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Neural correlates of PTSD in women with childhood sexual abuse with and without PTSD and response to paroxetine treatment: A placebo-controlled, double-blind trial

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Abstract

Objective: Childhood sexual abuse is the leading cause of posttraumatic stress disorder (PTSD) in women, and is a prominent cause of morbidity and loss of function for which limited treatments are available. Understanding the neurobiology of treatment response is important for developing new treatments. The purpose of this study was to assess neural correlates of personalized traumatic memories in women with childhood sexual abuse with and without PTSD, and to assess response to treatment.

Methods: Women with childhood sexual abuse with ($N = 28$) and without ($N = 17$) PTSD underwent brain imaging with High-Resolution Positron Emission Tomography scanning with radiolabeled water for brain blood flow measurements during exposure to personalized traumatic scripts and memory encoding tasks. Women with PTSD were randomized to paroxetine or placebo followed by three months of double-blind treatment and repeat imaging with the same protocol.

Results: Women with PTSD showed decreases in areas involved in the Default Mode Network (DMN), a network of brain areas usually active when the brain is at rest, hippocampus and visual processing areas with exposure to traumatic scripts at baseline while women without PTSD showed increased activation in superior frontal gyrus and other areas ($p < 0.005$). Treatment of

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Declaration of Competing Interest

No authors report potential conflicts of interests.

women with PTSD with paroxetine resulted in increased anterior cingulate activation and brain areas involved in the DMN and visual processing with scripts compared to placebo ($p < 0.005$).

Conclusion: PTSD related to childhood sexual abuse in women is associated with alterations in brain areas involved in memory and the stress response and treatment with paroxetine results in modulation of these areas.

1. Introduction

Posttraumatic Stress Disorder (PTSD) affects about 8% of Americans at some time in their lives (Kessler et al., 2005), is more common in civilians than in the military and is twice as common in women as in men (Kessler et al., 2005). The most common cause of PTSD in women is childhood sexual abuse (Kessler et al., 2005). Symptoms of PTSD, including intrusive memories, avoidance behaviors, sleep disturbance, and hyperarousal are the behavioral manifestation of stress-related changes in the brain (Bremner and Wittbrodt, 2020). The only medications approved by the Food and Drug Administration (FDA) for the treatment of PTSD are the Selective Serotonin Reuptake Inhibitor (SSRI) antidepressant medications, paroxetine and sertraline (Ballenger et al., 2000; Brady et al., 2000; Davis et al., 2016; Marshall et al., 2001; Stein et al., 2000; Tucker et al., 2001; Zohar et al., 2002). Evidence for their utility, however, is limited (Institute of Medicine, 2008). Understanding mechanisms in the brain underlying successful responses to treatment could be helpful in the development of new and better treatments (Bremner and Campanella, 2016; Bremner and Wittbrodt, 2020; Davis et al., 2016).

Brain imaging studies have outlined a network of brain areas mediating memory and the fear response in PTSD (Akiki et al., 2017; Boccia et al., 2016; Campanella and Bremner, 2016; Dixon et al., 2017; Etkin and Wager, 2007; Fitzgerald et al., 2018; Francati et al., 2007; Koch et al., 2016; Patel et al., 2012; Sartory et al., 2013; Thome et al., 2020; Wang et al., 2016). Brain imaging studies involving activation of PTSD symptoms using behavioral paradigms like trauma-related pictures, sounds and/or personalized scripts resulted in decreased function or failure of activation in the medial prefrontal cortex (mPFC)/anterior cingulate cortex (ACC) (Bremner et al., 1999a, 1999b; Dahlgren et al., 2018; Lanius et al., 2001, 2003; Lindauer et al., 2004; Offringa et al., 2013; Phan et al., 2006; Shin et al., 1997, 1999, 2004; Shin et al., 2001, 2005), ventromedial prefrontal cortex (Bluhm et al., 2012; Grupe et al., 2020; Milad et al., 2009; Phan et al., 2006; Rougemont-Bücking et al., 2011; Sanjuan et al., 2018), thalamus (Elman et al., 2018; Lanius et al., 2001, 2003; Schechter et al., 2012), fusiform gyrus (Cwik et al., 2017; Osuch et al., 2001), precuneus (Geuze et al., 2008a; Lanius et al., 2002; Werner et al., 2009), cuneus (Cortese et al., 2018; Cwik et al., 2017; Lindauer et al., 2004; Misaki et al., 2019; Morey et al., 2009; Ramage et al., 2013; Sun et al., 2019), visual association cortex (Bremner et al., 1999a; Gold et al., 2011; Lanius et al., 2001, 2003; Shin et al., 1997, 2004), temporal cortex (Chung et al., 2006; Geuze et al., 2008b; Werner et al., 2009), parietal cortex (Bremner et al., 1999a; Chung et al., 2006; Ke et al., 2016; Morey et al., 2008; Shin et al., 1997, 1999), parahippocampus (Sakamoto et al., 2005; Werner et al., 2009), hippocampus (Bremner et al., 1999a; Cisler et al., 2015b; Kim et al., 2012; Osuch et al., 2008; Yehuda et al., 2010, 2009), inferior frontal (Bremner et al., 1999a; Lanius et al., 2003; Sakamoto et al., 2005; Shin et al., 1997, 1999, 2001) middle and

superior frontal gyrus, (Aupperle et al., 2012; Cisler et al., 2015b; Cohen et al., 2013; Cwik et al., 2017; Hou et al., 2007; Morey et al., 2009; Shin et al., 1997, 1999, 2004; Shin et al., 2001)

Activation of PTSD symptoms was associated with increased function in the insula (Bruce et al., 2013; Fonzo et al., 2010a; Kaczkurkin et al., 2017; King et al., 2009; Mazza et al., 2015; Misaki et al., 2019; Morey et al., 2015; Moser et al., 2013; Nicholson et al., 2016; Osuch et al., 2001; Simmons et al., 2008; Whalley et al., 2013), dorsal anterior cingulate cortex (dACC) (Bremner et al., 1999a, 1999b; Britton et al., 2005; Fonzo et al., 2010a, b; Herringa et al., 2013; Milad et al., 2009, 2007; Misaki et al., 2019; Piefke et al., 2007; Ramage et al., 2013; Rougemont-Bücking et al., 2011), motor cortex (Barkay et al., 2012; Bremner et al., 1999b; Cohen et al., 2013; Cwik et al., 2017; Naegeli et al., 2018), and posterior cingulate cortex (Bremner et al., 1999a, 1999b; Brinkmann et al., 2017; Ke et al., 2016; Lanius et al., 2001; Ramage et al., 2013; Shin et al., 1997, 2005). There was increased function in the amygdala with fear-related tasks including fear conditioning, exposure to fearful or angry faces, and exposure to pictures with traumatic content (Armony et al., 2005; Bremner et al., 2005; Dickie et al., 2008; Etkin and Wager, 2007; Felmingham et al., 2009; Lieberman et al., 2017; McLaughlin et al., 2014; Morey et al., 2009; Patel et al., 2016; Protopopescu et al., 2005; Shin et al., 2004, 2005; Stevens et al., 2014, 2017).

Studies of functional brain connectivity at rest show similar results in PTSD (Akiki et al., 2017; Etkin et al., 2011; Etkin and Wager, 2007; Fitzgerald et al., 2018; Koch et al., 2016; Patel et al., 2012; Sartory et al., 2013; Schulze et al., 2019; Thome et al., 2020; Wang et al., 2016). These studies show altered function/connectivity in the hippocampus (Abdallah et al., 2017; Admon et al., 2013; Bluhm et al., 2009; Chen and Etkin, 2013; Chen et al., 2019; Jin et al., 2014; Lazarov et al., 2017; Malivoire et al., 2018; Metz et al., 2019; Miller et al., 2017a; Rabellino et al., 2018a, 2018b; Stevens et al., 2014; Zhang et al., 2017), parahippocampus (Jin et al., 2014; Misaki et al., 2018), insula (Birn et al., 2014; Etkin et al., 2019; Harricharan et al., 2020; Ke et al., 2018; Koch et al., 2016; Liu et al., 2017; Nicholson et al., 2020; Sripada et al., 2012a; Tursich et al., 2015; Vanasse et al., 2019; Zhang et al., 2016b), amygdala (Admon et al., 2009; Barredo et al., 2018; Disner et al., 2018; Jin et al., 2014; Koch et al., 2016; Nicholson et al., 2019, 2017; Satterthwaite et al., 2016; Simmons et al., 2008; Stevens et al., 2013; Sun et al., 2020; Weng et al., 2019; Yan et al., 2013; Yuan et al., 2019; Zhang et al., 2016a; Zhu et al., 2017), medial prefrontal cortex (Akiki et al., 2018; Amad et al., 2019; Birn et al., 2014; Clausen et al., 2017b; Disner et al., 2018; Gong et al., 2014; Jin et al., 2014; Kennis et al., 2015; Liu et al., 2016; Misaki et al., 2018; Sadeh et al., 2015) and other brain areas involved in memory and visual and spatial processing (Olivé et al., 2018; Olson et al., 2019; Reuveni et al., 2016) (Bluhm et al., 2009; Disner et al., 2018; Fu et al., 2019; Gong et al., 2014; Jeon et al., 2020; Ke et al., 2017; Koch et al., 2016; Lanius et al., 2010; Liu et al., 2016, 2017; Miller et al., 2017a, 2017b; Qin et al., 2012; Shaw et al., 2002; Terpou et al., 2018; Wang et al., 2016; Weng et al., 2019; Yan et al., 2013; Yin et al., 2011; Zhang et al., 2017, 2016b, 2016c; Zhu et al., 2015). A number of studies have shown decreased conductivity in the default mode network (DMN), a network of brain regions that are active when the brain is not engaged, including ventromedial prefrontal cortex (vmPFC), dorsomedial PFC (dmPFC), posterior cingulate cortex (PCC), precuneus, medial temporal lobe, and medial and lateral parietal cortices (Akiki et al., 2017; Jin et al.,

2017; Koch et al., 2016; Lei et al., 2015; Maron-Katz et al., 2020; Miller et al., 2017a, 2017b; Nicholson et al., 2020; Reuveni et al., 2016; Russman Block et al., 2017; Sripada et al., 2012b; Zhang et al., 2015; Zhu et al., 2019). Other studies showed altered connectivity in the salience network, which includes insula, parietal and lateral prefrontal cortex, and dACC (Koch et al., 2016; Misaki et al., 2018; Nicholson et al., 2020; Russman Block et al., 2017; Shang et al., 2014; Zhu et al., 2020).

Brain imaging studies have tracked the effects of successful treatment of PTSD on the brain (Bremner and Campanella, 2016; Campanella and Bremner, 2016). Studies showed increased connectivity in DMN with a variety of behavioral treatments (Bremner et al., 2017; Felmingham et al., 2007; Fonzo et al., 2017; King et al., 2016; Kluetsch et al., 2014; Lansing et al., 2005; Lee et al., 2019; Lindauer et al., 2008; Misaki et al., 2019; Nicholson et al., 2017; Pagani et al., 2007; Peres et al., 2007; Shou et al., 2017; Simmons et al., 2013; van Rooij et al., 2016; Yang et al., 2018; Zhu et al., 2018; Zotev et al., 2018). Open label studies and case reports with PET and SPECT showed increased medial prefrontal function in PTSD following treatment with the SSRI fluoxetine (Fernandez et al., 2001). Placebo-controlled studies of paroxetine in PTSD patients showed an increase in function in medial prefrontal, anterior cingulate (Fani et al., 2011) and orbitofrontal cortex (Zhu et al., 2015), and dorsolateral prefrontal cortex, and supplementary motor area (MacNamara et al., 2016) while decreased function was found in the medial temporal cortex with citalopram (Seedat et al., 2004). Other medication and neuromodulation treatment studies showed increased medial prefrontal function in PTSD (Metz et al., 2019) (Philip et al., 2018). (Wittbrodt et al., 2020, 2021).

Understanding the mechanism by which treatments act in the brain is potentially useful in developing new treatments for PTSD (Bremner and Campanella, 2016). The purpose of this study was to examine brain responses to personalized traumatic scripts in women with childhood sexual abuse with and without PTSD, and to examine neural correlates of response to treatment with paroxetine. This study built on our prior study of the effects of paroxetine versus placebo on men and women with PTSD from a variety of causes women (Fani et al., 2011) by looking at the effects of double-blind paroxetine treatment versus placebo on a more specific sample of women with PTSD related childhood sexual abuse that was independent from the sample in our earlier study, and comparing them to women with childhood sexual abuse without PTSD. We hypothesized based on prior studies involving behavioral, neuromodulation, and medication treatment of PTSD, including our prior study with paroxetine, that PTSD would be associated with a decrease in medial prefrontal cortex and other brain areas involved in the DMN at baseline in comparison to non-PTSD and that paroxetine would result in a greater increase in medial prefrontal cortex and other DMN areas in women with PTSD treated with paroxetine versus those treated with placebo.

2. Materials and methods

2.1. Institutional review board

The Emory University institutional review board provided approval for this study which is posted on ClinicalTrials.gov (ClinicalTrials.gov # NCT01681849). Verbal / written informed consent was provided by all participants before enrollment.

2.2. Participants

The participants were healthy women between the ages of 18 and 75 with a history of childhood sexual abuse. Women were included with childhood sexual abuse that began at age 13 or before, involving unwanted and repeated penetration or oral sex. Abused women were divided in those with and without PTSD. All women underwent brain imaging at baseline, and the women with PTSD were randomized to a double-blind study of paroxetine versus placebo followed by repeat brain imaging at three months while still on study medication. Fig. 1 presents the Consolidated Standards of Reporting Trials (CONSORT) for this study. Of the 135 individuals assessed for eligibility, 44 were excluded based on eligibility criteria and 91 consented to participate including 57 PTSD patients and 34 non-PTSD traumatized controls. Seven of the PTSD patients were excluded based on further screening and 22 lost interest or were lost to followup. Twenty-eight PTSD patients were randomized to paroxetine or placebo and scanned at baseline (15 paroxetine, 13 placebo). Post treatment scans were obtained on seven paroxetine and six placebo PTSD patients. Seventeen of the non-PTSD trauma controls lost interest or were lost to followup and 17 underwent the imaging protocol.

The diagnosis of schizophrenia, schizoaffective disorder, bipolar disorder, bulimia, or anorexia, as defined by The Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR) (APA, 2000), excluded individuals from participating. Further exclusion criteria were current pregnancy, traumatic brain injury, meningitis, or evidence or history of serious medical or neurological illness. Trained staff administered the Structured Interview for the Diagnostic and Statistical Manual of Mental Disorders (SCID) (First and Gibbon, 2004) for psychiatric diagnosis. The Clinician-Administered PTSD Scale for DSM-IV-TR (CAPS) was used to measure the severity of PTSD (Blake et al., 1995). The SCID and CAPS interviews were used to determine that PTSD was primarily related to childhood abuse. The Subjective Units of Distress Scale (SUDS) was used to measure behavioral responses to traumatic scripts in the scanner (Wolpe and Lazarus, 1966). Participants also completed the Early Trauma Inventory-Self Report-Short Form (ETI-SR-SF) (Bremner et al., 2007).

2.3. Study design

At the initial screening, a trained member of the research staff conducted a psychiatric interview and facilitated a written traumatic history of the participant. From there, the written traumatic experiences were converted into a 60-second script which was recorded by a member of the research team (Bremner et al., 1999a). Women with PTSD were randomized to receive three months of double-blind paroxetine 10–40 mg variable dose given once per day or placebo. Dosage was adjusted to be within the efficacious range based on prior studies in PTSD and to minimize side effects (Tucker et al., 2001). The study blinded assignment was kept by a research pharmacist who was not involved in the study.

2.4. Neuroimaging and analysis

During the second visit, participants underwent a high-resolution positron emission tomography (HR-PET) scan session consisting of auditory delivery of a series of both neutral and traumatic scripts. There were two neutral followed by two traumatic scripts delivered in fixed order. The neutral scripts were descriptions of nature designed to

induce neutral-to-positive affective responses. Scripts were recorded by a female voice. The scripts were two minutes in length and divided into two scripts one minute in length to correspond to the scanning time of the two trauma related scans. All scripts were delivered using headphones as the participant lay supine in the HR-PET scanner. The scripts were delivered while the participant rested with eyes open. Twenty mCi of radiolabeled water ($[^{15}O]H_2O$) produced by an on-site cyclotron was injected intravenously five seconds before the beginning of the script followed by a 90 second HR-PET scan of the brain to measure brain blood perfusion. Regional cerebral blood flow was measured using the High Resolution Research Tomograph (HRRT) brain dedicated HR-PET device (*CTI, Knoxville, TN*) (Schmand et al., 1999). Following all scans, participants were asked to complete the Subjective Units of Distress Scale, rating their level of distress from 0 (no distress) to 100 (extreme distress).

HR-PET image analysis was completed similar to previous research (Wittbrodt et al., 2019) within the statistical parametrical mapping (SPM12; www.fil.ion.ucl.ac.uk/spm) suite. Scans were pre-processed by spatially normalizing to a mean intensity image across individual scans, transformed into a common anatomical space (SPM PET Template), smoothed using a three-dimensional Gaussian filter at 5-mm full width half maximum, and then normalized to whole-brain activity. First level (individual) models were computed using the neutral script and traumatic script conditions with the factor of scan pairs. The first level model was grand mean scaled, estimated, and contrasts computed for activation (trauma scripts – neutral scripts) and deactivation (neutral scripts – trauma scripts).

2.5. Statistical analysis

Comparison between groups was completed using a two-sample *t*-test or Mann-Whitney-Wilcoxon test for continuous and Fisher's exact test for discrete variables, respectively. For assessments during the scripts, linear mixed-effects models were fit to the data (lme4; cran.r-project.org/web/packages/lme4) using between-participant fixed effects of PTSD versus non-PTSD group and within-participant fixed effects of script type (neutral, traumatic), random effect of participant, and baseline value as a covariate.

Regional brain blood flow changes between PTSD and non-PTSD and paroxetine versus placebo at baseline and after treatment were encoded similar to previous recommendations (Gläscher and Gitelman, 2008) resulting in t-statistic brain maps. For all types of analyses, a threshold of $p < 0.005$ (uncorrected) and a minimum voxel size of eleven was employed to minimize Type I and Type II errors in neuroimaging research (Lane et al., 1997). Significant cluster peaks were identified using the distance from the anterior commissure with x, y, and z coordinates transformed from Montreal Neurological Institute (MNI) space to those of the Talairach stereotaxic atlas (Talairach and Tournoux, 1988). Cluster peaks were identified using Brodmann Areas (BA) from the Talairach daemon (www.talairach.org). The *a priori* α level for non-brain imaging data was chosen at 0.05. All data are presented as mean ± SD.

3. Results

3.1. Demographics

Demographic variables including age, years of education, and body mass index were similar between PTSD and non-PTSD women. Early trauma exposure severity measured with the ETI-SR-SF was slightly higher in the PTSD group (Table 1). Early trauma, antidepressant usage and PTSD symptom levels at baseline are presented in Table 1. Comorbid diagnoses based on the SCID are presented in Table 2.

3.2. Psychometric measures during traumatic scripts

Exposure to traumatic scripts during the imaging session resulted in significant increases in distress measured by the SUDS (baseline to posttraumatic scripts) in both the traumatized PTSD (40 (33 SD) to 63 (37 SD), $p = 0.007$) and non-PTSD women (25 (23 SD) to 47 (29 SD), $p = 0.016$). There were no significant differences in the magnitude of increase in distress with traumatic scripts between traumatized women with and without PTSD.

3.3. Neuroimaging

Traumatized non-PTSD women showed activation with traumatic scrips in pre- and postcentral gyrus, frontal cortex (BA 9, 10, 45), precuneus, anterior cingulate (BA 32), cingulate (BA 31) and insula (Table 3). Decreases occurred in parts of the parietal and frontal cortex (Table 4). PTSD women also showed activation in pre- and post-central gyrus, cuneus, and frontal cortex (Table 5). Decreases were seen in fusiform gyrus, parahippocampus, and parts of the parietal cortex and frontal cortex (Table 6, Fig. 2). PTSD women had greater increases with traumatic scripts compared to non-PTSD in parts of the cingulate, frontal cortex and lentiform nucleus (Table 7). Non-PTSD women activated more (there was a relative decrease in activation in PTSD) in cerebellum, posterior cingulate (BA 30), parahippocampal gyrus, thalamus, parietal cortex, cuneus, precuneus, fusiform gyrus, left insula and temporal lobe (Table 8).

3.4. Effects of treatment on PTSD symptoms, reactivity and brain function

Three months of treatment of women with PTSD resulted in a significant reduction in symptoms as measured by the CAPS for the paroxetine group (31 (10 SD) baseline versus 20 (10) post-treatment ($p<0.05$)) but not the placebo group (30 baseline (5 SD) versus 25 posttreatment (6 SD)). After three months of treatment there were not significant increases in distress with traumatic scripts in either the PTSD paroxetine group (16 (27 SD) to 51 (39 SD), $p = 0.054$) or the PTSD placebo group (14 (23 SD) to 32 (38 SD), $p = 0.2$). There were no significant differences in the magnitude of increase in distress with traumatic scripts between the PTSD paroxetine and PTSD placebo groups. With treatment of PTSD patients there were greater increases in the anterior cingulate (BA 24, 32) with exposure to traumatic scripts in the paroxetine compared to the placebo group (Fig. 3). Increases were also seen in the precuneus, middle and superior frontal gyri (BA 46, 10) and temporal cortex (BA 22, 39).

4. Discussion

Women with childhood abuse-related PTSD in this study exposed to personalized traumatic scripts showed decreased function in parahippocampal gyrus, precuneus, cuneus, fusiform gyrus, insula, thalamus, posterior cingulate, dorsolateral prefrontal, parietal and temporal cortex compared to abused non-PTSD women. Treatment with paroxetine compared to placebo resulted in an improvement in symptoms of PTSD and increased function in anterior cingulate/medial prefrontal cortex, precuneus, dorsolateral prefrontal and temporal cortex.

The findings in this study are consistent with prior neuroimaging studies implicating several networks of interconnected brain areas with altered functional interconnectedness that respond to treatment in PTSD (Etkin et al., 2019). These include studies showing decreased connectivity in PTSD in the default mode network (DMN), a network of brain regions that are active when the brain is not engaged, including ventromedial prefrontal cortex (vmPFC), dorsomedial PFC (dmPFC), posterior cingulate cortex (PCC), precuneus, medial temporal lobe, and medial and lateral parietal cortices,(Akiki et al., 2017; Jin et al., 2017; Koch et al., 2016; Lei et al., 2015; Maron-Katz et al., 2020; Miller et al., 2017a, 2017b; Nicholson et al., 2020; Reuveni et al., 2016; Russman Block et al., 2017; Sripada et al., 2012b; Zhang et al., 2015; Zhu et al., 2019) in addition to related areas involved in visual processing including cuneus and fusiform gyrus as well as the hippocampus. Prior studies in PTSD have shown decreased function in precuneus (Geuze et al., 2008a; Lanius et al., 2002; Werner et al., 2009) and fusiform gyrus (Cwik et al., 2017; Osuch et al., 2001), and decreased connectivity in precuneus (Bluhm et al., 2009; Ke et al., 2017; Lanius et al., 2010; Liu et al., 2017; Yan et al., 2013; Yin et al., 2011), cuneus(Gong et al., 2014) and posterior cingulate (Bluhm et al., 2009; Ke et al., 2017; Miller et al., 2017a, 2017b; Qin et al., 2012) Studies also showed decreased connectivity between precuneus and posterior cingulate (Bluhm et al., 2009) as well as decreased connectivity between precuneus and other DMN brain regions. (Bluhm et al., 2009; Ke et al., 2017; Lanius et al., 2010; Liu et al., 2017; Yan et al., 2013; Yin et al., 2011) In addition to visual processing, which plays a critical role in assessment of threat, the precuneus plays a role in sense self, which may be relevant to disturbances in autobiographical memory in PTSD,(Germain et al., 2013; Geuze et al., 2008a; Klein and Ehlers, 2008; McNally et al., 1994; St Jacques et al., 2011, 2013; Thome et al., 2020) as well as lability of mood and other clinical aspects of PTSD. Fusiform gyrus is involved in memory for faces, which plays an obvious role in perception of threat. (Gur et al., 2002; Haxby et al., 1996)

PTSD was associated with decreases in other brain areas including dorsolateral prefrontal, parietal, and temporal cortex that were also responsive to treatment. Previous studies have shown decreases in parietal cortex function (Bremner et al., 1999a; Chung et al., 2006; Ke et al., 2016; Morey et al., 2008; Rauch et al., 1996; Sakamoto et al., 2005; Shin et al., 1997, 1999) and connectivity (Disner et al., 2018; Fu et al., 2019; Gong et al., 2014; Shaw et al., 2002; Weng et al., 2019; Zhang et al., 2017, 2016c; Zhu et al., 2015) in PTSD. The parietal cortex plays an important role in conceptualization of the self in space and time as well interpretation of visual information, both key to the stress response (Cornwell et al., 2007; Jonides et al., 1993; Luo et al., 2007; Selemon and Goldman-Rakic, 1988; van Rooij et al., 2015; Weber et al., 2005) Decreased function seen in PTSD in the temporal cortex (Chung

et al., 2006; Geuze et al., 2008b; Werner et al., 2009), as well as connectivity,(Shang et al., 2014) may be relevant to alterations in memory in PTSD. Problems with memory and concentration may also be driven by decreased function in the dorsolateral prefrontal cortex (middle and superior frontal gyrus (BA 46, 10). (Aupperle et al., 2012; Cisler et al., 2015b; Cohen et al., 2013; Cwik et al., 2017; Hou et al., 2007; Morey et al., 2009; Sakamoto et al., 2005; Scheibel et al., 2015; Shin et al., 1997, 1999, 2004; Shin et al., 2001; Werner et al., 2009) or connectivity between this area and other brain regions in DMN. (Olivé et al., 2018; Olson et al., 2019; Reuveni et al., 2016) The insula is connected to these regions in salience networks and altered connectivity has been seen in this region as well. (Birn et al., 2014; Etkin et al., 2019; Harricharan et al., 2020; Ke et al., 2018; Koch et al., 2016; Liu et al., 2017; Nicholson et al., 2020; Sripada et al., 2012a; Tursich et al., 2015; Vanasse et al., 2019; Yin et al., 2011; Zhang et al., 2016b) The current study showed a decrease in function in several DMN and visual association regions that similar to prior studies of acoustic stimulation (Lee et al., 2019) and paroxetine (Fani et al., 2011; MacNamara et al., 2016) as treatments for PTSD reversed with treatment.

The current findings of decreased function in the hippocampus and parahippocampal gyrus are similar to other studies in PTSD. These studies showed decreased function (Bremner et al., 1999a; Cisler et al., 2015a, 2015b; Kim et al., 2012; Osuch et al., 2008; Yehuda et al., 2010, 2009), and connectivity in the hippocampus (Abdallah et al., 2017; Admon et al., 2013; Bluhm et al., 2009; Chen and Etkin, 2013; Chen et al., 2019; Jin et al., 2014; Lazarov et al., 2017; Malivoire et al., 2018; Metz et al., 2019; Miller et al., 2017a; Rabellino et al., 2018a, 2018b; Stevens et al., 2014; Zhang et al., 2017), as well as decreased function (Werner et al., 2009) and connectivity (Jin et al., 2014; Misaki et al., 2018) in the parahippocampal gyrus in PTSD. The hippocampus mediates consolidation of short term memory or explicit memory into long term memory. (Zola-Morgan and Squire, 1990) and is sensitive to stress (Sapolsky, 2003). The parahippocampal gyrus also plays an important role in memory. (Zola-Morgan et al., 1989) In addition to processing explicit memory the hippocampus, like the medial prefrontal cortex, plays a role in fear extinction and is involved in response to context-specific traumatic reminders (Ritov et al., 2014). In PTSD, a failure of hippocampal activation is commonly observed during trauma reminders (Bremner et al., 1999a), potentially as a result of alterations in this brain area (Karl et al., 2006) with associated declarative memory deficits (Samuelson, 2011). Additionally, PTSD disrupts a memory network consisting of the hippocampus, anterior cingulate, and orbitofrontal cortex, that is employed in the recall of emotionally valenced words (Bremner et al., 2003). Alterations in verbal declarative memory of the type mediated by the hippocampus and parahippocampus are associated with PTSD.(Bremner and Vermetten, 2012) Prior studies showed an improvement in verbal declarative memory(Fani et al., 2009; Vermetten et al., 2003) and increase in hippocampal volume. (Vermetten et al., 2003) following treatment with paroxetine in PTSD

Replicating prior studies, treatment with paroxetine resulted in an increase in anterior cingulate/medial prefrontal (BA 24, 32) function in women with PTSD. Multiple studies have shown a decrease in anterior cingulate/medial prefrontal function (Bluhm et al., 2012; Bremner et al., 1999a, 1999b, 2004; Britton et al., 2005; Clausen et al., 2017b; Dahlgren et al., 2018; Elzinga and Bremner, 2002; Fonzo et al., 2010a; Frewen et al., 2012; Gold

et al., 2011; Grupe et al., 2020; Hopper et al., 2007; Hou et al., 2007; King et al., 2009; Lanius et al., 2001, 2004, 2003; Liberzon et al., 2003, 1999; Lindauer et al., 2004; New et al., 2009; Offringa et al., 2013; Phan et al., 2006; Pissiota et al., 2002; Shin et al., 1997, 1999, 2004; Shin et al., 2001, 2005; St Jacques et al., 2011, 2013; Yang et al., 2004) and connectivity (Akiki et al., 2018; Amad et al., 2019; Birn et al., 2014; Clausen et al., 2017b; Disner et al., 2018; Gong et al., 2014; Jin et al., 2014; Kennis et al., 2015; Liu et al., 2016; Misaki et al., 2018; Sadeh et al., 2015) in PTSD. Treatment with paroxetine (Fani et al., 2011; Zhu et al., 2015) transcutaneous vagal nerve stimulation (Wittbrodt et al., 2021) or hydrocortisone (Metz et al., 2019) in PTSD patients resulted in an increase in function in this region. Decreased function in this area may underlie deficient emotional regulation associated with traumatic remembrance (Etkin and Wager, 2007) due to a failure of inhibition of fear memories in the amygdala (Etkin et al., 2006). Increased anterior cingulate/medial prefrontal activity would facilitate inhibition of the amygdala leading to improved emotional regulation. This area is also part of the dorsal cognitive division, which is part of a distributed attentional network with reciprocal connections with the lateral prefrontal cortex, parietal cortex, and motor areas (Bush et al., 2000; Devinsky et al., 1995) that acts as a storage buffer of information before executing action (Heilbronner and Hayden, 2016) which confers advantage in fear extinction and/or emotional reappraisal (Clausen et al., 2017a; Etkin et al., 2011). These results suggest that paroxetine may have effects on brain circuits that span multiple aspects of emotional regulation and cognitive function.

The study has several limitations. The sample size is small, especially for the treatment portion, with only seven paroxetine completers and eight placebo completers. This fact limits generalizability of the findings. Therefore, the results should be considered as preliminary. The sample was limited to women with childhood sexual abuse-related PTSD and may not be generalizable to other PTSD populations. The scripts involved comparison of trauma scripts to neutral scripts, which does not separate trauma specific effects from general heightened emotional arousal, therefore it is not possible to determine if the brain effects are specific to trauma or just emotional experience in PTSD patients.

In summary this study showed that PTSD related to childhood sexual abuse in women was associated with a decrease in activation in medial prefrontal, Default Mode Network (DMN) and visual processing areas, and that treatment with paroxetine resulted in an improvement in PTSD symptoms as well as increased function in DMN and visual processing areas in addition to medial prefrontal cortex/anterior cingulate. Future studies are indicated to replicate and extend these findings. Modification of brain areas mediating emotion, memory, and the stress response may have implications for understanding successful treatment responses in PTSD.

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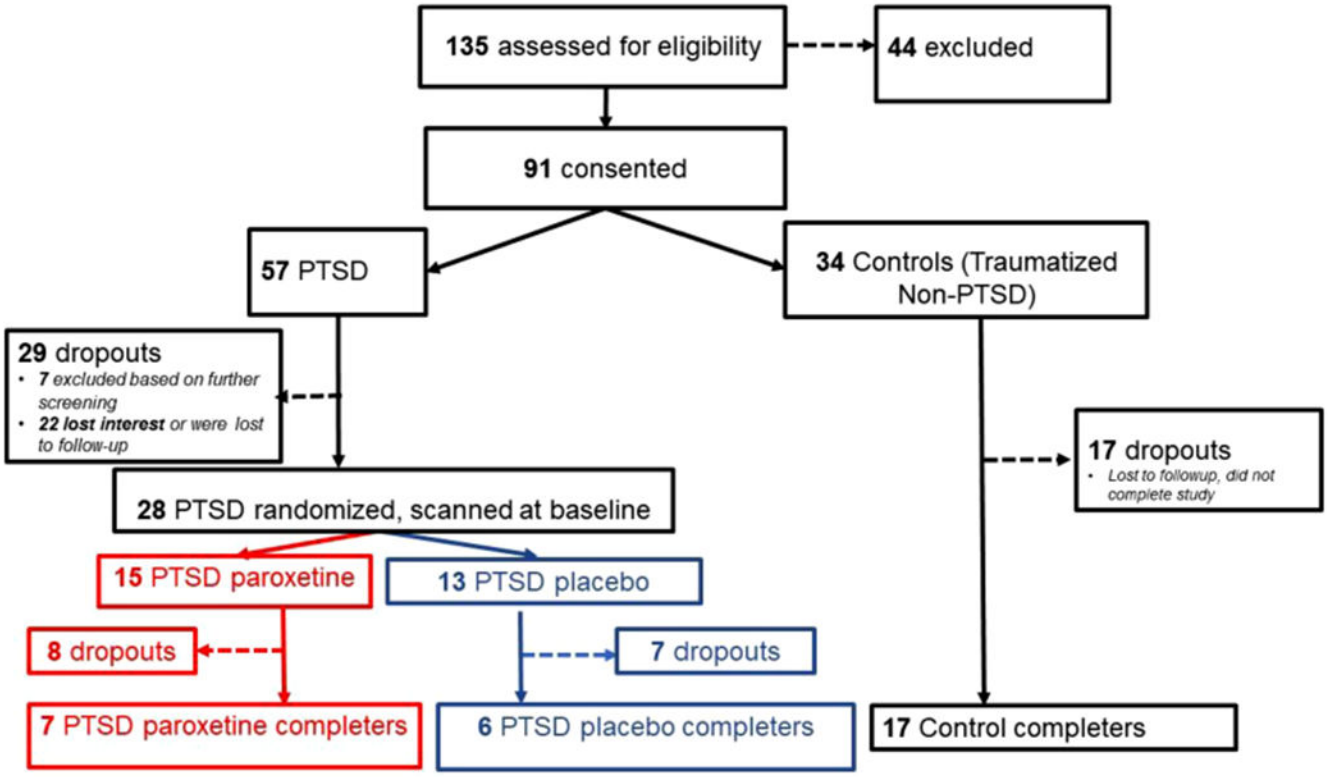

Fig. 1.

Consort diagram showing subject flow. Female subjects were screened and consented based on a history of early childhood sexual abuse and then divided into current PTSD and non-PTSD groups. Subsequent screening after consenting led to additional exclusions in the PTSD group and subjects who lost interest or were lost to followup in both groups. PTSD patients were then randomized to paroxetine or placebo and all subjects were scanned at baseline with personalized traumatic scripts and memory tasks. PTSD patients then underwent three months of double-blind treatment with paroxetine or placebo, during which time there were additional dropouts and patients lost to followup. Remaining patients were rescanned using the same protocol after three months.

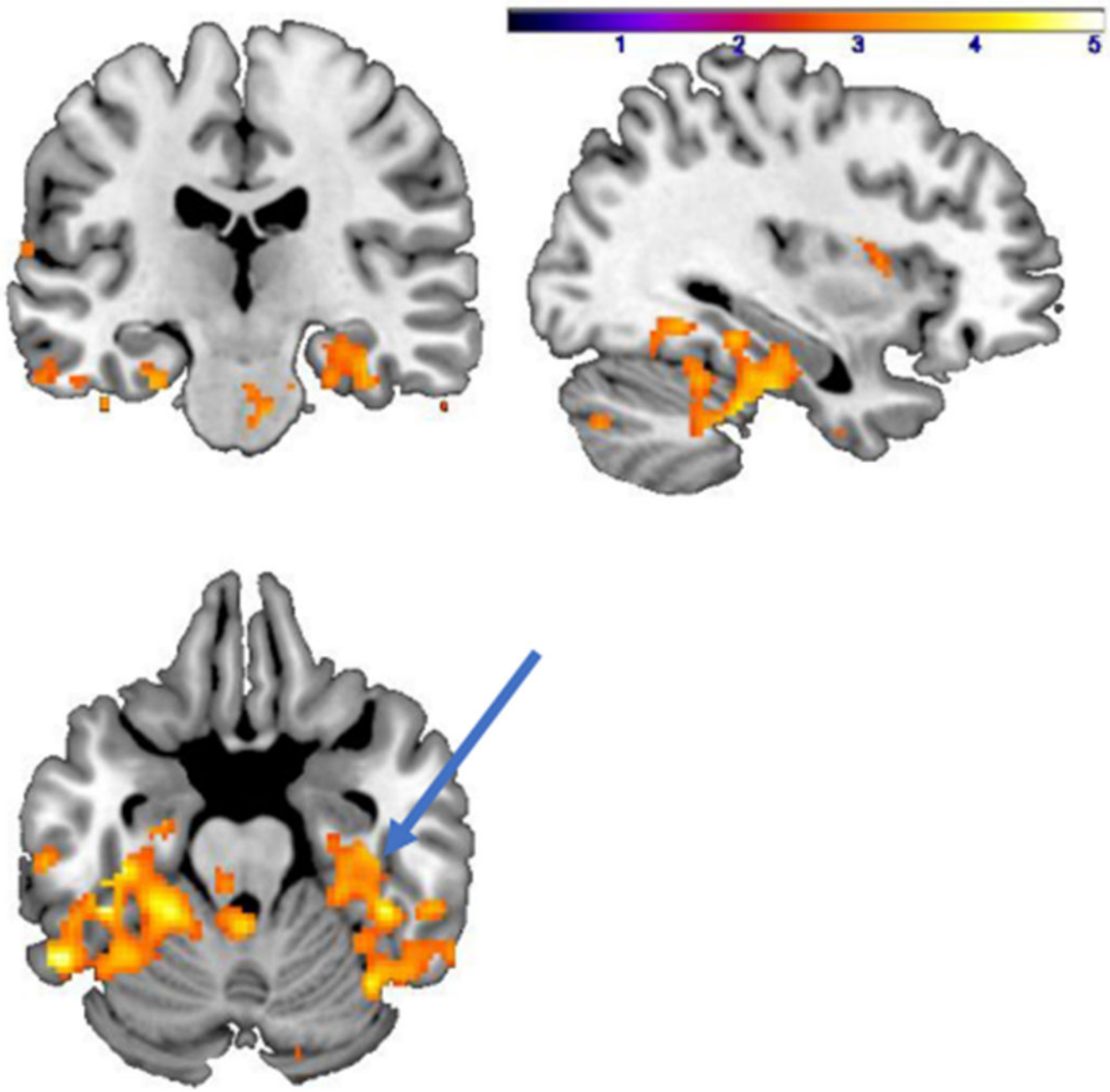

Fig. 2.

Areas representing decreased ($p < 0.005$) activation (yellow/orange) with traumatic scripts in PTSD patients at baseline (pre-treatment) compared to traumatized non-PTSD women showing decreased activation in right hippocampus (arrow). Color bar corresponds to z score.

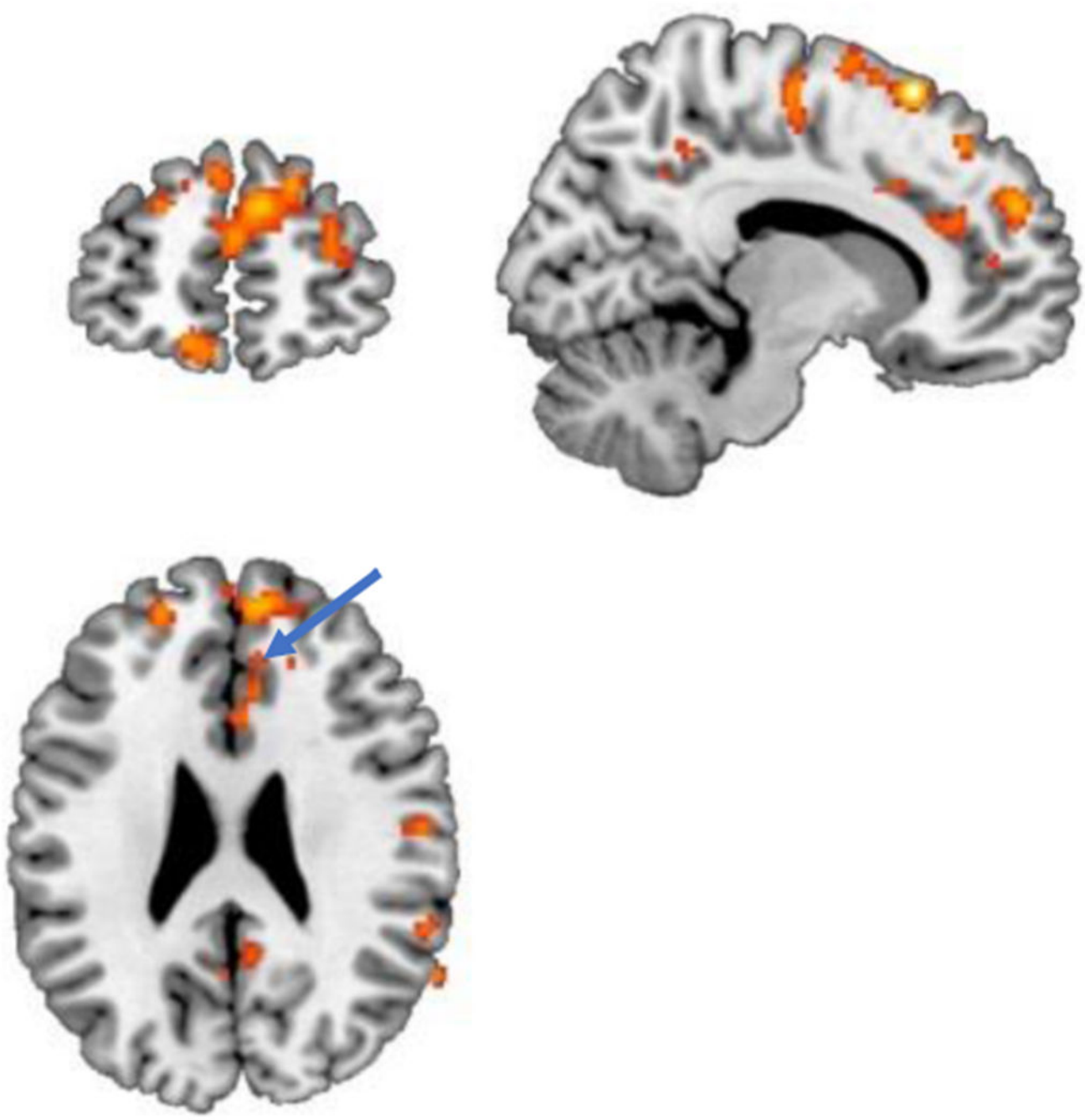

Fig. 3.

Areas representing greater ($p < 0.005$) activation (yellow/orange) with traumatic scripts in PTSD patients treated with paroxetine compared to PTSD patients treated with placebo after three months of treatment. There is increased activation in the anterior cingulate (BA 24, 32) (arrow). Increases were also seen in the precuneus, temporal cortex (BA 22, 39), and middle and superior frontal gyri (BA 46, 10).

Table 1

Co-Morbid Psychiatric Diagnoses in Traumatized Women with and without Posttraumatic Stress Disorder (PTSD).

Measure	PTSD (*n* = 28)	Non-PTSD (*n* 17)
Age (y)	43 ± 8	41 ± 10
Sex	28 F	17 F
BMI (kg·m^{-2}),	31.4 ± 9.3	31.6 ± 8.0
Race/Ethnicity		
White/Caucasian	12 (43%)	8 (47%)
Black/AA	12 (43%)	8 (47%)
White Hispanic	2 (7%)	1 (6%)
Black Hispanic	1 (4%)	0 (0%)
Asian/mixed	1 (4%)	0 (0%)
Years of Education	13 (3 SD)	14 (2 SD)
Marital Status		
Never Married	11 (39%)	6 (35%)
Married	5 (18%)	5 (29%)
Divorced	9 (32%)	6 (35%)
Separated	2 (7%)	0 (0%)
Widowed	1 (4%)	0 (0%)
Current Antidepressants	7 (25%)	5 (29%)
CAPS-Total Severity Score	71 ± 19	24 ± 11
ETI-SR-SF-Score	17 ± 5	12 ± 6

AA=African-American; CAPS = Clinician-Administered PTSD Scale; ETI-SR-SF = Early Trauma Inventory-Self Report Short Form; Data expressed as numbers with percentages or means with standard deviations (SD).

Table 2

Co-Morbid Psychiatric Disorders in Traumatized Women with and without Posttraumatic Stress Disorder.

Measure	PTSD (*n* = 28)	Non-PTSD (*n* = 17)
Major Depression		
Current	6 (21%)	1 (6%)
Past	5 (18%)	4 (24%)
Dysthymia		
Current	5 (18%)	1 (6%)
Past	0 (0%)	0 (0%)
Obsessive-Compulsive Disorder		
Current	1 (4%)	1 (6%)
Past	0 (0%)	0 (0%)
PTSD		
Current	28 (100%)	0 (0%)
Past	0 (0%)	4 (24%)
Social Phobia		
Current	1 (4%)	0 (0%)
Past	2 (7%)	1 (6%)
Panic Disorder with AG		
Current	2 (7%)	0 (0%)
Past	0 (0%)	2 (12%)
Panic Disorder without AG		
Current	1 (4%)	0 (0%)
Past	7 (25%)	4 (24%)
Generalized Anxiety Disorder		
Current	2 (7%)	0 (0%)
Past	0 (0%)	0 (0%)
Cocaine Dependence		
Current	0 (0%)	0 (0%)
Past	1 (4%)	0 (0%)
Alcohol Dependence		
Current	0 (0%)	0 (0%)
Past	1 (4%)	1 (6%)

AA=African-American; AG=Agoraphobia; CAPS = Clinician-Administered PTSD Scale; ETI-SR-SF = Early Trauma Inventory-Self Report Short Form; Data expressed in means.

Table 3

Increased Brain Activation with Traumatic Scripts in Traumatized Non-PTSD Women

Brain areas with significant ($p < 0.005$) activations during exposure to personalized trauma scripts in participants with posttraumatic stress disorder as measured with high-resolution positron emission tomography. Significant clusters are presented by size (number of voxels) and location (Brodmann area, cluster peak Talairach coordinates). Sub-cluster peaks are also identified.

Voxel Number	Brain Region	Brodmann Area	X	Y	Z	Z Score
1227	L. Transverse Temporal Gyrus	42	−58	−12	14	6.15
	L. Precentral Gyrus	4	−54	−14	28	5.52
	L. Postcentral Gyrus	3	−62	−12	28	5.49
749	R. Precentral Gyrus	4	62	−8	26	5.41
	R. Precentral Gyrus	6	58	−14	42	3.73
	R. Precentral Gyrus	4	48	−16	34	3.61
1223	R. Superior Frontal Gyrus	9	14	54	20	4.85
	L. Medial Frontal Gyrus	10	−2	60	20	4.51
97	L. Middle Temporal Gyrus	21	−60	−4	−20	5.20
	L. Inferior Temporal Gyrus	20	−58	−2	−30	3.15
438	R. Precuneus	31	16	−52	32	4.56
	R. Precuneus	31	6	−62	26	4.49
	R. Cingulate Gyrus	31	2	−52	28	3.53
80	L. Superior Temporal Gyrus	38	−40	16	−34	4.53
35	R. Inferior Frontal Gyrus	45	62	18	10	4.46
45	L. Declive		−16	−68	−18	4.45
21	L. Middle Temporal Gyrus	21	−50	6	−34	4.09
62	R. Superior Temporal Gyrus	38	50	14	−32	4.05
44	R. Fusiform Gyrus	20	64	−4	−26	3.89
	R. Middle Temporal Gyrus	21	60	4	−24	2.94
30	R. Inferior Temporal Gyrus	21	70	−16	−20	3.78
	R. Middle Temporal Gyrus	21	72	−22	−12	3.16
55	L. Insula	13	−34	−2	12	3.58
	L. Claustrum		−38	−10	4	2.79
53	R. Declive		20	−66	−22	3.48
19	R. Uvula		26	−84	−26	3.38
12	R. Superior Frontal Gyrus	8	16	42	46	3.31
17	R. Anterior Cingulate Gyrus	32	12	44	6	3.14
14	L. Cingulate Gyrus	31	−4	−38	36	3.08
11	L. Insula	22	−42	−26	0	2.87

Table 4

Decreased Brain Activation with Traumatic Scripts in Traumatized Non-PTSD Women

Brain areas with significant ($p < 0.005$) deactivations during exposure to personalized trauma scripts in participants with posttraumatic stress disorder as measured with high-resolution positron emission tomography. Significant clusters are presented by size (number of voxels) and location (Brodmann area, cluster peak Talairach coordinates). Sub-cluster peaks are also identified.

Voxel Number	Brain Region	Brodmann Area	X	Y	Z	Z Score
470	L. Middle Frontal Gyrus	6	−20	12	62	5.58
	L. Superior Frontal Gyrus	6	−22	2	70	4.38
	L. Middle Frontal Gyrus	6	−34	6	62	4.01
1200	R. Supramarginal Gyrus	40	56	−48	32	5.15
	R. Inferior Parietal Lobule	7	36	−58	48	4.92
	R. Inferior Parietal Lobule	40	42	−42	44	4.69
1121	R. Cerebellar Tonsil		42	−54	−44	4.99
	R. Inferior Temporal Gyrus	20	62	−52	−16	4.88
	R. Cerebellar Tonsil		46	−52	−34	4.69
633	R. Middle Frontal Gyrus	46	56	32	22	4.84
	R. Middle Frontal Gyrus	9	48	6	36	4.77
	R. Middle Frontal Gyrus	9	52	22	28	4.41
658	L. Superior Frontal Gyrus	10	−32	56	24	4.75
	L. Middle Frontal Gyrus	9	−48	30	30	4.36
	L. Middle Frontal Gyrus	8	−46	26	42	4.35
320	L. Superior Frontal Gyrus	10	−34	62	−6	4.68
	L. Superior Frontal Gyrus	11	−32	56	−14	4.06
	L. Superior Frontal Gyrus	11	−32	48	−16	3.81
669	L. Inferior Parietal Lobule	40	−58	−38	50	4.54
	L. Inferior Parietal Lobule	40	−44	−46	38	4.29
	L. Inferior Parietal Lobule	40	−44	−48	48	4.28
175	L. Thalamus		−10	−20	8	4.52
	L. Thalamus		−6	−12	6	3.55
	L. Thalamus		−4	−20	0	3.26
221	R. Middle Frontal Gyrus	6	30	−4	60	4.21
	R. Middle Frontal Gyrus	6	30	8	62	4.17
	R. Middle Frontal Gyrus	6	36	14	62	2.88
175	L. Extra-Nuclear	47	−34	22	−2	4.18
	L. Lentiform Nucleus		−24	18	0	3.42
566	L. Cingulate Gyrus	32	−6	30	28	4.17
	R. Medial Frontal Gyrus	8	8	22	46	3.92
	L. Medial Frontal Gyrus	8	−4	32	38	3.87
225	R. Caudate		18	16	4	4.04
	R. Insula	13	36	20	2	3.52
	R. Inferior Frontal Gyrus	47	36	28	−4	3.39

Voxel Number	Brain Region	Brodmann Area	X	Y	Z	Z Score
166	R. Declive		36	−64	−16	3.99
	R. Inferior Temporal Gyrus	37	48	−64	−4	3.26
	R. Declive		34	−58	−8	3.03
25	R. Precentral Gyrus	6	56	−2	50	3.92
14	R. Uncus	28	18	2	−30	3.86
42	L. Medial Frontal Gyrus	9	−4	42	28	3.66
	L. Anterior Cingulate		0	38	22	3.08
	L. Cerebellar Tonsil		−38	−48	−34	3.65
	L. Culmen		−28	−54	−16	3.61
	L. Cerebellar Tonsil		−38	−50	−44	3.46
87	R. Nodule		10	−52	−30	3.53
	R. Nodule		2	−54	−30	3.25
	R. Culmen		0	−60	−22	3.18
30	L. Cingulate Gyrus	31	−8	−10	44	3.50
32	R. Cingulate Gyrus	31	14	−22	42	3.49
16	R. Postcentral Gyrus	2	62	−24	48	3.49
54	R. Culmen		26	−40	−22	3.48
	R. Culmen		24	−48	−20	2.88
26	L. Culmen		−18	−34	−20	3.46
17	L. Cerebellar Tonsil		−22	−58	−44	3.45
53	R. Tuber		48	−76	−30	3.42
19	R. Fusiform Gyrus	19	52	−74	−14	3.42
19	R. Inferior Occipital Gyrus	18	40	−90	−10	3.36
61	L. Uvula		−6	−74	−32	3.33
	L. Inferior Semi-Lunar Lobule		−14	−76	−36	2.93
48	R. Transverse Temporal Gyrus	41	42	−24	14	3.27
14	L. Lentiform Nucleus		−28	2	0	3.27
32	L. Tuber		−34	−64	−30	3.26
19	L. Orbital Gyrus	47	−16	24	−22	3.26
20	L. Cuneus	17	−4	−96	2	3.25
27	R. Postcentral Gyrus	3	32	−30	62	3.23
41	R. Middle Temporal Gyrus	39	56	−54	10	3.22
	R. Middle Temporal Gyrus	21	60	−46	6	2.94
13	L. Precuneus	7	−16	−66	50	3.22
13	L. Middle Frontal Gyrus	6	−44	2	58	3.15
32	R. Paracentral Lobule	5	12	−36	54	3.15
	R. Paracentral Lobule	5	16	−32	48	3.07
21	L. Uvula		−10	−62	−34	3.14
24	R. Medial Frontal Gyrus	6	2	2	58	3.13
10	R. Culmen		32	−52	−20	3.12
47	L. Declive		−40	−68	−18	3.11

Voxel Number	Brain Region	Brodmann Area	X	Y	Z	Z Score
11	R. Middle Temporal Gyrus	21	58	−30	−4	3.11
14	L. Middle Frontal Gyrus	11	−40	38	−18	3.10
12	L. Paracentral Gyrus	6	−8	−30	52	3.08
14	L. Culmen		−44	−48	−24	3.08
13	L. Cuneus	18	−16	−94	10	3.07
19	R. Inferior Frontal Gyrus	45	48	14	14	3.05
33	L. Superior Parietal Lobule	7	−32	−60	46	3.04
	L. Superior Parietal Lobule	7	−28	−50	40	2.85
18	R. Middle Frontal Gyrus	10	40	62	2	2.96
18	L. Cingulate Gyrus	24	−10	4	48	2.96
11	R. Cuneus	17	8	−78	12	2.96
12	R. Inferior Temporal Gyrus	20	50	−16	−36	2.91
17	L. Fusiform Gyrus	20	−50	−34	−22	2.88
28	R. Middle Frontal Gyrus	10	46	48	18	2.81

Table 5

Increased Brain Activation with Traumatic Scripts in Women with PTSD

Brain areas with significant ($p < 0.005$) activations during exposure to personalized trauma scripts in participants with posttraumatic stress disorder as measured with high-resolution positron emission tomography. Significant clusters are presented by size (number of voxels) and location (Brodmann area, cluster peak Talairach coordinates). Sub-cluster peaks are also identified.

Voxel Number	Brain Region	Brodmann Area	X	Y	Z	Z Score
881	L. Precentral Gyrus	4	−52	−16	26	5.34
	L. Postcentral Gyrus	43	−66	−12	16	5.22
	L. Precentral Gyrus	6	−64	−4	22	4.33
705	R. Precentral Gyrus	6	64	−10	30	5.17
	R. Postcentral Gyrus	3	50	−16	36	5.04
	R. Postcentral Gyrus	43	64	−10	20	4.09
89	R. Cuneus	19	10	−90	40	4.34
	R. Cuneus	19	6	−86	34	3.69
11	L. Inferior Frontal Gyrus	47	−52	30	−4	4.24
46	R. Angular Gyrus	39	54	−70	36	4.16
57	R. Cingulate Gyrus	31	2	−52	24	3.80
56	R. Sup. Frontal Gyrus	9	20	44	36	3.79
57	L. Medial Frontal Gyrus	10	−6	60	12	3.66
	L. Medial Frontal Gyrus		−16	58	0	3.01
102	L. Precuneus	7	−8	−82	52	3.29
	R. Precuneus	7	2	−78	46	3.11
36	L. Superior Frontal Gyrus	8	−16	34	44	3.42
37	L. Precuneus	7	0	−58	40	3.36
18	R. Sup. Frontal Gyrus	10	22	48	−8	3.32
22	L. Angular Gyrus	39	−46	−72	38	3.23
17	L. Anterior Cingulate	32	−10	38	10	3.19
58	R. Medial Frontal Gyrus	10	18	56	6	3.19
	R. Medial Frontal Gyrus	10	16	62	0	3.11
15	R. Medial Frontal Gyrus	10	6	50	−10	3.14
13	R. Declive		20	−62	−22	3.02
12	L. Sup. Temporal Gyrus	38	−36	0	−10	2.93

Table 6

Decreased Brain Activation with Traumatic Scripts in Women with PTSD

Brain areas with significant ($p < 0.005$) deactivations during exposure to personalized trauma scripts in participants with posttraumatic stress disorder as measured with high-resolution positron emission tomography. Significant clusters are presented by size (number of voxels) and location (Brodmann area, cluster peak Talairach coordinates). Sub-cluster peaks are also identified.

Voxel Number	Brain Region	Brodmann Area	X	Y	Z	Z Score
11,124	R. Fusiform Gyrus	20	56	−38	−24	5.48
	L. Culmen		−38	−54	−24	5.40
	R. Tuber		56	−50	−24	5.17
1686	L. Middle Frontal Gyrus	8	−36	38	40	5.46
	L. Superior Frontal Gyrus	9	−32	50	30	5.09
	L. Middle Frontal Gyrus	10	−40	54	8	4.92
1344	R. Inferior Parietal Lobule	40	62	−36	44	5.13
	R. Inferior Parietal Lobule	40	46	−38	44	4.64
	R. Inferior Parietal Lobule	40	64	−40	36	4.04
721	R. Middle Frontal Gyrus	46	48	32	16	5.04
	R. Middle Frontal Gyrus	10	36	62	−12	4.78
	R. Middle Frontal Gyrus	10	42	56	−10	4.56
363	L. Cerebellar Tonsil		−2	−54	−34	5.01
	L. Culmen		−2	−46	−20	3.47
	R. Cerebellar Tonsil		16	−50	−38	3.25
299	R. Superior Frontal Gyrus	8	30	28	56	4.76
	R. Superior Frontal Gyrus	8	30	44	44	4.01
	R. Middle Frontal Gyrus	6	30	8	64	3.78
55	L. Middle Temporal Gyrus	21	−44	−34	−4	4.67
519	L. Insula	13	−32	22	0	4.60
	L. Lentiform Nucleus		−22	16	−8	4.00
	L. Caudate		−14	18	6	3.71
651	L. Precuneus	19	−28	−66	42	4.43
	L. Inferior Parietal Lobule	40	−50	−42	32	4.32
	L. Supramarginal Gyrus	40	−60	−48	32	3.94
182	R. Inferior Frontal Gyrus	9	48	10	26	4.29
	R. Inferior Frontal Gyrus	45	56	12	22	3.24
379	L. Middle Occipital Gyrus	18	−18	−86	12	4.28
	L. Middle Occipital Gyrus	19	−32	−88	16	3.97
	L. Middle Occipital Gyrus	19	−32	−84	8	3.89
422	R. Inferior Frontal Gyrus	47	34	24	−8	4.28
	R. Inferior Frontal Gyrus	47	44	18	0	4.12
	R. Inferior Frontal Gyrus	47	34	26	0	4.00
79	L. Uvula		−10	−74	−32	4.28
75	R. Posterior Cingulate	30	18	−56	12	4.13

Voxel Number	Brain Region	Brodmann Area	X	Y	Z	Z Score
305	R. Superior Frontal Gyrus	8	4	16	48	3.89
	R. Superior Frontal Gyrus	6	6	8	50	3.64
	L. Medial Frontal Gyrus	8	0	22	44	3.38
61	L. Thalamus		−4	−2	4	3.89
91	L. Precentral Gyrus	6	−42	−6	62	3.82
	L. Postcentral Gyrus	3	−44	−20	64	3.26
	L. Precentral Gyrus	4	−48	−10	58	2.95
33	L. Uncus	20	−22	−2	−42	3.82
	L. Uncus	36	−18	−8	−36	2.98
23	L. Inferior Temporal Gyrus	20	−38	−2	−40	3.78
55	L. Rectal Gyrus	11	−10	34	−24	3.74
18	R. Inferior Temporal Gyrus	20	38	−6	−46	3.72
35	R. Parahippocampal Gyrus	30	24	−36	4	3.71
19	R. Caudate		18	8	16	3.61
33	R. Superior Parietal Lobule	7	38	−66	52	3.56
22	R. Lentiform Nucleus		20	−8	−2	3.46
56	R. Uvula		16	−78	−24	3.44
48	L. Middle Temporal Gyrus	21	−50	−12	−14	3.42
18	R. Superior Temporal Gyrus	38	34	14	−44	3.42
48	R. Orbital Gyrus	47	18	18	−26	3.42
10	L. Insula	13	−32	−26	14	3.32
29	R. Insula	13	44	−20	12	3.31
31	L. Inferior Parietal Lobule	40	−52	−28	24	3.31
14	R. Precentral Gyrus	6	52	−2	56	3.31
74	R. Superior Temporal Gyrus	22	52	−4	6	3.31
	R. Superior Temporal Gyrus	22	46	−10	−2	3.26
10	R. Precentral Gyrus	6	36	−10	70	3.29
35	R. Middle Temporal Gyrus	21	62	−6	−12	3.28
20	R. Superior Temporal Gyrus	22	60	6	−4	3.27
25	L. Inferior Parietal Lobule	40	−62	−36	22	3.25
	L. Superior Temporal Gyrus	42	−62	−30	12	2.91
28	R. Precuneus	31	28	−76	22	3.03
14	R. Thalamus		8	−14	8	2.95
12	R. Superior Frontal	11	26	50	−18	2.94
28	L. Cingulate Gyrus	24	−6	−14	42	2.93
23	L. Thalamus		−2	−16	2	2.9
	L. Thalamus		−10	−18	8	2.88
16	L. Middle Occipital Gyrus	19	−44	−76	16	2.93
	L. Middle Occipital Gyrus	19	−42	−76	8	2.78
11	R. Middle Frontal Gyrus	11	32	36	−20	2.93
28	L. Cingulate Gyrus	32	−6	26	32	2.92

Voxel Number	Brain Region	Brodmann Area	X	Y	Z	Z Score
10	R. Middle Frontal Gyrus	10	26	62	22	2.92

Table 7

Greater Increases in Blood Flow with Traumatic Scripts in Women with PTSD versus Traumatized Non-PTSD Women

Brain areas with significant ($p < 0.005$) activations during exposure to personalized trauma scripts in participants with posttraumatic stress disorder as measured with high-resolution positron emission tomography. Significant clusters are presented by size (number of voxels) and location (Brodmann area, cluster peak Talairach coordinates). Sub-cluster peaks are also identified.

Voxel Number	Brain Region	Brodmann Area	X	Y	Z	Z Score
35	R. Lentiform Nucleus		20	−6	16	3.99
	R. Lentiform Nucleus		26	−12	14	3.33
55	R. Anterior Cingulate	32	12	48	−8	3.69
25	L. Precentral Gyrus	4	−48	−6	42	3.64
41	L. Anterior Cingulate	32	−2	44	12	3.47
18	L. Supramarginal Gyrus	40	−62	−52	24	3.41
25	R. Middle Frontal Gyrus	8	50	14	40	3.41
13	L. Medial Frontal Gyrus	25	−2	8	−16	3.39
30	L. Anterior Cingulate	24	−2	26	18	3.29
	L. Cingulate Gyrus	32	−4	30	26	2.87
12	R. Superior Frontal Gyrus	11	24	58	−20	3.29
21	R. Supramarginal Gyrus	40	58	−46	34	3.28
10	R. Precuneus	19	46	−78	40	3.19
12	L. Caudate		−12	−4	14	3.14
17	R. Subcallosal Gyrus	25	12	24	−10	3.09
20	L. Medial Frontal Gyrus	10	−12	64	−6	2.96
17	L. Superior Frontal Gyrus	11	−30	50	−16	2.95
15	L. Middle Frontal Gyrus	8	−24	28	42	2.94

Table 8

Greater Decreases in Blood Flow with Traumatic Scripts in Women with PTSD Versus Traumatized Non-PTSD Women

Brain areas with significant ($p < 0.005$) deactivations during exposure to personalized trauma scripts in participants with posttraumatic stress disorder as measured with high-resolution positron emission tomography. Significant clusters are presented by size (number of voxels) and location (Brodmann area, cluster peak Talairach coordinates). Sub-cluster peaks are also identified.

Voxel Number	Brain Region	Brodmann Area	X	Y	Z	Z Score
111	R. Inferior Semi-Lunar Lobule		34	−76	−38	4.75
	R. Pyramis		40	−68	−34	3.56
53	L. Tuber		−54	−52	−22	3.98
	L. Fusiform Gyrus	20	−52	−42	−22	3.04
74	R. Fusiform Gyrus	36	44	−38	−20	3.82
	R. Fusiform Gyrus	20	56	−38	−26	3.68
76	L. Declive		−20	−68	−18	3.69
18	L. Insula	13	−32	20	12	3.63
32	L. Insula	22	−44	−28	−4	3.59
61	L. Culmen		−2	−38	−22	3.56
16	R. Inferior Frontal Gyrus	11	22	24	−20	3.47
80	R. Parahippocampal Gyrus		30	−22	−16	3.47
	R. Parahippocampal Gyrus	36	30	−30	−14	3.04
	R. Culmen		32	−32	−22	2.84
31	L. Claustrum		−32	2	10	3.41
54	R. Inferior Temporal Gyrus	20	66	−12	−26	3.39
17	R. Culmen		16	−24	−26	3.37
22	R. Declive		38	−60	−22	3.37
43	R. Cerebellar Tonsil		36	−38	−34	3.33
21	L. Middle Temporal Gyrus	21	−54	−12	−12	3.29
14	R. Inferior Parietal Lobule	40	46	−34	40	3.29
56	L. Superior Temporal Gyrus	38	−38	14	−36	3.28
	L. Superior Temporal Gyrus	38	−42	16	−28	2.89
13	R. Middle Temporal Gyrus	21	60	6	−18	3.26
24	L. Superior Temporal Gyrus	22	−48	−4	4	3.25
48	R. Posterior Cingulate	30	22	−62	6	3.22
14	R. Middle Temporal Gyrus	22	52	−36	6	3.17
12	R. Cuneus	19	10	−90	24	3.16
14	R. Claustrum		30	12	6	3.15
15	R. Precuneus	31	6	−70	20	3.14
	R. Cuneus	18	10	−74	26	2.67
19	R. Inferior Semi-Lunar Lobule		2	−60	−40	3.09
	L. Cerebellar Tonsil		−4	−54	−36	2.69
37	R. Lingual Gyrus	18	22	−76	−8	3.06

Voxel Number	Brain Region	Brodmann Area	X	Y	Z	Z Score
15	L. Cuneus	17	−6	−92	6	3.01
11	L. Precentral Gyrus	6	−58	−6	36	2.99
10	L. Culmen		−36	−46	−20	2.89
10	L. Fusiform Gyrus	37	−44	−54	−14	2.89
10	L. Parahippocampal Gyrus	36	−22	−40	−10	2.89
20	R. Inferior Parietal Lobule	40	62	−30	36	2.88
	R. Inferior Parietal Lobule	40	58	−26	30	2.79
14	R. Lentiform Nucleus		16	−10	2	2.86
15	L. Thalamus		−16	−28	4	2.85
12	R. Middle Temporal Gyrus	20	42	4	−44	2.83