fMRI Study of Psychophysiological and Brain Responses to Script-Driven Imagery in Identical Twins Discordant for Trauma Exposure and PTSD

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Abstract

Background: Neuroimaging studies have demonstrated increased psychophysiologic responses as well as medial prefrontal cortex (mPFC) hyporesponsivity to both trauma-related and -unrelated emotional stimuli in posttraumatic stress disorder (PTSD). However, the origin of these biological abnormalities has not yet been identified.

Objective: To determine whether psychophysiological and functional brain abnormalities in the mPFC, specifically the rostral anterior cingulate cortex (rACC), seen in individuals with PTSD during script-driven imagery (SDI) are familial vulnerability factors, due to trauma exposure, or acquired characteristics of the disorder.

Method: Participants were male trauma-exposed individuals with PTSD (ExP+, *n*=11) and their trauma-unexposed identical co-twins (UxP+, *n*=11) as well as trauma-exposed individuals without PTSD (ExP-, *n*=13) and their trauma-unexposed co-twins (UxP-, *n*=13). We used functional magnetic resonance imaging (fMRI) and SDI to study blood-oxygen-level-dependent (BOLD) signal changes during the recollection and imagery of stressful versus neutral autobiographical scripts.

Results: No significant differences were found between groups for skin conductance response to stressful imagery versus neutral imagery. Voxelwise analyses of the fMRI data, however, revealed significant differences between the PTSD and Control twin pairs in the rACC for the stressful imagery versus neutral imagery contrast. Specifically, this main effect of Diagnosis represented greater BOLD decreases in the PTSD group during stressful imagery relative to neutral imagery and appeared to be largely driven by deactivation in ExP+ participants to stressful imagery relative to baseline.

Conclusions: Diminished rACC activation observed in individuals with PTSD appears to represent neither a familial vulnerability factor for PTSD nor a characteristic of trauma exposure, but instead is likely to be an acquired trait of the disorder itself.

Introduction

Posttraumatic stress disorder (PTSD) is a psychiatric disorder that can develop after exposure to traumatic events that involve actual or threatened death, serious injury, or sexual violence. Individuals with PTSD experience four different clusters of symptoms: intrusion symptoms, avoidance symptoms, negative alterations in cognition and mood, and alterations in arousal. In order to be diagnosed with PTSD, these symptoms must persist for at least one month and cause significant distress or impairment in functioning. However, symptom duration may vary, with approximately 50% of adults recovering in three months and others remaining symptomatic for over 50 years following trauma exposure (American Psychiatric Association, 2013).

The estimated lifetime prevalence for PTSD in the general population using DSM-IV criteria is 6.8% (Kessler et al., 2005), and rates of PTSD are even higher among veterans and individuals whose occupations increase the risk of trauma exposure, such as firefighters and police officers. The National Vietnam Veterans Readjustment Study (NVVRS) estimated current and lifetime prevalences of PTSD among male theater veterans between 15 and 30%; combined with a 22.5% lifetime prevalence of partial PTSD, these findings suggested that nearly half of male Vietnam theater veterans suffered from symptoms of PTSD over the course of their lifetimes (Weiss et al., 1992). Though the high rates reported by the NVVRS have been controversial, Dohrenwend et al. (2006) fully adjusted for impairment of functioning and

documentation of exposure and found current and lifetime prevalences of 9.1% and 18.7%, respectively, supporting the NVVRS's finding that the Vietnam War took a severe psychological toll on U.S. veterans.

Furthermore, individuals with PTSD are significantly more likely to meet diagnostic criteria for another mental disorder. Data from the National Comorbidity Survey indicates that 88.3% of men and 79% of women with PTSD have a lifetime history of at least one other psychiatric disorder, the most common being depressive, anxiety, and substance use disorders (Kessler et al., 1995).

Although many people experience traumatic events, only some of these individuals ultimately develop PTSD, implying that pre-existing vulnerability or protective factors may influence the likelihood of developing PTSD in response to trauma. The identification of neurobiological characteristics of PTSD as vulnerability or protective factors could facilitate the development of better screening measures to identify individuals at an increased or decreased risk for developing PTSD, respectively.

Symptom Provocation in PTSD

In order to assess the psychophysiological and neural correlates of PTSD symptoms, researchers have designed and implemented symptom provocation tasks, in which participants are presented with trauma-related sounds, images, or autobiographical accounts of trauma exposure (Lanius et al., 2006; Sartory et al., 2015). Script-driven imagery (SDI) involves the preparation of personal "scripts" that describe the participant's own experiences, including the one(s) underlying their PTSD. While in the psychophysiology laboratory or neuroimaging scanner, participants listen to their autobiographical scripts and are instructed to recall and visualize the events described during a condition referred to as "imagery" (Pitman et al., 1987).

Psychophysiology. Script-driven imagery studies of psychophysiological responses in PTSD have found elevated heart rate (HR), skin conductance (SC), and electromyogram (EMG) responses to trauma-related scripts in trauma-exposed individuals with PTSD as compared to trauma-exposed individuals without PTSD (Orr et al., 1998; Orr et al., 1993; Pitman et al., 1987). In one of the first studies of SDI in PTSD, Pitman et al. (1987) assessed psychophysiologic arousal during combat imagery in Vietnam combat veterans and found that personalized scripts generated greater symptomatology in participants with PTSD than in those without. Though there was only a trend towards significant group differences for HR, individuals with PTSD had significantly larger differences in SC and EMG between combat and neutral imagery than trauma-exposed controls. A later study of World War II and Korean combat veterans by Orr et al. (1993) found significant main effects of Diagnosis and Script type as well as Diagnosis by Script interaction for HR, SC, and EMG responses; that is, combat-exposed individuals with PTSD had greater psychophysiologic responses to combat imagery than did combat-exposed individuals without PTSD. However, significant group differences in physiological responses were limited to combat-related traumatic imagery and did not extend to combat-unrelated traumatic ("other stressful"), positive, or neutral imagery. Interestingly, despite the group differences in psychophysiologic responses, there were no significant group differences in self-reported levels of valence, arousal, or vividness of imagery across individualized combat scripts. In a similar study of women who experienced childhood sexual abuse, Orr et al. (1998) found significantly larger HR responses to trauma-related imagery in participants with current PTSD compared to trauma-exposed participants both with and without a lifetime history of PTSD. Participants with current PTSD also had significantly larger corrugator EMG response in comparison to trauma-exposed participants without a lifetime history of PTSD only. Again,

significant group differences in psychophysiologic responses were observed only in trauma-related imagery and not the imagery of other stressful life experiences.

Brain Activation. Both positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) studies of script-driven imagery have implicated paralimbic and prefrontal regions as neural substrates underlying PTSD (Britton et al., 2005; Gold et al., 2011; Lanius et al., 2001; Rauch et al., 1996; Shin et al., 1999; Shin et al., 2004). Shin and Handwerger (2009) conceptualize PTSD as a stress-induced fear circuitry disorder that involves abnormalities in the amygdala, medial prefrontal cortex (mPFC), and hippocampus, all of which are involved in emotion regulation and the detection of and response to fear. Studies of PTSD suggest exaggerated activation of the amygdala, a structure involved in fear conditioning and the detection of threat; this hyperactivity may account for the exaggerated fear response characteristic of PTSD as well as the persistence of traumatic memories. Studies have also shown diminished activation in ventral portions of the mPFC (vmPFC), which play an important role in fear extinction and extinction retention as well as emotion regulation. In PTSD, the vmPFC may also fail to inhibit the amygdala. Lastly, the hippocampus is a critical structure in encoding episodic memories and thus facilitates memory for context during fear extinction and conditioning. Studies of individuals with PTSD have found abnormalities in hippocampal activation and volume, which may be associated with memory impairments in PTSD.

In a PET study of individuals with PTSD, Rauch et al. (1996) investigated the neuroanatomy of PTSD by using trauma-related scripts to achieve a symptomatic state. They found regional cerebral blood flow (rCBF) increases in limbic and paralimbic structures, including the insular, medial temporal, and anterior cingulate cortices as well as the amygdala, during trauma-related SDI. These findings were accompanied by decreases in the left inferior

frontal and middle temporal cortices. Although this study suggested that PTSD symptoms are mediated by the paralimbic and limbic structures, the lack of a control group of any kind limited their findings. A subsequent study of SDI in trauma-exposed individuals with and without PTSD (Shin et al., 1999) found that while all subjects exhibited rCBF increases in the orbitofrontal cortex and anterior temporal poles, participants with PTSD experienced significantly greater increases in these regions. Compared to trauma-exposed individuals without PTSD, those with PTSD exhibited diminished activation in the rostral anterior cingulate gyrus, but there was no significant amygdala activation in either group. Similarly, an fMRI study of SDI in PTSD by Lanius et al. (2001) found that trauma-exposed individuals with PTSD experienced lower levels of activation to trauma-related imagery in the thalamus, medial frontal cortex, and anterior cingulate gyrus compared to trauma-exposed individuals without PTSD.

Shin et al. (2004) measured both psychophysiologic responses and rCBF changes in Vietnam combat veterans with and without PTSD to examine the relationship between the amygdala and medial prefrontal regions during SDI. They observed a significant interaction between Diagnosis and Condition for both SC and EMG, but not HR, responses, with greater SC and EMG response increases to trauma-related stressful versus neutral imagery in the PTSD group compared to the trauma-exposed control group. They observed significant group differences in medial frontal gyrus activation to traumatic versus neutral scripts, with individuals with PTSD exhibiting greater decreases in rCBF than those without PTSD. In trauma-exposed participants with PTSD, rCBF changes in the medial frontal gyrus were negatively correlated with bilateral rCBF changes in the amygdala; these correlations remained significant even when participants with comorbid depression were excluded from the analyses. Furthermore, PTSD

symptom severity was positively correlated with rCBF in the right amygdala and negatively correlated with rCBF in the medial frontal gyrus during traumatic imagery.

In a later study by this same group, Gold et al. (2011) examined psychophysiologic responses and rCBF changes during trauma-unrelated stressful scripts versus neutral scripts in the same cohort of Vietnam veterans. They observed an interaction between Diagnosis and Condition for EMG responses and a trend for SC responses, with higher responses in participants with PTSD during trauma-unrelated stressful versus neutral imagery as compared to participants without PTSD. Furthermore, they found that individuals with PTSD exhibited a greater rCBF decrease in anterior cingulate cortex (ACC) activation during the same contrast. However, significant correlations between measures of PTSD symptomatology and ACC deactivation did not emerge. This study not only replicated previous neuroimaging findings of brain activation to traumatic versus neutral scripts in PTSD, but also extended them to include trauma-unrelated stressful scripts.

A PET study by Britton et al. (2005) assessed psychophysiological responses and corticolimbic blood flow during SDI of neutral and traumatic experiences related to combat or highly stressful events in trauma-exposed veterans with and without PTSD as well as trauma-unexposed controls. Although they did not observe a significant main effect of Diagnosis or an interaction between Diagnosis and Condition for SCR, they found unique patterns of activation in each of the three study groups. Healthy controls exhibited increased amygdala and decreased vmPFC activation to stressful versus neutral scripts, while trauma-exposed veterans without PTSD exhibited decreased activation in both the amygdala and vmPFC to combat versus neutral scripts. Unlike both control groups, trauma-exposed veterans with PTSD neither activated nor deactivated the amygdala to combat versus neutral scripts. They hypothesized that decreased

activation of the amygdala in both groups of trauma-exposed veterans compared to healthy controls may reflect a compensatory change or mechanism by which subjects attempt to cope with intense, stressful memories. Most important, they found that participants with PTSD, unlike participants in both control groups, exhibited deactivation in the rostral anterior cingulate cortex (rACC) rather than the vmPFC, suggesting that individuals with PTSD may fail to regulate emotional cues and reminders of traumatic events via ineffective top-down inhibition of the amygdala by the rACC.

The Current Study

Although previous studies have identified biological abnormalities in PTSD using SDI, the origin of these abnormalities is not entirely clear. They may reflect a vulnerability factor for developing PTSD after trauma exposure, the effect of trauma exposure itself, or an acquired characteristic of PTSD (Pitman et al., 2006). To address this question, the current study sought to examine the origin of psychophysiological and functional brain abnormalities found during SDI in PTSD using an identical twin, case-control design.

We studied 24 twin pairs discordant for trauma exposure, i.e., each twin pair consisted of a trauma-exposed individual and his trauma-unexposed, identical co-twin. In approximately half of the twin pairs, the trauma-exposed twin had chronic PTSD (P+); in the other half, the trauma-exposed twin had no history of PTSD (P-). Given that identical twins have the same genetic makeup and much of the same early developmental environment, any biological difference between a trauma-exposed individual and his trauma-unexposed, identical co-twin should reflect an acquired characteristic of trauma exposure or PTSD. On the other hand, if individuals with PTSD and their identical co-twins share a biological abnormality that significantly differs from individuals without PTSD and their identical co-twins, then this abnormality likely represents a

familial vulnerability factor for PTSD. Because the trauma-unexposed co-twins included in the study did not meet the exposure criterion for PTSD, this study necessitated the use of trauma-unrelated, stressful scripts to assess the origins of psychophysiological and functional brain abnormalities during SDI.

Using this model, we sought to replicate previous findings of psychophysiological and functional brain abnormalities in PTSD and to determine the origin of these abnormalities. In line with previous research, we expected to find decreased activation in the medial prefrontal cortex during stressful imagery versus neutral imagery in trauma-exposed individuals with PTSD compared to those without PTSD. We hypothesized that these differences in activation could represent either a familial vulnerability factor for PTSD or an acquired characteristic of PTSD but would not be likely to reflect trauma exposure, as previous studies controlled for trauma-exposure in their designs. Given the inconsistent literature, we predicted that mPFC, specifically rACC, activation might be negatively correlated with measures of PTSD symptom severity. Consistent with previous research, we did not expect to find group differences in amygdala activation. We also did not expect to find significant differences in SC responses to trauma-unrelated stressful scripts versus neutral scripts given that these psychophysiologic differences appear to be specific to trauma-related scripts.

Method

Participants

Participants were 24 pairs of male identical twins recruited from the Vietnam Era Twin (VET) Registry and the University of Washington Twin Registry. Participants were separated into experimental groups based on exposure to trauma and diagnosis of PTSD: trauma-exposed participants with current PTSD (ExP+, n=11) and their trauma-unexposed co-twins without

PTSD (UxP+, *n*=11) and trauma-exposed control participants without a history of PTSD (ExP-, *n*=13) and their trauma-unexposed co-twins (UxP-, *n*=13). The majority of the ExP+ participants were exposed to trauma in combat during the Vietnam War (*n*=10), though one experienced trauma in a motor vehicle accident (*n*=1). All combat-exposed twins without PTSD were exposed to trauma in combat (*n*=13). Twin pairs consisting of a trauma-exposed individual with PTSD and his co-twin were referred to as PTSD twin pairs, while twin pairs consisting of a trauma-exposed individual without PTSD and his co-twin were referred to as Control twin pairs. Collectively, participants with trauma exposure comprised the exposed (Ex) group, and their co-twins with no trauma exposure comprised the unexposed (Ux) group.

Demographics and Psychometrics

Among the exclusion criteria for this study were serious contraindicating medical conditions, such as strokes, seizures, or major head trauma involving loss of consciousness for more than ten minutes. Forty-three participants were right-handed, four were left handed (1 UxP+, 2 ExP-, 1 UxP-), and one was ambidextrous (1 UxP+).

Each subject completed the Structured Clinical Interview for DSM-IV (SCID) and Clinician-Administered PTSD Scale (CAPS) to determine PTSD diagnostic status and symptom severity. The SCID was also used to assess for non-PTSD Axis I disorders. Participants in the ExP+ group met diagnostic criteria for the following current comorbid disorders: major depressive disorder (*n*=1), specific phobia (*n*=2), social phobia (*n*=1), alcohol or substance abuse/dependence (*n*=2), dysthymia (*n*=2), and generalized anxiety disorder (*n*=1). Participants in the UxP+ group met diagnostic criteria for current panic disorder (*n*=1) and alcohol or substance abuse/dependence (*n*=2), while participants in the ExP- group met diagnostic criteria only for current alcohol or substance abuse/dependence (*n*=1). Participants in the UxP- group

did not meet criteria for any current comorbid disorders. Ten individuals were currently taking selective serotonin reuptake inhibitors (SSRIs) or another class of antidepressants at the time of the study (7 ExP+, 1 UxP+, 2 UxP-).

During their visits, participants completed various psychometrics, including the Beck Depression Inventory (BDI), Michigan Alcohol Screening Test (MAST), Traumatic Life Events Questionnaire (TLEQ), Childhood Trauma Questionnaire (CTQ), and Beck Depression Inventory (BAI).

Procedures

Script-Driven Imagery Task. The day before the functional magnetic resonance imaging (fMRI) session, all participants were interviewed and asked to provide both oral and written details about two neutral and two stressful trauma-unrelated personal events; trauma-exposed participants only were asked to provide details about two trauma-related personal events. After describing each event, participants were asked to examine a list of bodily responses and choose those that they experienced during each event. Scripts describing each event were composed in the second person, present tense and recorded in a neutral voice for playback during the fMRI session the next day. These scripts included up to five of the bodily responses selected by the participant.

During the fMRI session, participants were studied in each of the three conditions with two different scripts per condition. Given their lack of trauma exposure, trauma-unexposed participants (UxP+ and UxP-) were presented with previously developed standard scripts during the trauma condition; these scripts related to either combat exposure in Vietnam or motor vehicle accidents, according to the type of trauma their co-twin experienced. Before entering the scanner, participants were instructed to close their eyes, listen carefully to each script, and recall

and imagine each event as if they were experiencing it again. Following this period, referred to as "imagery," participants heard a chime that signaled relaxation and recovery. Participants were then asked to rate each script on levels of valence (happiness/pleasure), arousal, and vividness of imagery using separate visual analog scales (0=absent and 12=maximal). Psychophysiological data were collected for each script at baseline (30 seconds), read (when the scripts are orally presented, approximately 30 seconds), imagery (30 seconds), recovery (30 seconds); neuroimaging data were collected for the same periods as well as during rating (60 seconds).

Psychophysiological Responses. Participants' skin conductance responses (SCRs) were measured via an MR-compatible Coulbourn Instrument according to previously established procedures. The equipment was programmed with a sampling rate of 5 Hz, and in vivo metric Ag/AgCl electrodes filled with an isotonic electrolyte paste were placed on the dorsal surface of each subject's non-dominant hand. SCR data were recorded and averaged for each script during the baseline, read, imagery, and recovery periods. Difference scores for the read, imagery, and recovery conditions were generated by subtracting the average SCR values during baseline from the average SCR values during each condition. The resulting difference scores for stressful and neutral imagery were averaged across runs for each participant, and stressful versus neutral imagery difference scores were calculated by subtracting the average neutral imagery difference scores from the average stressful imagery difference scores.

Functional Magnetic Resonance Imaging. All fMRI scans were completed at the Massachusetts General Hospital (Charlestown, MA) using a 3.0 Tesla whole body high-speed scanner (Siemens Medical Systems, Iselin, NJ) with a 12-channel gradient head coil. Following an automated scout image and shimming procedures, high-resolution structural MRI images (three-dimensional magnetization-prepared rapid acquisition with gradient echo; repetition

time=2.53 sec, flip angle=7°) with a 1.00-mm slice thickness were collected. fMRI blood-oxygen-level-dependent (BOLD) images were acquired for each script during baseline, read, imagery, recall, and rating using a gradient echo T2*-weighted sequence (repetition time=2.50 sec, echo time=30 msec, flip angle=90°). Functional images were collected in 46 coronal slices perpendicular to the anterior commissure-posterior commissure line (thickness=2.50 mm, 0.5 mm skip).

Statistical Analyses

For the remainder of this thesis, we will be focusing on the stressful imagery versus neutral imagery contrast with a specific focus on neural activation in the medial prefrontal cortex, specifically the rostral anterior cingulate cortex (rACC) and medial frontal gyrus.

Psychophysiological Data. IBM SPSS Statistics (Version 22) was used to conduct separate 2 (Diagnosis: PTSD, Control) x 2 (Exposure: Ex, Ux) analyses of variance (ANOVA) on each psychophysiological and behavioral dependent variable. A main effect of Diagnosis showing a significant difference between PTSD and Control twin pairs (in the absence of an interaction between Diagnosis and Exposure) would be consistent with a familial vulnerability factor for developing PTSD. A main effect of Exposure would indicate that the differences are due to exposure to trauma independent of PTSD diagnosis. A Diagnosis by Exposure interaction in which trauma-exposed twins with PTSD differ from all other groups would suggest that the results are an acquired characteristic of PTSD. We then entered current antidepressant use in Ex twins as another between-groups variable and conducted a 2 (Diagnosis) x 2 (Medication: Yes, No) x 2 (Exposure) repeated measures ANOVA to assess for the effect of medication on our results. Correlational analyses were run to assess the relationships between psychophysiological arousal and subjective ratings, neural activation, and scores on selected psychometric tests.

fMRI Data. Two types of analyses were performed on the fMRI data: whole-brain voxelwise comparisons and ANOVAs of fMRI data extracted from regions of interest.

Whole-brain voxelwise comparisons were performed with the statistical parametric mapping (SPM2) software package. Functional images were corrected for motion and coregistered to each participant's high-resolution structural MRI image. The images were then spatially normalized in a standard stereotactic space (Montreal Neurological Institute, MNI) and smoothed (8 mm). To analyze the data, we used an approach consisting of hierarchical levels of analysis. First, contrast images comparing stressful imagery to neutral imagery were created for each participant as well as each twin pair. To examine the main effect of Diagnosis, the contrast images of each Ex twin and his Ux co-twin were averaged to generate contrast maps; then, a two-group t-test was used to compare the maps of the PTSD twin pairs to those of the Control twin pairs. To assess the main effect of Exposure, a paired t-test was used to compare the contrast images in the Ex versus Ux groups. Finally, to assess the Diagnosis by Exposure interaction, contrast images showing the differences in response between each Ex twin and his Ux co-twin were used in a two-group t-test comparing the PTSD and Control twin pairs. Given our strong a priori hypotheses, we applied a significance threshold of $p < 0.001$, one-tailed and uncorrected (z-score ≥ 3.09) to activations in the rostral anterior cingulate cortex (rACC). For regions about which we had no a priori predictions, we applied a more conservative significance threshold of $p < 0.00002$, two-tailed and uncorrected (z-score ≥ 4.27).

Following the whole-brain voxelwise analyses, we defined functional regions of interest (ROIs) in the medial prefrontal cortex and extracted data from these ROIS for all participants using the MarsBaR SPM toolbox. These data were further analyzed in SPSS using separate 2 (Diagnosis: PTSD, Control) x 2 (Exposure: Ex, Ux) repeated measures ANOVAs followed by 2

(Diagnosis) x 2 (Medication: Yes, No) x 2 (Exposure) repeated measures ANOVAS to covary for current antidepressant use in the Ex twins. Correlational analyses were also performed with the extracted data to determine whether activation in the Ex and Ux twins were correlated with the Ex twin's CAPS scores and other clinical measures.

Results

Demographic and Clinical Characteristics

Table 1 summarizes the demographic and clinical characteristics of the participants. Consistent with their diagnoses, ExP+ participants exhibited significantly higher CAPS B ($F(1,22) = 39.3$, $p < .001$), CAPS C ($F(1,22) = 23.6$, $p < .001$), CAPS D ($F(1,22) = 34.51$, $p < .001$), and total CAPS scores ($F(1,22) = 33.82$, $p < .001$) than ExP- participants. There was a significant main effect of Exposure for TLEQ scores, with a greater number of critical events ($F(1,22) = 5.53$, $p = .028$), critical events with fear and horror ($F(1,22) = 4.46$, $p = .046$) , and total occurrences ($F(1,22) = 3.97$, $p = .043$) in Ex twins versus their Ux co-twins. There was also a trend towards significance for a main effect of Exposure for BDI scores ($F(1,22) = 3.97$, $p = .059$), with what appeared to be higher levels of depression symptoms in Ex participants than Ux participants. Lastly, there was both a significant main effect of Exposure ($F(1,22) = 4.90$, $p = .038$) and a significant Diagnosis by Exposure interaction for BAI scores ($F(1,22) = 5.69$, $p = .026$), showing that Ex participants had significantly higher levels of anxiety symptoms than Ux participants and that ExP+ participants scored significantly higher than UxP+, ExP-, and UxP- participants. No other effects were significant.

Table 1. Demographic and Clinical Characteristics of Trauma-Exposed Individuals With and Without PTSD and Their Trauma-Unexposed Identical Co-Twins

	PTSD Pairs[a]				Control Pairs[b]				Mixed-Model Analysis of Variance[c]					
	Exposed[d]		Unexposed[d]		Exposed[e]		Unexposed[e]		Diagnosis		Trauma Exposure		Interaction	
Measure	Mean	SD	Mean	SD	Mean	SD	Mean	SD	F	p	F	p	F	p
Age (years)	60.55	6.64	60.55	6.64	62.54	3.80	62.54	3.80	.848	.367				
Education (years)	13.91	2.98	13.73	3.61	15.81	3.72	15.19	2.66	1.72	.203	1.07	.313	.315	.580

CAPS[f] B: Re-experiencing	11.91	7.87			.46	1.20			39.3	<.001				
CAPS C: Avoidance	17.00	11.3			1.08	2.40			23.6	<.001				
CAPS D: Hyperarousal	16.27	5.93			1.31	2.14			34.51	<.001				
CAPS Total	45.18	20.1			2.85	4.36			33.82	<.001				
MAST[g]	5.00	5.73	3.09	5.05	2.31	2.84	2.69	4.01	.846	.368	1.15	.294	2.61	.120
TLEQ[h] Critical Events	7.36	3.29	5.36	3.64	6.00	2.27	4.85	2.70	.850	.367	5.53	.028	.398	.535
TLEQ Critical Events with Fear and Horror	3.82	3.16	1.82	1.83	2.00	2.12	1.92	2.06	1.10	.305	4.46	.046	3.82	.063
TLEQ Total Occurrences	21.55	10.2	14.09	15.5	16.31	7.40	11.15	7.61	1.72	.204	4.60	.043	.153	.699
Childhood Trauma Questionnaire	39.74[i]	12.5	37.63[i]	11.0	38.33[j]	8.04	37.42[j]	10.4	.039[k]	.845	.508[k]	.485	.079[k]	.782
BDI[l]	7.82	7.87	4.64	8.33	4.62	4.35	3.23	2.83	1.08	.311	3.97	.059	.615	.441
BAI[m]	8.45	8.00	2.27	4.38	2.69	1.75	2.92	5.19	2.38	.137	4.90	.038	5.69	.026

[a] Presence of current trauma-related PTSD in the exposed twin.
[b] Absence of current or past trauma-related PTSD in the exposed twin.
[c] df = 1, 22 unless otherwise noted.
[d] N=11 unless otherwise noted.
[e] N=13 unless otherwise noted.
[f] Clinician Administered PTSD Scale.
[g] Michigan Alcoholism Screening Test.
[h] Traumatic Life Events Questionnaire.
[i] N= 9.
[j] N=12.
[k] df = 1,19.
[l] Beck Depression Inventory.
[m] Beck Anxiety Inventory.

Ratings Data

No significant effects were found on ratings of valence, arousal, or vividness of imagery during stressful or neutral imagery. There was, however, a trend towards a significant main effect of Diagnosis on ratings of arousal during stressful imagery, with the ExP+ (6.500 ± 2.99) and UxP+ groups (6.833 ± 4.31) reporting *lower* levels of arousal than the ExP- (9.045 ± 2.03) and UxP- groups (7.909 ± 2.41; $F(1,22) = 3.38$, $p = .082$). We found a similar trend towards a main effect of Diagnosis on ratings of arousal in stressful imagery versus neutral imagery ($F(1,17) = 4.06$, $p = .060$), with smaller differences between ratings of arousal to stressful versus neutral imagery in the ExP+ (-.625 ± 3.02) and UxP+ groups (.250 ± 5.32) compared to the ExP- (2.909 ± 2.31) and UxP- groups (2.318 ± 3.5). There were no significant correlations between ratings of valence, arousal, and vividness of imagery and measures of PTSD symptom severity.

Skin Conductance Response Data

Similarly, no significant effects were found on skin conductance response (SCR) during stressful imagery versus neutral imagery, although there was a trend towards a significant Diagnosis by Exposure interaction ($F(1,22) = 3.95$, $p = .062$), with participants in the ExP+ group (-1.626 ± .115) showing lower SCRs during stressful imagery versus neutral imagery than their UxP+ co-twins (.0979 ± .275), as well as participants in the ExP- group (-.0766 ± .442) and their UxP- co-twins (-.0982 ± .396). There were no significant correlations between SCR and measures of PTSD symptom severity.

Table 2. Psychophysiologic Responses to and Ratings for Stressful and Neutral Imagery Conditions

	PTSD Pairs				Control Pairs				Mixed-Model Analysis of Variance[a]					
	Exposed[b]		Unexposed[b]		Exposed[c]		Unexposed[c]		Diagnosis		Trauma Exposure		Interaction	
Measure	Mean	SD	Mean	SD	Mean	SD	Mean	SD	F	p	F	p	F	p
Stressful Imagery														
SCR[d]	-.0171	.130	.1443	.343	.1175	.289	.1534	.442	.327	.575	1.65	.215	.668	.424
Rating 1[e]	2.111	2.04	3.111	1.87	1.773	1.82	2.136	1.27	1.30	.269	1.61	.221	.350	.561
Rating 2[f]	6.500	2.99	6.833	4.31	9.045	2.03	7.909	2.41	3.38	.082	.196	.663	.657	.428
Rating 3[g]	9.389	1.73	8.444	2.51	10.23	1.79	9.500	1.50	2.44	.136	1.97	.177	.033	.857
Neutral Imagery														
SCR	.1456	.144	.0464	.106	.1942	.327	.2516	.300	2.37	.142	.077	.785	1.08	.313
Rating 1	8.778	3.30	7.944	1.47	7.727	2.09	7.591	2.46	.684	.419	.523	.479	.270	.609
Rating 2	6.688[h]	2.84	6.875[h]	1.75	6.136	1.12	5.591	2.42	2.18[i]	.159	.057[i]	.813	.241[i]	.630
Rating 3	9.625[h]	2.10	8.563[h]	1.78	9.682	1.54	9.00	1.56	.223[i]	.642	2.06[i]	.169	.098[i]	.758

[a] df = 1,18 unless otherwise noted.
[b] *n*=9 unless otherwise noted.
[c] *n*=11 unless otherwise noted.
[d] Skin conductance response.
[e] Valence.
[f] Arousal.
[g] Vividness of imagery.
[h] *n*=8.
[i] df = 1,17.

Table 3. Difference Scores for Psychophysiologic Responses and Ratings for Stressful Imagery Versus Neutral Imagery

	PTSD Pairs				Control Pairs				Mixed-Model Analysis of Variance[a]					
	Exposed[b]		Unexposed[b]		Exposed[c]		Unexposed[c]		Diagnosis		Trauma Exposure		Interaction	
Measure	Mean	SD	Mean	SD	Mean	SD	Mean	SD	F	p	F	p	F	p
SivNi[d] SCR	-.1626	.115	.0979	.275	-.0766	.442	-.0982	.396	.162	.692	2.84	.109	3.95	.062
SivNi Rating 1	-6.667	4.24	-4.833	2.33	-5.955	3.02	-5.455	3.09	.002	.968	1.54	.230	.504	.487
SivNi Rating 2	-.625[e]	3.02	.250[e]	5.32	2.909	2.31	2.318	3.51	4.06[f]	.060	.024[f]	.880	.629[f]	.428
SivNi Rating 3	-.125[e]	2.07	-.063[e]	3.02	.545	1.54	.500	1.82	.715[f]	.410	.000[f]	.990	.007[f]	.935

[a] df = 1,18 unless otherwise noted.
[b] *n*=9 unless otherwise noted.
[c] *n*=11 unless otherwise noted.

[d] Stressful imagery versus neutral imagery.
[e] *n*=8.
[f] df = 1,17.

fMRI Data

As previously mentioned, we focused our analyses on activation in the medial prefrontal cortex, specifically the anterior cingulate cortex (ACC) and medial frontal gyrus, during stressful imagery versus neutral imagery for this thesis.

Within-Group Analyses. ExP+ participants demonstrated significantly decreased activation in the rostral ACC (rACC; -2, 32, 24, z = 3.16; and 18, 36, 30, z = 4.25), dorsorostral ACC (drACC; 10, 26, 30, z = 3.84), and dorsal ACC (dACC; -2, 12, 34, z = 3.10) to stressful imagery versus neutral imagery, while their UxP+ co-twins demonstrated significantly increased activation in the subgenual ACC (sgACC; -12, 24, -6, z = 3.89) and dorsolateral prefrontal cortex (dlPFC; -12, 54, 40, z = 3.35). ExP- participants showed significant decreases in activation to stressful versus neutral imagery in the dACC (-4, 18, 40, z = 3.41; 16, 20, 38, z = 3.58; and -10, 28, 28, z = 3.11). Their UxP- co-twins, however, did not have any significant changes in activation in the mPFC.

Between-Group Analyses. Compared to the ExP- group, participants in the ExP+ group showed significantly decreased activation to stressful versus neutral imagery in the dorsomedial prefrontal cortex (dmPFC; 0, 44, 40, z = 3.52; and 2, 26, 56, z = 3.83), dACC (4, 14, 30, z = 3.61), and rACC (16, 36, 26, z = 3.11). There were no significant differences in activation between the UxP+ and UxP- groups.

Twin Design Analyses. Assessing for the main effect of Diagnosis, we found that the PTSD twin pairs demonstrated significantly decreased activation to stressful imagery versus neutral imagery in the rACC (-12, 28, 30, z = 3.19) and dACC (4, 6, 32, z = 3.64; and -10, 24, 32, z = 3.22) compared to the Control twin pairs (See Figure 1). The voxelwise tests for the

main effect of Exposure and the Diagnosis by Exposure interaction yielded no statistically significant results in the mPFC.

Table 4. Results of Voxelwise fMRI Analyses of Data From Script-Driven Imagery Task in Trauma-Exposed Individuals With and Without PTSD and Their Trauma-Unexposed Identical Co-Twins[a]

Comparison	Region	Z Score	Coordinates (x. y, z)[b]
Combat-exposed PTSD twins			
Stressful > Neutral	None		
Neutral > Stressful	rACC[c]	3.16	-2, 32, 24
	drACC[d]	3.84	10, 26, 30
	rACC	4.25	18, 36, 30
	dACC[e]	3.10	-2, 12, 34
	Left insula	3.60	-48, 16, 8
	Left insula	3.58	-42, 14, -2
Combat-exposed Control twins			
Stressful > Neutral	sgACC[f]	3.89	-12, 24, -6
	dlPFC[g]	3.35	-12, 54, 40
	Left insula	3.21	-36, 12, -12
	Right amygdala	3.09	28, -8, -14
Neutral > Stressful	None		
Combat-unexposed PTSD co-twins			
Stressful > Neutral	None		
Neutral > Stressful	dACC	3.41	-4, 18, 40
	dACC	3.58	16, 20, 38
	dACC	3.11	-10, 28, 28
	Left insula	4.25	-48, 4, 8
Combat-unexposed Control co-twins			
Stressful > Neutral	Right amygdala	3.39	20, 0, -34
Neutral > Stressful	Left insula	3.66	-50, 24, -18
Combat-exposed twins			
PTSD > Control	None		
Control > PTSD	dmPFC[h]	3.52	0, 44, 40
	dACC	3.61	4, 14, 30
	dmPFC	3.83	2, 26, 56
	rACC	3.11	16, 36, 26
	Right insula	3.29	40, 2, 4
	Left insula	3.74	-34, 12, -10
	Left insula	3.61	-44, 12, -2
Combat-unexposed twins			
PTSD > Control	None		
Control > PTSD	None		
Main Effect of Diagnosis			
PTSD > Control	None		
Control > PTSD	rACC	3.19	-12, 28, 30
	rACC	3.00 (ns)	12, 34, 28
	dACC	3.64	4, 6, 32
	dACC	3.22	-10, 24, 32
	Inferior temporal lobe	3.23	-40, -8, -28
	Inferior temporal lobe	3.60	40, 20, -32
	Brainstem	3.66	2, -22, -32
	Left insula	3.22	-34, 28, 6
	Left insula	3.47	-32, 12, -12
	Right insula	3.28	50, -6, 8

Main Effect of Exposure			
Exposed > Unexposed	None		
Unexposed > Exposed	None		
Diagnosis by Exposure Interaction			
PTSD > Control, Ex > Ux	None		
Control > PTSD, Ex > Ux	Left insula	3.23	-40, -2, 12

[a] Stressful imagery versus neutral imagery contrast images were used in these analyses.
[b] Montreal Neurological Institute coordinates.
[c] Rostral anterior cingulate cortex.
[d] Dorsorostral anterior cingulate cortex.
[e] Dorsal anterior cingulate cortex.
[f] Subgenual anterior cingulate cortex.
[g] Dorsolateral prefrontal cortex.
[h] Dorsomedial prefrontal cortex.

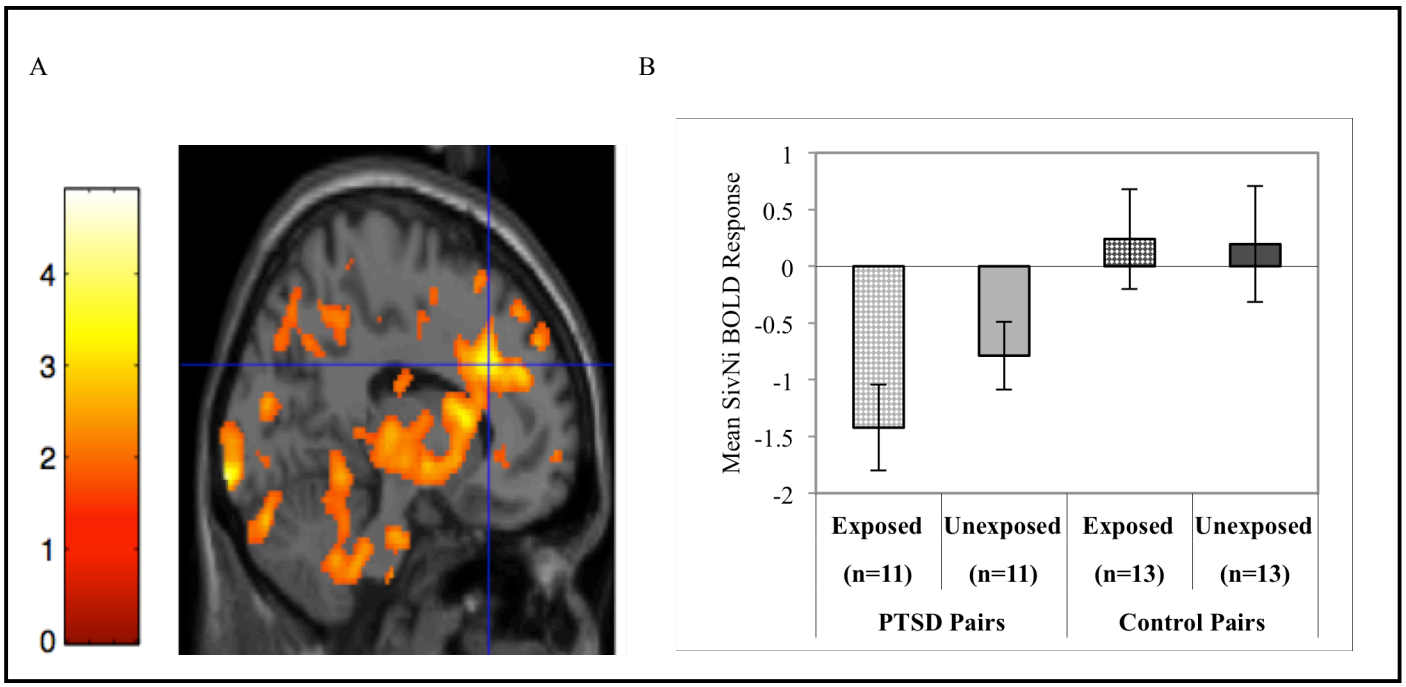

Figure 1. Main effect of PTSD diagnosis on blood oxygen level-dependent (BOLD) signal in the rostral anterior cingulate cortex (-12, 28, 30) during stressful imagery versus neutral imagery in script-driven imagery. A. BOLD response in the rACC that is diminished in trauma-exposed twins with PTSD and their unexposed identical co-twins compared with trauma-exposed individuals without PTSD and their unexposed identical co-twins. B. The accompanying bar graph presents group mean differences in BOLD response to stressful imagery versus neutral imagery. Error bars represent standard error of the mean.

In order to take a closer look at the pattern of activation in the rACC (-12, 28, 30) that emerged in the main effect of Diagnosis, we first extracted data from the stressful versus neutral imagery condition (Figure 1). A separate 2 (Diagnosis) x 2 (Exposure) repeated measures ANOVA of the extracted data confirmed that the main effect of Diagnosis was in fact significant

($F(1,22) = 7.992$, $p = .010$). We then entered medication in the Ex twins as another between-groups variable and reanalyzed the extracted data using a 2 (Diagnosis) x 2 (Medication) x 2 (Exposure) repeated measures ANOVA. None of the effects involving Medication were significant, indicating that anti-depressant use in the Ex twins was unlikely to have moderated our findings. Additionally, although no longer technically significant, the main effect of Diagnosis for rACC activation during stressful versus neutral imagery neared significance ($F(1,20) = 3.851$, $p = .064$).

We noticed that the pattern of activation in the rACC that emerged in the main effect of Diagnosis was not entirely consistent with the results of the within- and between-group analyses, which suggested that significantly decreased rACC activation occurred only in the ExP+ group and, furthermore, significant between-group differences in rACC activation occurred only in Ex participants. In order to take a closer look at this rACC activation (-12, 28, 30) in the main effect of Diagnosis, we extracted data from each imagery condition versus resting baseline (Figure 2). Figure 2 suggests that the main effect of Diagnosis is being driven by an interaction in the stressful imagery versus baseline comparison. However, an ANOVA on the extracted values from the main effect of Diagnosis ROI in the rACC showed that the Diagnosis by Exposure interaction in the stressful imagery versus baseline activation was not significant ($F(1,22) = 1.84$, $p = .189$).

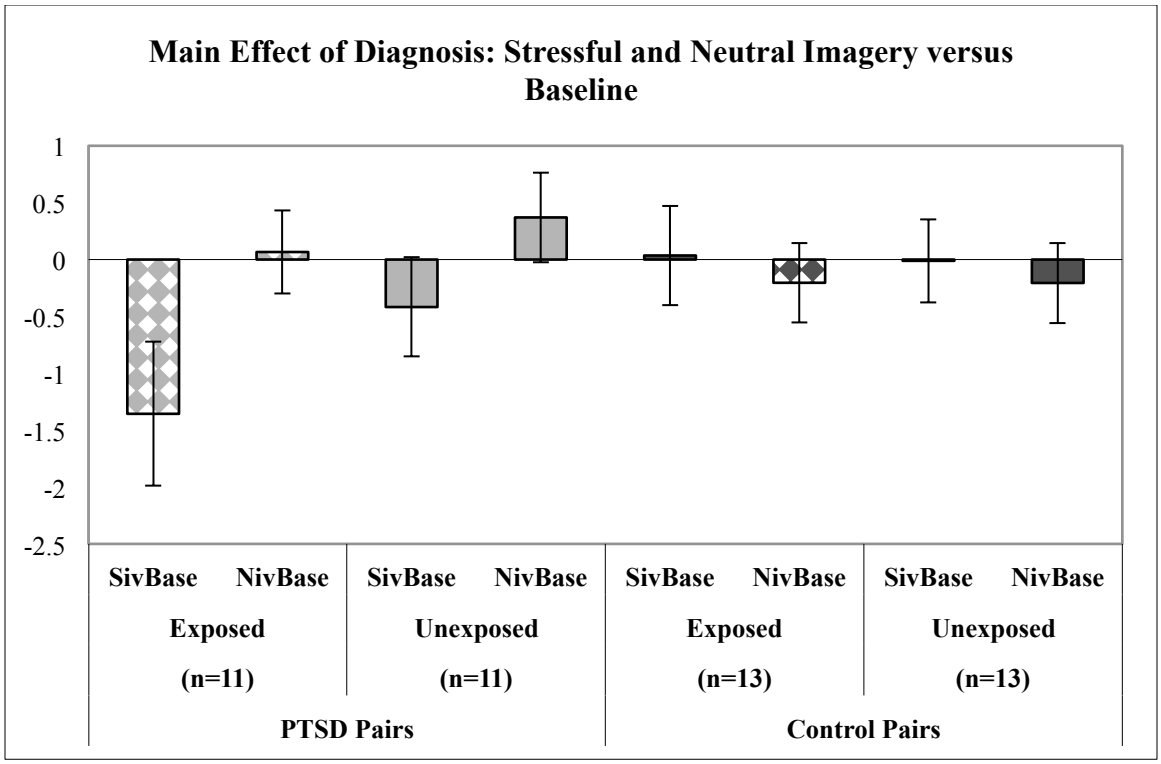

Figure 2. Extracted BOLD signal data from stressful and neutral imagery conditions versus baseline in the rACC (-12, 28, 30).

Table 5. Extracted data from rACC activation[a] during stressful and neutral imagery conditions.

	PTSD Pairs				Control Pairs				Mixed-Model Analysis of Variance[b]					
	Exposed (*n*=11)		Unexposed (*n*=11)		Exposed (*n*=13)		Unexposed (*n*=13)		Diagnosis		Trauma Exposure		Interaction	
rACC activation	Mean	SD	Mean	SD	Mean	SD	Mean	SD	F	p	F	p	F	p
SivNi	-1.423	1.25	-.7877	.992	.2399	1.59	.1947	1.84	7.99	.010	.584	.453	.777	.388
SivBase	-1.356	2.10	-.4176	1.45	.0356	1.57	-.0113	1.32	2.62	.120	1.51	.233	1.84	.189
NivBase	.0662	1.21	.3701	1.31	-.2043	1.27	-.2059	1.27	1.64	.214	.144	.708	.147	.705

[a] Region of interest coordinates -12, 28, 30.
[b] df = 1,22.

Correlational Analyses

Stressful Imagery versus Neutral Imagery. If the main effect of Diagnosis in the rACC reflects a familial vulnerability factor, then activation in that region in the Ux twins should correlate with measures of their Ex co-twins' PTSD symptomatology (as measured by CAPS scores). However, this correlation was not significant ($r(22) = -.134$, $p = .532$). There was a significant negative correlation between rACC activation in the Ex subjects and their own CAPS

scores ($r(22) = -.419$, $p = .042$), meaning that greater PTSD symptom severity was associated with lower levels of rACC activation.

We then ran correlations to assess for potential relationships between rACC activation and avoidance, specifically numbing, in the Ex twins. Although there was not a significant correlation between rACC activation and self-reported levels of arousal ($r(21) = -.066$, $p = .765$), there was a trend towards a significant negative correlation between rACC activation and measures of avoidance symptoms (CAPS C scores; $r(22) = -.382$, $p = .065$), suggesting that higher avoidance is associated with lower rACC activation. We also found a significant negative correlation between rACC activation and item 9 of the CAPS ($r(22) = -.412$, $p = .045$), which assesses for markedly diminished interest in significant activities, a symptom of emotional numbing.

In the ExP+ group, no significant correlations were detected between rACC activation in the stressful imagery versus neutral imagery contrast and measures of PTSD symptom severity, SCR difference scores, or ratings of valence, arousal, and vividness of imagery. There was an unexpected significant positive correlation between rACC activation and BAI scores ($r(9) = .668$, $p = .025$).

Stressful Imagery versus Baseline. If the trend for a Diagnosis by Exposure interaction on stressful imagery versus baseline activation in the rACC reflects an acquired characteristic of PTSD, then measures of the ExP+ subjects' symptom severity should correlate with their own rACC activation but not their UxP+ cotwins' rACC activation. However, ExP+ participants' CAPS scores were significantly correlated with neither their own rACC activation ($r(9) = .047$, $p = .892$) nor their UxP+ co-twins' rACC activation ($r(9) = .114$, $p = .739$).

In the ExP+ group, no significant correlations were detected between rACC activation and measures of PTSD symptom severity or SCRs in the stressful imagery versus baseline contrast. There was a trend towards a significant negative correlation between BOLD activation in the rACC and ratings of vividness of imagery ($r(7) = -.649$, $p = .059$).

Discussion

This study sought to replicate previous findings of psychophysiological and functional brain abnormalities observed in individuals with PTSD during SDI and, moreover, to determine the origin of these abnormalities. We hypothesized that decreased activation in the mPFC, specifically the rACC, in individuals with PTSD during SDI would not reflect exposure to trauma, but instead either a familial vulnerability factor or an acquired characteristic of PTSD. We predicted that this rACC activation might be negatively correlated with measures of PTSD symptom severity. Based on the literature, we did not expect to find significant group differences in amygdala activation or SCRs to stressful imagery versus neutral imagery.

We found significantly decreased mPFC activity within the ExP+ and ExP- groups, significantly increased mPFC activity within the UxP+ group, and no significant changes in mPFC activity within the UxP- group to stressful imagery versus neutral imagery. Additionally, compared to the ExP- group, the ExP+ group exhibited significantly decreased mPFC activity to stressful imagery versus neutral imagery. These findings are consistent with and replicate the results of previous research (Britton et al., 2005; Gold et al., 2011; Lanius et al., 2001; Shin et al., 1999; Shin et al., 2004), which identified decreased medial prefrontal activity in individuals with PTSD during both traumatic and other stressful imagery.

A significant main effect of Diagnosis on rACC activation emerged in the rACC (-12, 28, 30) in the twin design analyses. We found that ExP+ individuals and their UxP+ co-twins

exhibited significantly greater deactivation to stressful imagery versus neutral imagery than ExP- individuals and their UxP- co-twins. In other words, decreased rACC activity during SDI appeared to be a familial vulnerability factor for developing PTSD. However, this main effect of Diagnosis appeared to be modified by an interaction between Diagnosis and Exposure (though it was not significant), with ExP+ individuals deactivating more than all other groups to stressful imagery versus baseline. Despite the fact that individuals with PTSD were the only trauma-exposed participants currently taking antidepressants, which have been shown to increase function of the ACC in response to traumatic scripts during SDI (Fani et al., 2011), medication use in Ex twins did not appear to moderate the main effect of Diagnosis on rACC activation as indicated by the covariate analyses. Thus, we concluded that rACC deactivation during SDI appears to be an acquired characteristic of PTSD rather than a familial vulnerability factor. Our next step is to replicate the analyses described above using SPM8, a newer version of the statistical parametric mapping software that ought to allow for better spatial normalization and more refined statistical analyses.

We did not find any significant correlations between rACC activation during stressful imagery versus neutral imagery in the ExP+ group and measures of overall PTSD symptomatology. This is not surprising, as the PTSD literature has been inconsistent on this issue, with some studies reporting no correlations between activation of medial prefrontal cortical regions and symptom severity during symptom provocation (Gold et al., 2011; Phan et al., 2006) and others reporting negative correlations (Shin et al., 2004; Offringa et al., 2013). It is possible that the absence of significant correlations in the current study stems from the fact that stressful scripts do not provoke PTSD symptomatology to the same extent as traumatic scripts used in other studies. However, even studies that employ very subtle emotional stimuli

have still found negative correlations between rACC activation and PTSD symptom severity (e.g., Offringa et al., 2013).

Additionally, we found a positive correlation between rACC activation during stressful versus neutral imagery and BAI scores in the ExP+ group, which suggests that higher levels of anxiety are associated with higher levels of activation in the rACC in trauma-exposed individuals with PTSD. This finding is not only counterintuitive, as we would have expected a negative correlation between rACC activation and BAI scores, but also inconsistent with previous studies of symptom provocation in PTSD, most of which have not identified a significant relationship between activation in the rACC and BAI (e.g., Offringa et al., 2013). This finding may represent a Type I error in which the null hypothesis, that there would be no significant correlation, was rejected despite the fact that it is actually true.

The trend towards significantly lower self-reported levels of arousal during stressful imagery in the PTSD group compared to the Control group is consistent with previous findings (Frewen et al., 2012; Orr et al., 1993) and may reflect avoidance, namely numbing, in trauma-exposed individuals with PTSD as well as their trauma-unexposed identical co-twins. Frewen et al. (2012) identified a negative relationship between emotional numbing symptoms and dmPFC response to imagery of both positive and negative events in individuals with PTSD. Similarly, Hopper et al. (2007) found that self-reported levels of avoidance during SDI were negatively correlated with rACC activation in PTSD, and they speculated that increased avoidance might indirectly reflect increased re-experiencing given the overlap in neural activation. Consistent with these findings, we found a trend towards a significant negative correlation between CAPS C scores and rACC activation across trauma-exposed individuals, indicating that greater avoidance symptoms may predict decreased rACC activation. We also found that rACC activation was

negatively correlated with markedly diminished interest in significant activities, a symptom of emotional numbing. We did not, however, detect a significant correlation between rACC activation and lower self-reported levels of arousal, which would be indicative of numbing; this may be due to the fact that our study did not have enough power to detect a significant correlation.

Consistent with our initial hypothesis, analysis of skin conductance response data revealed no significant effects. The lack of significant psychophysiologic differences between groups during stressful imagery versus neutral imagery is consistent with findings by Orr et al. (1998; 1993), who found psychophysiologic differences only to trauma-related imagery in two distinct samples of individuals with PTSD. For trauma-exposed individuals, stressful personalized scripts are likely not as stressful as their trauma-related scripts; Orr et al. (1993) posited that these scripts reflected the most traumatic events in the subjects' life histories. Just as the use of personalized scripts over standardized scripts increases cue specificity, the use of traumatic scripts over stressful scripts may result in better symptom provocation, especially for individuals with PTSD whose traumatic scripts describe the events that largely contributed to their development of PTSD. Gold et al. (2011), however, found significantly greater SC and EMG responses to stressful versus neutral imagery in participants with PTSD compared to trauma-exposed controls without PTSD. The discrepancy between the findings of the current study and the study by Gold et al. could due to a variety of factors, especially the fact that they performed a one-tailed test to assess for between-group differences in psychophysiological responses rather than a more conservative two-tailed test. In addition, the study included younger participants with both higher rates of comorbidity and higher average scores of PTSD symptom severity.

Although not significant, we identified a trend towards a Diagnosis by Exposure interaction in SCRs, with the ExP+ group showing lower SCRs to stressful imagery versus neutral imagery than other groups. This finding may suggest numbing in our sample of individuals with PTSD, given both the trend towards significantly lower self-reported levels of arousal in the PTSD group and the trend towards a significant correlation between rACC activation and measures of avoidance (CAPS C scores). However, we did not detect a significant correlation between SCR and measures of avoidance, again likely due to our small sample size and subsequent lack of power.

Limitations of this study include the small sample size and the inclusion of only men, the vast majority of whom experienced the same type of trauma. The generalizability of our findings may also be limited by the fact that we studied an older group of trauma-exposed adults suffering from chronic PTSD; thus, it is possible that our findings would not extend to younger groups of individuals with PTSD or individuals with recent onset PTSD. Although we covaried for current antidepressant use in the Ex twins in our analyses, which did not appear to moderate rACC activation, we did not have any measures in place to control for past treatment history and its potential effects on brain activation during SDI (i.e., permanent changes in activation following cognitive behavioral therapy). Lastly, in the absence of dizygotic twins, the twin case-control design cannot differentiate between genetic and environmental factors of familial vulnerability.

Conclusion

Distinct from previous studies, the current study utilized an identical co-twin, case-control design to determine the origin of psychophysiological and brain responses to SDI in PTSD. Our findings were consistent with studies finding decreased activation of the rACC in individuals with PTSD during trauma-related and -unrelated imagery. However, unlike previous

studies, we were able to conclude that rACC deactivation in trauma-exposed individuals with PTSD during stressful versus neutral imagery is likely neither a familial vulnerability factor nor due to trauma exposure, but instead an acquired characteristic of PTSD. If it is in fact an acquired characteristic, this abnormality in activity of the rACC, a corticolimbic structure involved in emotion regulation, has important clinical implications for individuals with PTSD. Because our findings suggest a relationship between rACC activation and avoidance, therapies that aim to alleviate the symptoms of PTSD should also incorporate aspects that would foster more adaptive methods of emotion regulation. In order to provide optimal treatment, future neuroimaging studies ought to investigate neural predictors of differential treatment response in individuals with PTSD.

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