Heterogeneity of response to symptom provocation. Journal of Psychiatric Research, 155, 45–56.

Lanius, R. A., Williamson, P. C., Bluhm, R. L., Densmore, M., Boksman, K., Gupta, M., et al. (2005). Functional connectivity of dissociative responses in posttraumatic stress disorder: A functional magnetic resonance imaging investigation. Biological Psychiatry, 57, 873–884.

Lanius, R. A., Williamson, P. C., Boksman, K., Densmore, M., Gupta, M., Neufeld, R. W., et al. (2002). Brain activation during script-driven imagery induced dissociative responses in PTSD: A functional magnetic resonance imaging investigation. Biological Psychiatry, 52, 305–311.

Lanius, R. A., Williamson, P. C., Densmore, M., Boksman, K., Gupta, M., Neufeld, R. W. (2001). Neural correlates of traumatic memories in posttraumatic stress disorder: A functional MRI investigation. American Journal of Psychiatry, 158, 1920–1922.

Marmar, C. R., Weiss, D. S., & Metzler, T. J. (1997). The peritraumatic dissociative experiences questionnaire. In J. P. Wilson & T. M. Keane (Eds.), Assessing psychological trauma and PTSD (pp. 412–428). New York: Guilford Press.

Milad, M. R., Quinn, B. T., Pitman, R. K., Orr, S. P., Fischl, B., & Rauch, S. L. (2005). Thickness of ventromedial prefrontal cortex in humans is correlated with extinction memory. Proceedings of the National Academy of Sciences, 102, 10706–10711.

Milad, M. R., Rauch, S. L., Pitman, R. K., & Quirk, G. J. (2006). Fear extinction in rats: Implications for human brain imaging and anxiety disorders. Biological Psychology, 73, 61–71.

Miller, E. K., & Cohen, J. D. (2001). An integrative theory of prefrontal cortex function. Annual Review of Neuroscience, 24, 167–202.

Nishith, P., Griffin, M. G., & Poth, T. L. (2002). Stress-induced analgesia: Prediction of posttraumatic stress symptoms in battered versus nonbattered women. Biological Psychiatry, 51, 867–874.

Ongur, D., Ferry, A. T., & Price, J. L. (2003). Architectonic subdivision of the human orbital and medial prefrontal cortex. Journal of Comparative Neurology, 460, 425–449.

Phan, K. L., Fitzgerald, D. A., Nathan, P. J., Moore, G. J., Uhde, T. W., & Tancer, M. E. (2005). Neural substrates for voluntary suppression of negative affect: A functional magnetic resonance imaging study. Biological Psychiatry, 57, 210–219.

Phelps, E. A., Delgado, M. R., Nearing, K. I., & LeDoux, J. E. (2004). Extinction learning in humans: Role of the amygdala and vmPFC. Neuron, 43, 897–905.

Pitman, R. K., Orr, S. P., Forgue, D. F., de Jong, J. B., & Claiborn, J. M. (1987). Psychophysiologic assessment of posttraumatic stress disorder imagery in Vietnam combat veterans. Archives of General Psychiatry, 44, 970–975.

Pitman, R. K., van der Kolk, B. A., Orr, S. P., & Greenberg, M. S. (1990). Naloxone reversible analgesic response to combat-related stimuli in posttraumatic stress disorder. Archives of General Psychiatry, 47, 541–544.

Shin, L. M., Orr, S. P., Carson, M. A., Rauch, S. L., Macklin, M. L., Lasko, N. B. (2004). Regional cerebral blood flow in the amygdala and medial prefrontal cortex during traumatic imagery in male and female Vietnam veterans with PTSD. Archives of General Psychiatry, 61, 168–176.

Sierra, M., & Berrios, G. E. (1998). Depersonalization: Neurobiological perspectives. Biological Psychiatry, 44, 898–908.

Steele, J. D., & Lawrie, S. M. (2004). Segregation of cognitive and emotional function in the prefrontal cortex: A stereotactic meta-analysis. Neuroimage, 21, 868–875.

Vogt, B. A. (1993). Structural organization of cingulated cortex: Areas, neurons, and somatodendritic receptors. In B. A. Vogt & M. Gabriel (Eds.), Neurobiology of cingulate cortex and limbic thalamus (pp. 19–70). Boston: Birkhauser.