An fMRI Study of the Recollection of Stressful Events in Identical Twins Discordant for PTSD and Trauma Exposure

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Abstract

Posttraumatic Stress Disorder (PTSD) is a potentially debilitating mental health condition that can occur after exposure to trauma. Previous research has shown heightened psychophysiological responses and blunted anterior cingulate cortex (ACC) activation in PTSD during recollection of traumatic events. However, fewer studies have examined responses to the recollection of other stressful but trauma-unrelated life events in PTSD. The origin of these biological abnormalities in PTSD, whether they are acquired signs of PTSD or familial vulnerability factors, is unknown. In the current case-control twin study, twenty-six male, monozygotic twin pairs (12 PTSD; 14 Non-PTSD) discordant for trauma exposure completed script-driven imagery (SDI) using stressful, trauma-unrelated autobiographical narratives. Skin conductance, brain activation, and subjective responses to the recollection and imagery of Stressful versus Neutral life events were measured. Results indicate that lack of skin conductance response modulation across conditions and reduced rostral ACC activation may be acquired characteristics of PTSD.

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An fMRI Study of the Recollection of Stressful Events in Identical Twins Discordant for PTSD and Combat Exposure

Posttraumatic stress disorder (PTSD) is a relatively common but serious mental health condition that can occur following exposure to traumatic events such as combat, natural disasters, violent crime, death of a loved one, or abuse. The characteristic symptoms associated with this disorder include: 1) intrusive thoughts or recollections of the event, including nightmares and flashbacks; 2) avoidance of people, places, or reminders of the trauma; 3) alterations in mood and cognition; and 4) hyper-arousal/hyper-vigilance symptoms (American Psychiatric Association [APA], 2013). Additionally, symptom-related distress from PTSD reduces global functioning resulting in impairment of social, occupational life (APA, 2013).

Symptom provocation studies have been used to identify the biological pathways and systems that mediate or moderate PTSD symptomatology. One commonly used symptom provocation paradigm is script-driven imagery (SDI), in which participants are asked to recall and imagine descriptions of personal life events while psychophysiological and brain responses are measured. According to previous research, individuals with PTSD exhibit increased psychophysiological responses (e.g., heart rate, skin conductance, and lateral frontalis electromyographic responses) relative to trauma-exposed participants without PTSD (Pitman et al., 1987; 1990; Orr, Pitman, Lasko, & Herz, 1993; Orr et al., 1998; Shalev, Orr, & Pitman, 1993; Shin et al., 2004; reviewed in Orr, McNally,

Rosen, & Shalev, 2004). These types of elevated psychophysiological responses in PTSD correlate with increased hyper-arousal symptoms (reviewed in Orr & Roth, 2000). Additionally, heightened psychophysiological responses (reduced extinction of fear-conditioned corrugator electromyogram responses and increased skin conductance response to loud tones) before experiencing a traumatic event predict greater symptom severity after exposure (Guthrie & Bryant, 2006; Orr et al., 2012). Some research using SDI has failed to find heightened psychophysiological responses in PTSD (e.g., Davis et al., 1996); however Orr and Roth (2000) have addressed this discrepancy suggesting that relatively low PTSD symptom severity in participants of some studies may explain the inconsistent results (for review see Orr, McNally, Rosen, & Shalev, 2004).

Neuroimaging studies have consistently reported decreased activation of the medial prefrontal cortex (mPFC) including the anterior cingulate cortex (ACC) during traumatic versus neutral SDI in individuals with PTSD compared to control participants (Bremner et al., 1999; Shin et al., 1999; 2004; Lanius et al., 2001; 2003; Liberzon, Britton & Phan, 2003; Lindauer et al., 2004). Furthermore, PTSD symptom severity is inversely correlated with mPFC activation (Osuch et al., 2001) and positively correlated with amygdala activation (Shin et al., 2004) in some, but not all studies (Lanius et al., 2002, Gold et al., 2011).

More recent studies in veteran populations have begun to examine the psychophysiological and brain responses during the recollection and imagery of stressful but trauma-unrelated personal events in order to allow for comparisons between trauma unexposed individuals and therefore characterize the effect of trauma exposure itself. For example, Gold and colleagues (2011) have shown that recollection of such stressful events still elicits elevated SCR response and functional brain abnormalities in PTSD; compared to trauma-exposed control participants. Veterans with PTSD showed diminished ACC activation in response to stressful, trauma-unrelated versus neutral SDI. Britton and colleagues (2005) used SDI to compare regional cerebral blood flow (rCBF) in combat veterans with and without PTSD as well as in age-matched combat-unexposed control subjects. These researchers found that contrasts between Stressful scripts with Neutral scripts produced deactivation in the mPFC (rostral ACC) for all subjects, but the greatest deactivation was in the combat veterans with PTSD.

Although previous research has provided evidence for increased psychophysiological responses and diminished mPFC responses to the recollection and imagery of traumatic and stressful life events in PTSD, the origin of these abnormalities remains unclear. They may be associated with the development of PTSD, reflect familial vulnerability factors that increase the risk of PTSD after exposure to trauma, or result from exposure to trauma independent of the development of PTSD.

Determining the origin of these abnormalities has important clinical implications. For example, individuals with a familial vulnerability for PTSD might avoid careers associated with increased exposure to trauma (e.g., the military, firefighting) or could receive early psychoeducation/intervention if any such trauma exposure occurred. In contrast, acquired characteristics could potentially assist in the diagnosis of PTSD or in the assessment of treatment response.

In an attempt to resolve the origin of these psychophysiological and mPFC response abnormalities in PTSD, we examined SCR and fMRI responses to SDI in monozygotic (identical) twins discordant for trauma exposure. Since identical twins share similar DNA and developmental environment, trauma-unexposed co-twins (Ux), are the best proxy for what their trauma-exposed twins (Ex) would have been like had they not been exposed to trauma (Pitman et al., 2006). Two types of twin pairs were included: PTSD (P+) twin pairs in which the trauma-exposed twin had a current diagnosis of PTSD and non-PTSD (P-) twin pairs in which the trauma-exposed twin did not have any history of PTSD. Based on previous findings, we hypothesized that during SDI trauma-exposed individuals with PTSD (ExP+) and their identical co-twins (UxP+) would show exaggerated psychophysiological responses (measured by skin conductance responses (SCR)) and decreased fMRI activation in the mPFC (particularly the ACC) as compared to trauma-exposed individuals without PTSD (ExP-) and their identical co-twins (UxP-). Additionally, we

hypothesized that more severe symptoms (measured by the CAPS) would be positively correlated with the magnitude of SC responses and inversely correlated with ACC activation within the ExP+ group. In the event that a familial vulnerability factor was identified, we also planned to examine the relationship between CAPS scores from the Ex participants and the fMRI activation data from the Ux participants; we predicted significant inverse correlations between these variables would provide further evidence of a familial vulnerability for PTSD.

Method

Participants

Participants were male identical twins recruited from the Vietnam Era Twin (VET) Registry (Henderson et al., 1990), the University of Washington Twin Registry (Strachan et al., 2013), or by advertisements on electronic media. There were four distinct participant groups: Trauma-exposed veterans with current combat-related PTSD (ExP+, *N*=12) and their trauma-unexposed identical co-twins without PTSD (UxP+, *N*=12), as well as trauma-exposed veterans without a history of combat-related PTSD (ExP-, *N*=14) and their trauma-unexposed identical co-twins (UxP-, *N*=14). All ExP+ participants had trauma exposure from either combat during the Vietnam War (*N*=11) or due to a motor vehicle accident (*N*=1). All ExP- participants had trauma exposure from combat during the Vietnam War (*N*=14) or during the invasion of Kuwait (*N*=1). No participants reported neurological disorders or major head trauma

involving loss of consciousness for more than ten minutes. After a complete description of the study was provided to the subjects, written informed consent was obtained. Institutional Review Boards from the Partners Healthcare System at Massachusetts General Hospital and the VET registry approved this research.

Demographic and Clinical Characteristics

Subjects were administered the Clinician-Administered PTSD Scale (CAPS; Blake et al., 2002) and the Structured Clinical Interview for the DSM-IV (SCID; First, Spitzer, Gibbon, & Williams, 2002) in order to determine PTSD diagnostic status/symptom severity and comorbidity, respectively. Four of the ExP+ participants reported partial remission of PTSD symptoms; however all of these subjects reported at least mild to moderate current PTSD symptoms (as defined by Weathers, Keane, & Davidson, 2001) and were therefore included in the data analyses. Participants also completed the Childhood Trauma Questionnaire (CTQ; Bernstein et al., 1994), Traumatic Life Events Scale (TLEQ; Kubany et al., 2000), Beck Depression Inventory (BDI; Beck & Steer, 1987), Beck Anxiety Inventory (BAI; Beck & Steer, 1993), and the Michigan Alcohol Screening Test (MAST; Selzer, 1971).

Script-Driven Imagery Task Procedures

Before the fMRI session, participants took part in an interview in which they provided (both orally and in writing) detailed descriptions of two neutral and two stressful, but trauma un-related autobiographical events.

In addition, the ExP+ and ExP- also provided descriptions of two trauma-related autobiographical events, but the findings associated with those scripts will not be reported here. After describing each event, participants examined a list of psychophysiological bodily response cues (e.g. “heart races” and “labored breathing”) and circled those responses (if any) that they experienced during each event. Immediately after this interview, the investigators wrote scripts (i.e. narratives describing each event) in the second person and present tense, including the bodily response cues that each participant selected. The scripts were audio-recorded in a neutral male voice for playback during fMRI scanning the next day.

Each participant was studied in three conditions (neutral, stressful trauma-unrelated and trauma-related) with two different scripts per condition. Instead of autobiographical trauma-related scripts, UxP+ and UxP- participants were presented with standard traumatic scripts (combat- or motor vehicle accident-related depending on their co-twin's type of trauma exposure) developed from previous studies (Pitman et al., 1987, 1990; Orr, Pitman, Lasko, & Herz, 1993; Orr et al., 1998). Before each scan, participants were instructed to close their eyes, listen carefully to the script, and imagine the described event as vividly as possible, as if they were actually participating in it. Psychophysiological and neuroimaging data were collect at five different periods during each script 1) baseline (30s) when participants focused on a fixation point; 2) read (approximately 50s) when they listened to the recorded scripts; 3) imagery (30s) when

they recalled and imagined the script as vividly as possible as if reliving the experience; 4) recovery (30s) when they relaxed and recovered from the imagery period, and 5) rating (60s) when they rated each script according to levels of valence, arousal, and vividness of imagery.

Psychophysiological Parameters

Participants' SC level was measured via an isolated skin conductance coupler (Coulbourn Instruments LLC, Whitehall, PA) in the fMRI laboratory (Massachusetts General Hospital, Charlestown, MA) according to established procedures (Pitman et al., 1987; 1990; Orr et al., 1998; Shin et al., 1999; 2004). The equipment was programmed with a sampling rate of 10Hz. Invivo Metric Ag/AgCl electrodes filled with an isotonic conductive paste were placed on the hypothenar surface of subject's non-dominant hand in accordance with published guidelines (Fowles et al., 1981).

Within the baseline and imagery periods (for each script), recordings were averaged. For each script type, the mean SC level during the baseline period was subtracted from the mean SC level during the imagery period, yielding a "response" (i.e., change) score. Additionally, script condition contrasts (e.g., Stressful-Neural) were calculated using the baseline subtracted difference scores; for example, the Stressful-Neutral contrast was actually (Stressful(Imagery-Baseline)) - (Neutral(Imagery-Baseline)). As two scripts for each condition were presented, the SCRs collected during both scripts were averaged and used for the final

analyses. Due to constraints associated with the magnetic field, SCR was the only psychophysiological measure we were able to obtain. Additionally, due to unmeasurable SCR, data were not usable from three of the P+ twin pairs (adjusted *N*=9) and two of the P- twin pairs (adjusted *N*=12).

Subjective Ratings

During the rating period for each script, participants rated the intensity of several emotions using separate visual analog scales (0=absent and 12=maximal; Pitman et al., 1987, 1990; Orr et al., 1998; Shin et al., 1999, 2004). The rated emotions included valence (happiness/pleasure), arousal (excitement), and vividness of imagery.

In order to determine whether script content varied according to diagnosis group or trauma-exposure, five independent raters scored each script for valence, arousal, and vividness on the same scale (0-12) that each participant rated their own scales during scanning. These independent raters were blind to group, but due to content of the scripts detailing trauma, they were not blind to trauma-exposure. In addition, these raters also tallied the number of physiological phrases (e.g. "My heart is pounding") present in each script. Since these participants were twins who may have had shared experiences, the content of the scripts for each twin in a pair were compared and rated on whether or not the experience described may have been a shared experience. Two different nominal tallies were collected 1) whether both twin's in a pair provided a

script for the same event, which we will refer to as "shared script" and 2) whether an event provided by a twin was likely to be experienced by his co-twin as well (e.g. the death of a parent) even if the co-twin did not describe that same event for his own script, referred to as "shared event". The time when the script event occurred was also recorded for assessment. Because many events occurred a long time ago, specific dates and times were not always recollected and general timeframe estimates (e.g. "the mid-eighties") were provided by many participants. Given, the nominal quality of these data, it was impossible to calculate an accurate time since the event occurred for all participants' scripts. Instead, each event was ranked by the decade in which it occurred (1950s-2000s); any events after 2010 were ranked as 1) occurring after 2010 but before a year before the scan, 2) within 1 year prior to the scan, 3) and within a month of the scan.

Data Analysis

Twin Study Design. Analyses of psychophysiological and subjective ratings were completed using IBM SPSS Statistics (version 22) to conduct 2x2 (PTSD Diagnosis by Trauma Exposure) mixed-model analysis of variance (ANOVA). A between-subjects Main Effect of PTSD Diagnostic Group (P+ versus P-) would identify familial vulnerability to the development of PTSD. A within-subjects Main Effect of Trauma Exposure (Ex versus Ux) would suggest that the behavioral and psychophysiological results are a consequence of exposure to combat independent of the

development of PTSD. A PTSD Diagnosis x Trauma Exposure Interaction Effect, in which the ExP+ participants differed from all the other individuals, would be indicative of an acquired feature of PTSD. Pearson correlations were used to assess the relationship between SC reactivity and neural activation with PTSD symptom severity.

Functional Magnetic Resonance Imaging (fMRI) Parameters. All fMRI scans were completed using a Siemens Trio Tim 3 Tesla MRI at the Massachusetts General Hospital (MGH, Charlestown, MA) using a 12-channel head coil. FMRI blood-oxygen-level dependent (BOLD) images were acquired using a gradient echo T2-weighted sequence (repetition time=2.5 sec, echo time=30msec, flip angle=90) in 46 coronal slices (thickness=2.5mm, 20% distance factor, 0.5mm skip). Total scan time for each run was approximately 10 minutes. One P+ twin pair (adjusted *N*=11) and one P- twin pair (adjusted *N*=13) were excluded from fMRI analyses due to movement during the scan.

Whole-brain voxelwise comparisons were performed using the statistical parametric mapping (SPM2) software package (www.fil.ion.ucl.ac.uk/spm/software/smp2). Each participant's functional images were co-registered to his high-resolution structural MRI image (memprage), spatially normalized in standard stereotactic space (Montreal Neurological Institute, MNI), and smoothed (8mm). To approximate our mixed model in SPM2, we used an approach that consists of hierarchical levels of analysis in which each level’s random-effects analysis absorbs

the random effects from the level beneath it. The first level required contrasting two conditions (e.g. Stressful Imagery versus Neutral Imagery) to generate a contrast map of the two conditions. The second level of analysis generated a contrast map of the responses of the Ex and Ux member of a twin pair. At this level, for the purpose of analyzing the main effect of PTSD diagnosis, these responses were averaged; for analyzing the main effect of Exposure and the PTSD Diagnosis x Combat interaction, their difference was calculated (as in a paired t-test). At the third level of analysis, the P+ and P- subjects' data were contrasted (as in an independent t-test) to yield the final result. Following the whole-brain vowelwise analyses, we extracted the data for individual subjects from identified loci of interest using the MarsBaR SPM toolbox (Brett, Anton, Valabregue, & Poline, 2002) and further analyzed these results using SPSS. Given our a priori hypotheses, we applied a significance threshold of 0.001, one-tailed and uncorrected (z score ≥3.09), to activations in the mPFC. For regions about which we had no a priori predictions, we applied a more conservative significance threshold of 0.00002, two-tailed and uncorrected (z score ≥ 4.27). All regions of interest (ROIs) were verified with the Talairach and Tournoux atlas (1988).

Results

The demographic and clinical characteristics of the study participants are summarized in Table 1. All subjects were well matched in terms of age, years of education, current depressive state (measured by

the BDI), magnitude of childhood trauma (measured by the CTQ), and alcohol use (measured by the MAST). Consistent with PTSD diagnosis, ExP+ subjects reported significantly greater PTSD symptom severity (measured by the CAPS) compared to ExP- participants; this was true for all subscales of the CAPS (re-experiencing, avoidance, and hyper-arousal) as well as total overall score. A main effect of trauma exposure was demonstrated for all subscales of the TLEQ (a measure of traumatic life events) verifying that trauma-exposed participants had experienced more trauma than trauma-unexposed participants. A PTSD Diagnosis x Trauma Exposure Interaction was observed for anxiety ratings (measured by the BAI) and was driven by high anxiety ratings from ExP+ individuals.

Psychophysiological and Subjective Script Rating Results

The results for the Stressful (trauma-unrelated) and Neutral imagery SCR and subjective rating data are presented in Table 2. No significant effects were noted for any of the SCR or subjective ratings dependent variables in either the individual Stressful or Neutral conditions. When Stressful-Neutral difference scores (Stressful(Imagery-Baseline) - Neutral(Imagery-Baseline)) were calculated, a significant Interaction Effect emerged for SCR. This may be due to a lack of modulation or change in the ExP+ participants' SCR during the Stressful(Imagery-Baseline) contrast (Figure 1A) compared to the more dynamic SCR during the Neutral(Imagery-Baseline) contrast (Figure 1B). Pearson correlations indicated no significant relationship between Stressful-Neutral difference

scores and PTSD symptom severity. Additionally, there was a significant Main Effect of PTSD Diagnosis for arousal ratings during the Stressful-Neutral contrast indicating that the ExP+ and UxP+ individuals rated the Neutral scripts more arousing and the Stressful scripts less arousing than the ExP- and UxP- participants.

A comparison of the independent subjective ratings of the scripts is provided in Table 3. There was a Main Effect of Diagnosis for the imagery ratings of the Neutral scripts (for script 1, script 2, and average) indicating that the P+ twins' scripts were rated as having significantly less imagery compared to the P- twins. There was also a Main Effect of Exposure for the average valence ratings for the Neutral scripts indicating that exposed twins' scripts had higher positive ratings. No other effects were significant. Given that all significant results were localized to the Neutral scripts, the authors considered the scripts to be well matched according to the independent ratings. Chi Square analyses indicated the groups were well-matched for number of shared scripts (Stressful script 1: $X^2(1, N=45)=7.44$, $p=.059$; Stressful script 2: $X^2(1, N=45)=1.339$, $p=.720$; Neutral script 1: equal frequencies; Neutral script 2: equal frequencies) and shared events (Stressful script 1: $X^2(1, N=45)=7.72$, $p=.260$; Stressful script 2: $X^2(1, N=45)=5.10$, $p=.532$; Neutral script 1: $X^2(1, N=45)=3.58$, $p=.311$; Neutral script 2: $X^2(1, N=45)=5.470$, $p=.792$). Additional Chi Square analyses of the frequencies of time since the events from the scripts were all non-significant (Stressful script 1: $X^2(1, N=45)=21.25$,

p=.624; Stressful script 2: X^2(1, N=45)=29.29, p=.209; Neutral script 1: X^2(1, N=45)=14.77, p=.254; Neutral script 2: X^2(1, N=45)=2.81, p=.421).

Functional MRI Results

Results of the whole brain voxelwise analyses for the Stressful versus Neutral Imagery contrast are listed with ROIs and Montreal Neurological Institute (MNI) coordinates in Table 4. Main Effects of Diagnosis with the P+ subjects showed significantly less activation in the dorsal and rostral anterior cingulate cortex (dACC and rACC) compared to the P- participants. No significant Main Effect of Exposure or Interaction Effect was seen. In order to fully examine the Main Effect of Diagnosis, activation values for each subject were extracted from each condition (Stressful versus Baseline, Neutral versus Baseline, and Stressful versus Neutral, Figure 2). A 2x2 (PTSD Diagnosis Group by Trauma Exposure) mixed-model ANOVA comparing the Stressful Imagery - Neutral Imagery extracted activations confirmed the Main Effect of Diagnosis (F(1,22)=7.99, p=.010), but the plotted data (Figure 2C) illustrates that this Main Effect of Diagnosis is driven by reduced rACC activation in the ExP+ participants during Stressful Imagery. This is more indicative of an Interaction Effect, even though no such effect was found to be significant.

Additionally, several trends for activation differences in the insula, brainstem, and inferior temporal lobe were found, but as they were not *a priori* ROIs, they did not reach the statistical significance threshold (z

score ≥ 4.27). We have included areas close to threshold in Table 3 to help inform future studies.

Correlations with rACC Activation. Pearson correlations indicated that Ex twins' activation in the rACC negatively correlated with their CAPS scores: intrusive symptoms ($r(22)=-.378$, $p=.035$. 1-tailed), avoidance symptoms ($r(22)=-.382$, $p=.033$, 1-tailed), hyperarousal symptoms ($r(22)=-.396$, $p=.028$, 1-tailed), and total PTSD symptoms ($r(22)=-.419$, $p=.021$, 1-tailed; Figure 3). However, Ux twins' rACC activation did not significantly correlate with their Ex twins' CAPS scores. Additionally, SCR Stressful-Neutral difference scores (Imagery-Baseline) did not significantly correlate with rACC activation.

Covariate Analyses

Controlling for Significant Difference in BAI Scores. Because a significant Interaction Effect indicated that the ExP+ participants had significantly higher BAI scores than the other participants, the SCR and extracted fMRI ANOVAs were re-run as an analysis of covariance (ANCOVA) controlling for BAI. When BAI was a covariate in the analyses, the previously significant Interaction Effect for SCR (Stressful(Imagery-Baseline) - Neutral(Imagery-Baseline) became a trend ($F(1,18)=4.26$, $p=.054$); however the Main Effect of Diagnosis in the rACC remained significant ($F(1,21)=14.55$, $p=.001$).

Controlling for Selective Serotonin Reuptake Inhibitor (SSRI) Use. Orr and colleagues (2004) have suggested that SSRI medications

can affect psychophysiological reactivity. Therefore we ran ANCOVAs controlling for SSRI use (including Serotonin and Norepinephrine Reuptake Inhibitors (NSRIs) Noradrenergic and Specific serotonergic Antidepressant (NaSSA); see Table 5 for frequency of use). When covarying for SSRI use, the Stressful(Imagery-Baseline) - Neutral(Imagery-Baseline) SCR Interaction Effect was no longer significant. The Main Effects of Exposure and PTSD Diagnosis remained non-significant. ANCOVAs controlling for SSRI use reduced the significance of the brain activation results. When covarying for SSRI use, the Stressful Imagery - Neutral Imagery fMRI activation in the rACC Main Effect of Diagnosis became a trend ($F(1,20)=3.851$, $p=.064$).

Discussion

The results of the present study were able to replicate and extend previous research of SDI in PTSD. A significant Interaction Effect for Stressful - Neutral SCR difference scores during was attributed to the ExP+ participants' high SCR during both the Baseline and Imagery conditions for the Stressful scripts. The ExP+ individuals displayed very little change in SCR during Stressful (Imagery-Baseline) while the other groups demonstrated more dynamic fluctuations in SCR throughout the task. The ExP+ participants also consistently had the highest levels of baseline SC throughout each condition of the task and reported higher levels of state anxiety as measured by the BAI. These results are consistent with previous research indicating increased

psychophysiological responses in PTSD during trauma-related scripts (Pitman et al., 1987; 1990; Orr, Pitman, Lasko, & Herz, 1993; Orr et al., 1998; Shalev, Orr, & Pitman, 1993; Shin et al., 2004; Gold et al., 2011; reviewed in Orr, McNally, Rosen, & Shalev, 2004) although we were unable to replicate SCR correlations with PTSD symptom severity. Our results indicate that ExP+ individuals show high rates of arousal throughout the entire task, which could be interpreted as high, arousal and anxiety as an acquired characteristic of PTSD.

However it is important to note that average SC level during Stressful Imagery in the ExP+ participants (*M*=4.17) does not represent a large magnitude SCR (for review see Orr, McNally, Rosen, & Shalev, 2004). In fact, all groups showed relatively low magnitude SCRs, which could be due to a variety of confounding factors including older age, time since the events, etc. Additionally, the results from the ANCOVA analyses controlling for SSRI use indicate that SSRI medication may moderate the psychophysiological response to SDI, with SSRI use blunting the Stressful-Neutral Imagery SCR. However, this does not seem to be true for rACC activation. Taken together with the low magnitude of the SCR response, this suggests a cautious approach should be taken in the interpretation of these results.

The fMRI analyses showed a Main Effect of PTSD Diagnosis during the Stressful Imagery versus Neutral Imagery contrast, which the P+ subjects displayed less activation in the dACC and rACC compared to the

P- participants. Extraction of the activation data indicated that the Main Effect of Diagnosis was driven by reduced rACC activation during Stressful Imagery-Baseline in the P+ participants, which is more indicative of an Interaction Effect suggesting that reduced mPFC activation during the Stressful-Neutral contrast is an acquired characteristic of PTSD. These results are consistent with previous research implicating reduced mPFC (specifically ACC) activation in PTSD during trauma-related SDI scripts (Bremner et al., 1999; Shin et al., 1999; 2004; Lanius et al., 2001; 2003; Liberzon, Britton & Phan, 2003; Lindauer et al., 2004) as well as trauma-unrelated Stressful scripts (Britton et al., 2005; Gold et al., 2011). Our findings particularly extend the previous results from Britton and colleagues (2005), who reported that Ex individuals with and without PTSD as well as Ux controls all showed decreased activation in the mPFC during Stressful-Neutral SDI. However, they noted that the ExP+ participants had the largest deactivation compared to the other groups, which is also indicated in the current study.

Additionally, correlation analyses indicated that Ex twins' activation in the rACC negatively correlated with PTSD symptom severity replicating prior work suggesting that mPFC activation during SDI is inversely related to symptom severity in the mPFC (Osuch et al., 2001). However, our results did not indicate a significant correlation between the Ux twins' rACC activation with their Ex twins' CAPS scores, which provides further

support that reduced rACC activation is an acquired characteristic of PTSD rather than a familial vulnerability factor.

Analyses of the demographic and clinical state variables indicated that our groups were well matched with the exception of anxiety; the ExP+ participants reported significantly higher BAI (a self-report scale of anxiety) scores. Additionally, analyses of the subjective ratings demonstrated that P+ individuals rated the Neutral scripts as more arousing than P- individuals, even though independent ratings of scripts suggested that they were well matched, providing evidence for heightened arousal in ExP+ participants as well as their identical co-twins. Both these results may be reflective of higher overall baseline anxiety in ExP+ as a characteristic of PTSD. When anxiety (via BAI) was controlled for in the analyses, the fMRI results remained significant, but the previously significant Interaction Effect of SCR became a trend (p=.054). Given that anxiety symptoms are part of the clinical presentation of PTSD (APA, 2013), it is unsurprising that controlling for this specific subset of symptomatology might affect the results. Psychophysiological reactivity during SDI has been shown to be higher in PTSD compared to other anxiety disorders (Pitman et al., 1990), and even though our SCR result was no longer significant after controlling for anxiety the fact that a trend was still apparent suggests that anxiety symptoms in PTSD cannot completely account for variance driving the between-group differences.

Limitations and Future Directions

The interpretation of these results should be considered cautiously. A major limitation of this study is the small subject sample size, which limits statistical power. Given the unique inclusion/exclusion criteria for this study (identical twins discordant for both trauma exposure and PTSD), recruitment for this study was incredibly challenging despite the authors' best efforts to maximize recruitment efforts. This issue was further exacerbated by data lost to unmeasurable SCR and motion artifacts. The repeated-measures analyses techniques employed for this twin study design helped maximize statistical power, but the sample size may have contributed to Type II errors.

This study was also limited by the characteristics of the study sample, and therefore generalization to a broader population should be considered with caution. Only male subjects were successfully recruited for the study. Previous research in PTSD has identified gender differences in both psychophysiological and brain activation responses with females reporting higher psychophysiological response (Kleim, Wilhelm, Glucksman, & Ehlers, 2010) and males indicating increased activation in the amygdala (Shin et al., 2004) during SDI. In addition, almost all Ex participants reported trauma exposure from combat. Many SDI studies have recruited subject samples with specific types of trauma such as exposure to childhood sexual abuse (Bremner et al., 1999; Shin et al., 1999; Lanius et al., 2001; 2002; 2003), police work (Lindauer et al., 2004), or combat (Liberzon, Britton. & Phan, 2003; Shin et al., 2004;

Britton, Phan, Taylor, Fig, & Liberzon, 2005; Gold et al., 2011), while relatively few studies have recruited samples with mixed types of trauma exposure (Rauch et al., 1996; Osuch et al., 2001). It is important to note that the results from studies focusing on a more homogenous type of trauma may only apply to that specific type of trauma exposure. Furthermore, participants from the current study reported exposure to trauma typically occurred decades ago. Although time since the traumatic event is less concerning given evidence suggesting that the effects of trauma and PTSD can be long lasting. For example, 9.1% of Vietnam veterans surveyed more than decade after the war still met diagnostic criteria for PTSD directly related to their experiences in Vietnam and 84.8% of these individuals currently reported more than slight impairment of global functioning (Dohrenwend et al., 2006).

Additionally, the clinical presentation of subjects can have significant effects on the results. We've briefly discussed the role of anxiety symptomatology above, but Orr and Roth (2000) have also addressed discrepancies in PTSD psychophysiological data (such as Davies et al., 1996) by suggesting that lower PTSD symptom severity may reduce the effect size of psychophysiological results. Our sample of ExP+ individuals all presented with a moderate PTSD symptom severity (as defined by Weathers, Keane, & Davidson, 2001), but the authors acknowledge that these data came from a larger neuroimaging study which required participants to travel to Boston and complete two full days

of cognitive testing and clinical assessment. As such, subjects needed to be high-functioning and well enough to endure such a rigorous protocol, and there is the possibility that the design of the study may have unintentionally excluded more severely symptomatic participants and may have increased the likelihood of Type II errors.

Conclusions

This study has provided some support for a lack of modulation or change of SCR activation during the Stressful(Imagery-Baseline) SDI contrast as an acquired characteristic of PTSD, which has important clinical implications considering that acquired characteristics could potentially assist in the diagnosis of PTSD or in the assessment of treatment response. In fact, recent research has shown that SCR response to SDI has high convergent validity with the CAPS in regard to PTSD diagnosis (Bauer et al., 2013). The fMRI results suggested a Main Effect of PTSD Diagnosis indicated a potential familial vulnerability factor for individuals with PTSD and their identical co-twins have reduced rACC activation during Stressful versus Neutral Imagery; however further inspection of the extracted data indicated that this result was driven by reduced rACC activation in the PTSD participants during Stressful Imagery, which was more indicative of an acquired characteristic of PTSD. In regard to neural activation, the critical question about the origin of brain activation abnormalities in SDI remains unanswered. More research is

needed in order to fully characterize the pathogenesis and symptom progression of PTSD.

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Table 1

Demographic and Clinical Characteristics for Trauma-Exposed Participants with (P+) and Without (P-) PTSD and Their Trauma-Unexposed Identical Co-Twins

	PTSD Pairs (P+)				Non-PTSD Pairs (P-)				Mixed-Model Analysis of Variance[a]					
	Exposed (N=11)		Unexposed (N=11)		Exposed (N=13)		Unexposed (N=13)		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	0.848	.367				
Education (years)	14.09	2.91	13.36	3.88	15.81	3.78	15.15	2.73	1.78	.195	2.78	.109	0.008	.930
CAPS														
Re-experiencing	12.73	7.89			0.46	1.20			**23.62**	**<.001**				
Avoidance	18.82	11.01			1.08	2.40			**27.15**	**<.001**				
Hyper-arousal	17.00	7.31			1.31	2.14			**32.98**	**<.001**				
Total	48.55	21.77			2.85	4.36			**37.66**	**<.001**				
TLEQ														
Critical Events (CE)	7.36	3.29	5.36	3.64	6.00	2.27	4.85	2.70	0.85	.367	**5.53**	**.028**	0.40	.535
CE with Fear & 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
Total Occurrences	21.55	10.23	14.09	15.55	16.31	7.40	11.15	7.61	1.72	.204	**4.60**	**.043**	0.15	.699
CTQ[b]	39.74	12.50	37.63	11.00	38.33	8.04	37.42	10.45	0.04	.845	0.51	.485	.079	.782
BDI	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	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**
MAST	5.00	5.73	3.09	5.05	2.31	2.84	2.69	4.01	0.85	.368	1.15	.294	2.61	.120

[a]df=1,22 unless noted otherwise
[b]df=1,19

Table 2

SCR and Subjective Ratings for SDI Stressful and Neutral Imagery Conditions

	PTSD Pairs (P+)				Control Pairs (P-)				Mixed-Model Analysis of Variance[a]					
	Exposed N=9		Unexposed N=9		Exposed N=12		Unexposed N=12		Diagnosis		Trauma Exposure		Interaction	
Measure	Mean	SD	Mean	SD	Mean	SD	Mean	SD	*F*	*p*	*F*	*p*	*F*	*p*
Stressful SCR														
Stressful Baseline	4.19	4.22	3.82	1.75	3.92	2.49	3.54	2.33	0.07	.788	0.27	.609	0.00	.993
Stressful Imagery - Stressful Baseline	-0.02	0.13	0.14	0.34	0.11	0.28	0.13	0.43	0.23	.638	1.50	.235	0.92	.350
Stressful Ratings														
Valence	2.11	2.04	2.94	1.83	2.25	2.40	2.13	1.21	0.35	.563	0.33	.572	0.61	.446
Arousal	6.50	2.99	6.89	4.35	9.29	2.12	8.04	2.34	4.13	.056	0.25	.627	0.89	.358
Imagery	9.39	1.73	8.44	2.51	10.25	1.71	9.29	1.60	2.10	.164	2.65	.120	0.00	.991
Neutral SCR														
Neutral Baseline	3.94	4.09	3.73	1.79	3.64	2.37	3.10	2.13	0.23	.637	0.30	.588	0.06	.810
Neutral Imagery - Neutral Baseline	0.15	0.14	0.05	0.11	0.18	0.32	0.23	0.30	1.83	.192	0.14	.728	1.04	.320
Neutral Ratings														
Valence	8.78	3.30	7.94	1.47	7.88	2.06	7.75	2.41	0.44	.516	0.56	.463	0.31	.586
Arousal	7.28	3.19	7.44	2.36	6.38	1.35	5.88	2.51	2.34	.142	0.06	.807	0.25	.625
Imagery	9.72	1.99	8.72	1.73	9.54	1.54	9.00	1.49	0.01	.922	1.92	.179	0.17	.683
Stressful- Neutral SCR														
Stressful Baseline - Neutral Baseline	0.25	0.30	0.09	0.19	0.28	0.23	0.44	0.48	2.73	.115	0.00	1.00	3.32	.084
Stressful (Imagery-Baseline) - Neutral (Imagery-Baseline)	-0.16	0.11	0.10	0.27	-0.07	0.42	-0.10	0.38	0.16	.695	2.92	.104	**4.53**	**.047**
Stressful-Neutral Ratings														
Valence	-6.67	4.24	-5.00	2.33	-5.63	3.10	-5.63	3.01	0.04	.846	0.77	.390	0.77	.390
Arousal	-0.78	2.86	-0.56	5.66	2.92	2.20	2.17	3.39	**5.81**	**.026**	0.09	.770	0.30	.592
Imagery	-0.33	2.03	-0.29	2.90	0.71	1.57	0.29	1.88	1.40	.251	0.08	.775	0.14	.708

[a]df=1,19

Table 3

Independent Subjective Ratings for Autobiographical Scripts

	PTSD Pairs (P+)				Control Pairs (P-)				Mixed-Model Analysis of Variance[a]					
	Exposed		Unexposed		Exposed		Unexposed		Diagnosis		Trauma Exposure		Interaction	
Measure	Mean	SD	Mean	SD	Mean	SD	Mean	SD	*F*	*p*	*F*	*p*	*F*	*p*
Stressful Script 1														
Valence	0.31	0.10	0.44	0.42	0.27	0.18	0.40	0.24	0.17	.682	3.35	.082	0.00	.991
Arousal	9.77	0.58	9.70	0.78	9.67	0.83	10.18	0.73	0.73	.405	1.05	.318	1.74	.202
Imagery	10.42	0.64	10.34	0.84	10.57	0.56	10.29	0.67	0.07	.798	0.71	.410	0.22	.646
Physiological Cues	4.12	1.26	3.91	1.32	4.10	1.39	4.54	0.65	0.57	.458	0.15	.706	1.16	.295
Stressful Script 2														
Valence	0.33	0.21	0.34	0.19	0.33	0.19	0.47	0.31	0.92	.350	1.09	.308	0.72	.408
Arousal	10.05	1.28	10.12	0.94	10.50	0.58	9.72	1.20	0.00	.952	1.82	.192	2.61	.122
Imagery	10.49	0.85	10.54	0.54	11.02	0.40	10.63	0.67	2.40	.137	0.89	.358	1.56	.226
Physiological Cues	4.33	0.79	3.94	1.13	3.97	0.91	4.38	1.28	0.01	.908	0.00	.975	1.88	.185
Stressful Script Avg														
Valence	0.32	0.11	0.39	0.28	0.30	0.17	0.44	0.22	0.06	.812	2.60	.122	0.23	.640
Arousal	9.91	0.76	9.91	0.69	10.08	0.61	9.95	0.75	0.22	.645	0.12	.736	0.13	.727
Imagery	10.45	0.63	10.44	0.54	10.80	0.42	10.46	0.60	1.03	.323	1.28	.271	1.10	.306
Physiological Cues	4.23	0.86	3.93	1.11	4.04	0.98	4.46	0.84	0.25	.624	0.09	.772	2.91	.104
Neutral Script 1														
Valence	6.52	0.90	5.62	0.77	6.37	0.93	6.38	0.88	1.46	.242	2.54	.126	2.69	.117
Arousal	2.65	1.16	2.44	0.94	2.27	1.54	1.97	1.04	1.01	.326	0.76	.393	0.02	.879
Imagery	9.60	0.44	9.48	0.63	9.99	0.59	10.06	0.38	**7.19**	**.014**	0.04	.850	0.52	.481
Physiological Cues	2.11	0.77	1.98	1.19	2.49	1.40	2.88	1.26	2.10	.163	0.27	.610	1.05	.318
Neutral Script 2														
Valence	6.77	0.84	6.28	0.74	6.50	0.71	6.26	0.53	0.47	.500	2.89	.105	0.33	.571
Arousal	2.01	0.82	1.90	0.74	2.07	0.98	1.87	0.93	0.01	.936	0.68	.419	0.08	.785
Imagery	9.28	0.60	9.52	0.82	10.07	0.54	9.85	0.41	**6.84**	**.017**	0.01	.932	2.79	.110
Physiological Cues	1.70	0.94	2.26	1.15	2.05	1.12	2.62	1.26	0.80	.381	3.99	.060	0.00	.985
Neutral Script Avg														
Valence	4.43	0.53	3.97	0.33	4.29	0.43	4.21	0.36	0.17	.681	**4.67**	**.043**	2.39	.138
Arousal	1.55	0.49	1.45	0.45	1.45	0.81	1.28	0.58	0.37	.549	1.00	.330	0.06	.814
Imagery	6.29	0.25	6.33	0.47	6.69	0.32	6.64	0.23	**9.20**	**.007**	0.00	.960	0.37	.556
Physiological Cues	1.27	0.55	1.41	0.71	1.51	0.79	1.83	0.80	1.51	.233	2.13	.160	0.32	.581

[a]df=1,20

Table 4

Whole Brain Functional MRI Analyses for SDI

Comparison	Region	Z Score	MNI Coordinates (x. y, z)
Main Effect of Diagnosis			
P+ > P-	None	-	-
P- > P+	**Dorsal ACC**	**3.64**	**4, 6, 32**
	Dorsal ACC	**3.22**	**-10, 24, 32**
	Rostral ACC	**3.19**	**-12, 28, 30**
	Left insula	3.47	-32, 12, -12
	Right insula	3.28	50, -6, 8
	Left insula	3.22	-34, 28, 6
	Brainstem	3.66	2, -22, -32
	Inferior temporal lobe	3.60	40, 20, -32
	Inferior temporal lobe	3.23	-40, -8, -28
Main Effect of Exposure			
Ex > Ux	None	-	-
Ux > Ex	None	-	-
PTSD Diagnosis by Exposure Interaction			
P+ > P-, Ex > Ux	None	-	-
P- > P+, Ex > Ux	Left insula	3.23	-40, -2, 12

Significance threshold of 0.001, one-tailed and uncorrected (Z score ≥3.09)

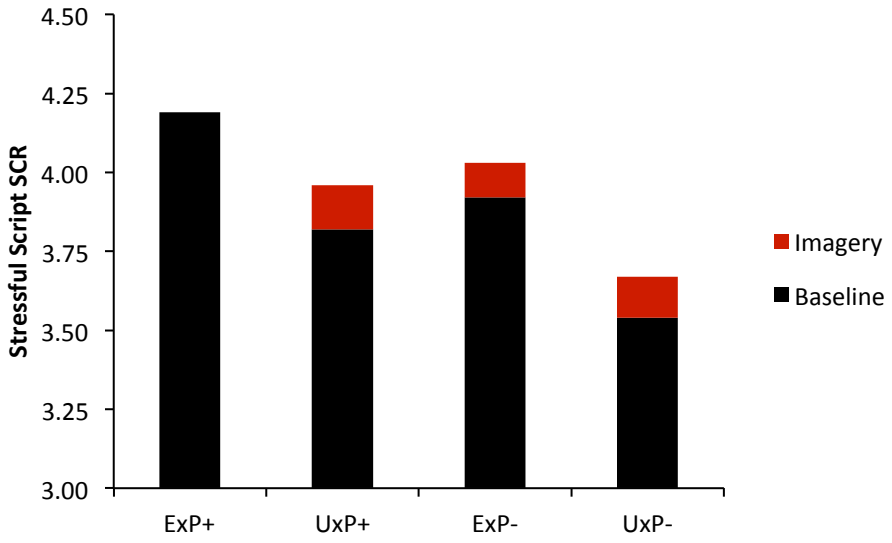
Table 5

Current SSRI Medication Use Frequencies

	PTSD Pairs (P+)		Non-PTSD Pairs (P-)	
SSRI Medication	Exposed (N=11)[a]	Unexposed (N=11)	Exposed (N=13)	Unexposed (N=13)[a]
Currently Taking SSRIs	7	1	0	2
Not Currently Taking SSRIs	3	10	13	10

[a]One Participant did not report current medications

A SCR Stressful (Imagery-Baseline) Contrast



B SCR Neutral (Imagery-Baseline) Contrast

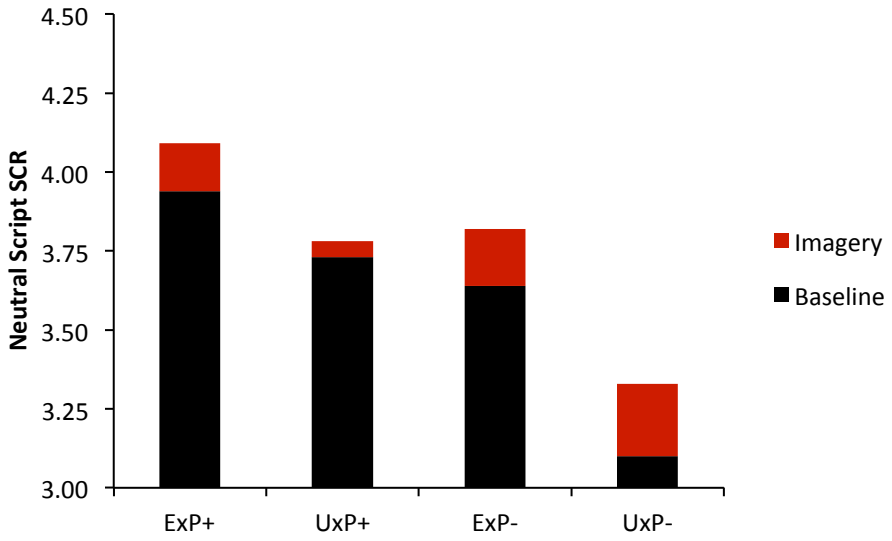
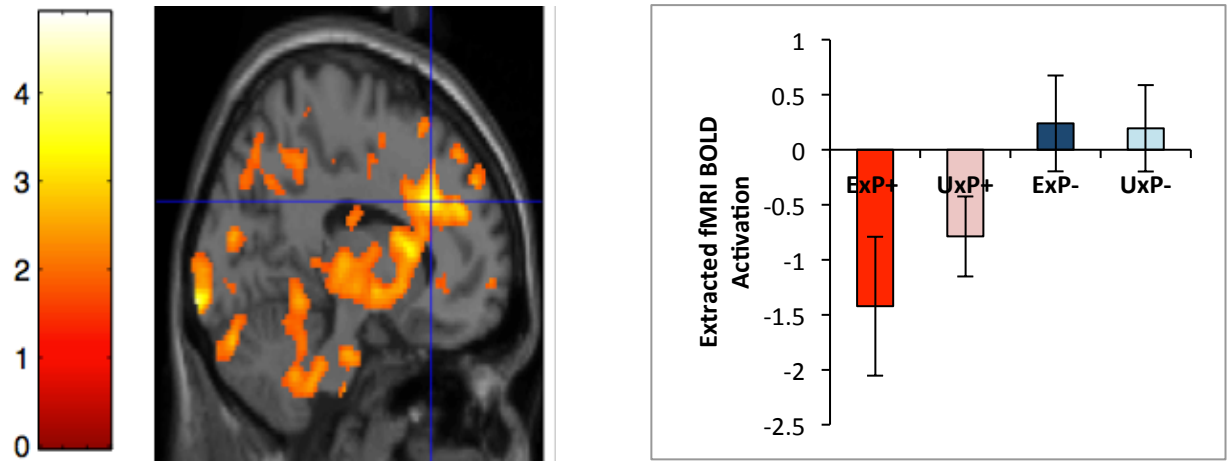


Figure 1. SCR Imagery - Baseline Contrasts for the Stressful and Neutral Script Conditions.

A ROI rACC (-12, 28, 30)

B Stressful-Neutral Imagery



C Stressful(Imagery-Baseline) versus Neutral(Imagery-Baseline)

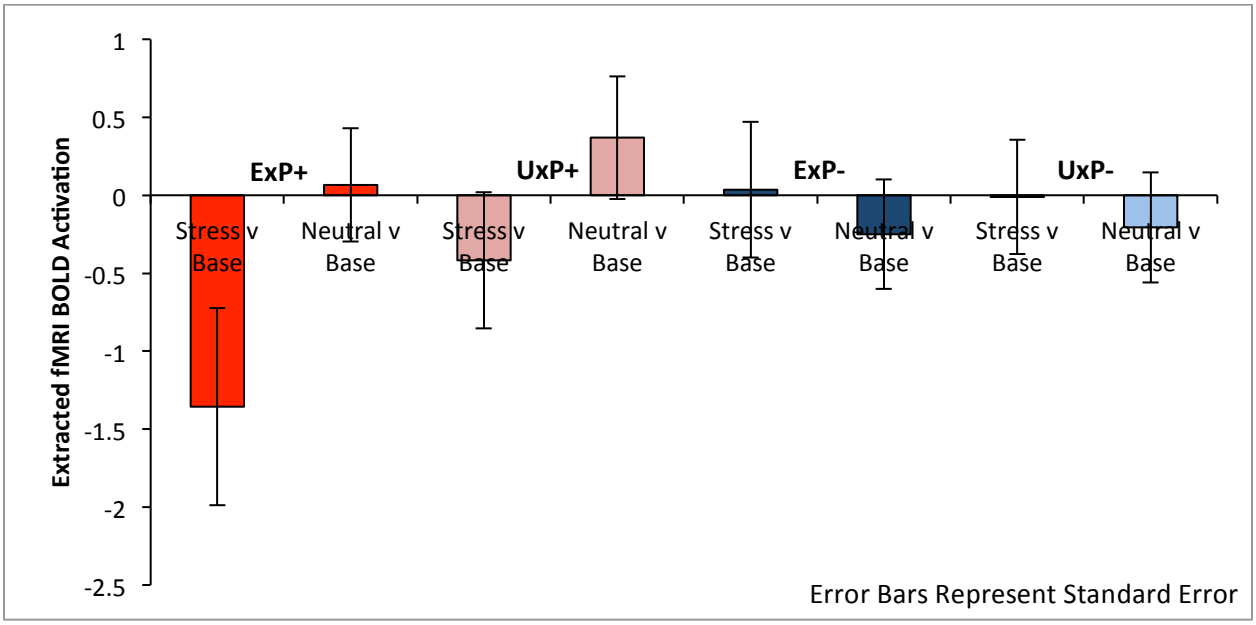


Figure 2. Extracted fMRI BOLD activation during SDI Stressful versus Neutral Imagery from one of the significant ROIs (rACC: -12, 28, 30; z=3.19) represented in A) BOLD ROI, B) the mean Stressful-Neutral Imagery BOLD activation patterns as well as C) the BOLD activation further broken down by Stressful-Baseline and Neutral-Baseline, which indicates that the Main Effect of Diagnosis may be due to an interaction with the ExP+ participants showing decreased rACC activation compared to all other subjects.

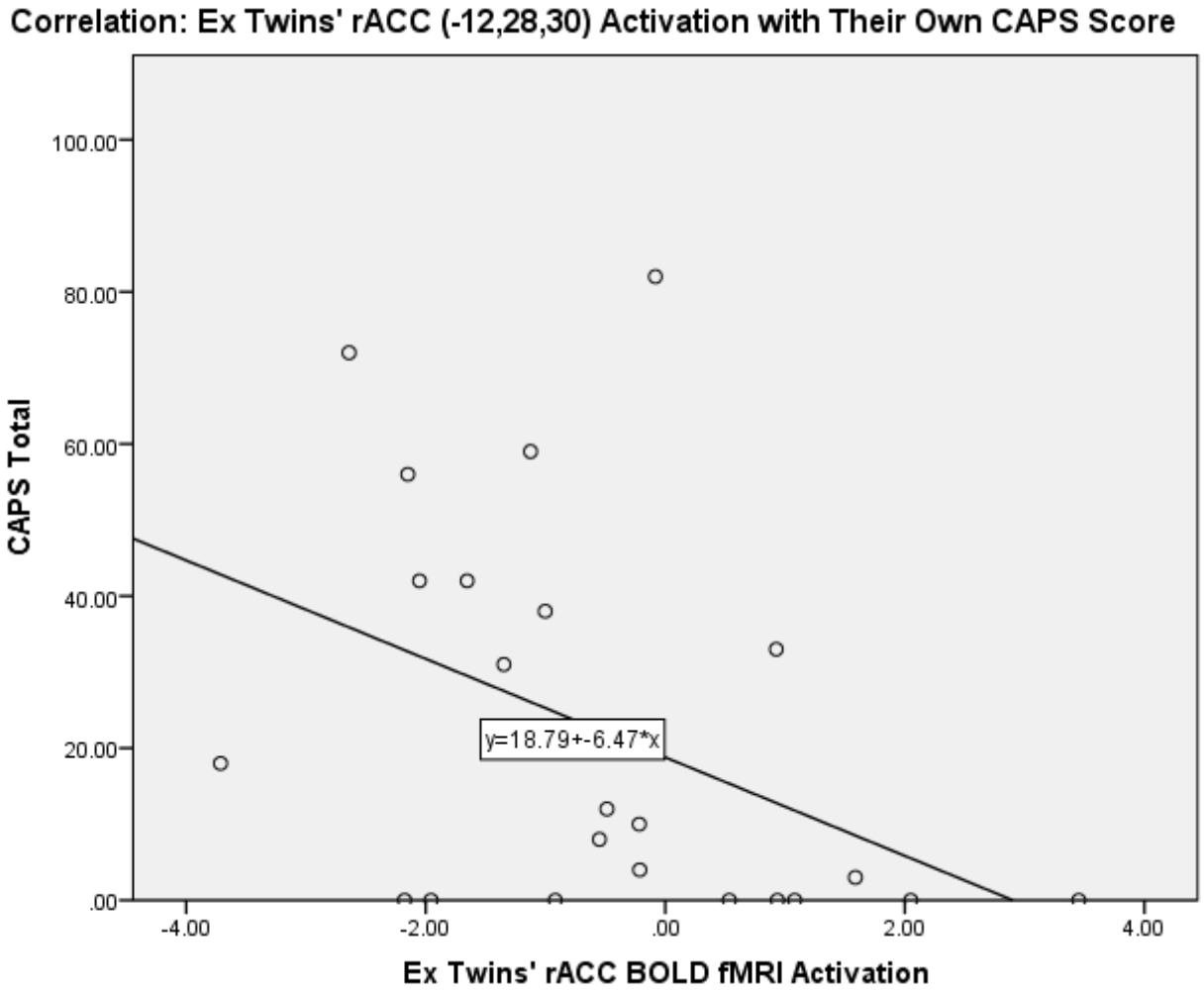


Figure 3. Correlation Analysis of BOLD rACC Activation during Stressful-Neutral Imagery with Ex Participants Own CAPS Scores (r(22)=-.419, p=.021, 1-tailed).