Functional reorganization of neural networks during repeated exposure to the traumatic memory in posttraumatic stress disorder: An exploratory fMRI study

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Abstract

Background: Repeated exposure to the traumatic memory (RETM) is a common component of treatments for posttraumatic stress disorder (PTSD). This treatment is based on a fear extinction model; however, the degree to which this treatment actually engages and modifies neural networks mediating fear extinction is unknown. Therefore, the purpose of the current exploratory study was to define the dynamic changes in neural processing networks while participants completed a novel adaptation of RETM.

Method: Participants were adult women (\(N = 16\)) with PTSD related to physical or sexual assault. Prior to scanning, participants provided written narratives of a traumatic event related to their PTSD as well as a neutral control event. RETM during fMRI consisted of 5 sequential presentations of the blocked narrative types, lasting three minutes each. Self-reported anxiety was assessed after each presentation.

Results: Relative to changes in functional connectivity during the neutral control script, RETM was associated with strengthened functional connectivity of the right amygdala with the right hippocampus and right anterior insular cortex, left amygdala with the right insular cortex, medial PFC with right anterior insula, left hippocampus with striatum and dorsal cingulate cortex, and right hippocampus with striatum and orbitofrontal cortex. Greater PTSD severity generally led to less changes in functional connectivity with the right insular cortex.

Conclusions: These results provide evidence that RETM engages and modifies functional connectivity pathways with neural regions implicated in fear extinction. The results also implicate the engagement of the right insular cortex and striatum during RETM and suggest their importance in human fear extinction to trauma memories. However, comorbidity in the sample and the lack of a control group limit inferences regarding RETM with PTSD populations specifically.

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Posttraumatic stress disorder is characterized by re-experiencing, avoidance, and hyperarousal symptoms (APA, 2000) and is associated with marked quality of life impairments (Olatunji et al., 2007). To date, the most evidence-based and widely disseminated psychological treatment for PTSD is prolonged exposure (PE) (Foael et al., 1999; Foa et al., 1991). While PE is a well-supported intervention, it is of limited efficacy with only ~60% of treatment completers entering remission (Foa et al., 1999; Resick et al., 2002; Schnurr et al., 2007). Thus, research efforts directed at improving the efficacy of PE is necessary.

One important treatment component of PE is repeated exposure to the trauma memory (RETM). In PE, this is termed imaginal exposure and takes the form of the individual recounting the trauma narrative repeatedly while providing indices of distress. Therapeutic response to traumatic memory exposure is based on a fear extinction model (Foael and Kozak, 1986; Foa et al., 1991; Rothbaum and Davis, 2003); thoughts and memories of the traumatic event are conceptualized as conditioned stimuli (CS+) that trigger anxiety responses (i.e., the conditioned response) due to their association with the traumatic event (i.e., the unconditioned stimulus, US). Repeated exposure to the traumatic memory (CS+) in a safe context is theorized to weaken the predictive value of the CS+ to predict the US and thereby weaken the ability of the
traumatic memory or reminders to elicit anxiety/distress responses.

The purpose of the present exploratory study was to identify the in vivo neural mechanisms engaged and modified during repeated exposure to the traumatic memory. This intent was motivated by the assumptions that this would 1) provide important inferences regarding the mechanisms of treatment action and 2) facilitate development and testing of adjunctive methods to enhance these mechanisms (e.g., pharmacological agonists such as d-cycloserine).

We focused on mechanisms of neural functional connectivity changes with neural regions implicated in fear extinction during analogue exposure therapy conducted during FMRI, given that exposure to the trauma narrative is based on a fear extinction model (Foa et al., 1986, 1991; Rothbaum and Davis, 2003). Extensive basic science research has demonstrated that fear extinction involves the interaction between three separate neural structures (Davis and Whalen, 2001), memory (Squire, 1992), and indeed, these three regions are also generally implicated in salience detection (Foote et al., 1999; Rothbaum and Davis, 2003). We only examine the neural mechanism changes during RETM among individuals with a current diagnosis if PTSD and we did not recruit a trauma-exposed group without PTSD as a comparison sample. First, RETM as a treatment would not be provided to a trauma-exposed individual without PTSD, thus there would be little clinical utility of identifying neural mechanism changes during RETM among these individuals. Second, trauma-exposed individuals without PTSD exhibited resilience, thus it might expected that they would exhibit significantly different neural responses to RETM that would not necessarily be informative about the neural mechanisms of change among individuals with PTSD, which again limits the clinical utility of this comparison. Accordingly, given that this is the first investigation of the in vivo changes in neural mechanisms during RETM among individuals with PTSD, this study is exploratory in nature, conducted specifically among individual with a current diagnosis of PTSD, and we broadly hypothesized that RETM engages and modifies functional connectivity with the key nodes implicated in fear extinction.

1. Method

1.1. Participants

Seventeen adult women with PTSD related to either physical or sexual assault were enrolled into the study. One woman moved excessively during the scan causing intractable signal artifact, and her data were subsequently removed from analyses. This resulted in a final sample of 16 participants. Table 1 lists demographic and clinical characteristics of this sample. Inclusion criteria were 1) a history of either physical or sexual assault, 2) a current diagnosis of PTSD, and 3) that participants were stable on any psychiatric medications for at least 4 weeks. Exclusion criteria included psychotic disorders, a primary substance use disorder, or internal metal objects. Participants were recruited from outpatient mental health clinics and from community wide advertisements. All study procedures were approved by the local institutional review board.

Assaultive trauma histories were characterized using the trauma assessment section of the National Women’s Survey and National Survey of Adolescents (Kilpatrick et al., 2000, 2003; Resnick et al., 1993), a structured interview used in prior epidemiological studies of assault and mental health functioning among adult women and adolescents. Specific assaultive events were assessed with behaviorally specific dichotomous questions and included: 1) sexual assault (i.e., anal penetration, vaginal penetration, oral sex on the perpetrator, oral sex from the perpetrator, digital penetration, fondling, forced fondling of the perpetrator), 2) physical assault (i.e., attacked with a weapon, attacked with a stick, club, or bottle, attacked without a weapon, threatened with a weapon, attacked with fists), and 3) severe abuse from a caregiver (i.e., beaten with fists or an object to the point where bruising or bleeding occurred).

Psychological disorders were assessed with the Structured Clinical Interview for DSM-IV Disorders (SCID) (First et al., 2002) administered by trained clinical interviewers and supervised by a licensed clinical psychologist. Participants additionally completed the Posttraumatic Stress Checklist-Civilian Version (Blanchard et al., 1996) and Beck Depression Inventory-II (Beck et al., 1996).
1.3. fMRI acquisition and image preprocessing

See the supplementary material for description of 3T fMRI acquisition and preprocessing.

1.4. Data analysis

We probed in vivo changes in functional organization of a fear extinction network through whole-brain seedmaps of functional connectivity with the mPFC, bilateral amygdala, and bilateral hippocampi (see Supplementary Fig. 1). The anatomical coordinates were taken from prior fear extinction, fear reversal, and emotion regulation fMRI studies (Delgado et al., 2008; Phelps et al., 2004; Schiller and Delgado, 2010; Schiller et al., 2008). While the amygdala and hippocampus seed regions were 6 mm radius spheres (48 $3 \times 3 \times 3$ mm voxels), the mPFC seed region was an 8 mm radius sphere (100 $3 \times 3 \times 3$ mm voxels) in order to extend into both the left and right subgenual cingulate cortex. The specific anatomical coordinates of the centroid of each ROI (XYZ), in MNI space, were: mPFC = 0, 36, 0; right amygdala = 19, −5, −15; left amygdala = −19, −5, −15; right hippocampus = 27, −17, −13; left hippocampus = −28, −17, −13.

For each exposure presentation singular value decomposition was used to extract the first principal component of the voxels’ timecourses within each ROI separately. These ROI principal component timecourses were then separately regressed onto the timecourses of every other voxel in the brain, for each exposure epoch and for each narrative type separately, resulting in whole-brain seedmaps of functional connectivity with the seed region. We then used mixed models (Bryk and Raudenbush, 1987; Raudenbush and Bryk, 2002) to characterize growth curves of brain-wide functional connectivity with the seed regions over the five exposure epochs. Briefly, this approach models repeated measurements as ‘nested’ within the individual, such that a growth curve (for each voxel) is characterized separately for each individual (i.e., first-level analyses), and group level statistics are then computed on these individual-level parameters (i.e., second-level analyses). We modelled linear growth curves, using ordinary least squares regression, consisting of two parameters: an intercept (representing the initial degree of functional connectivity) and a slope (representing the linear change in functional connectivity across the five exposure epochs). The sign of the slope (positive or negative) indicates whether the functional connectivity increased or decreased across the exposure epochs. This was done in a mass-univariate whole brain approach separately for each ROI. That is, we characterized the growth curves of functional connectivity between the right amygdala and every other voxel in the brain, between the left amygdala and every other voxel in the brain, the mPFC and every other voxel in the brain, etc. We then created whole-brain contrast maps, in which we compared the growth curve parameter of interest (i.e., the slope) between the trauma narrative exposure and the neutral narrative exposure. This comparison controls for the effect of repeated recounting of a memory per se and other confounds such as change over time and scanner drift, allowing more precise inferences regarding dynamic changes in neural processing mechanisms that are specific to trauma narrative exposure. We controlled for whole-brain multiple corrections with cluster-level thresholding, with a corrected $p < .05$ defined as 16 contiguous voxels surviving an uncorrected $p < .005$ based on Monte Carlo simulations (Forman et al., 1995).

The relationship between individual differences in PTSD symptom severity and in vivo brain connectivity changes were assessed through whole-brain robust regression analyses, in which PCL scores were regressed onto each individual’s voxel-wise slope parameters while also controlling for the intercept and slope.

Table 1

Demographic and clinical characteristics of the 16 adult women in this sample.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean (or frequency)</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>33.8</td>
<td>10.8</td>
</tr>
<tr>
<td>Ethnicity</td>
<td>44% Caucasian</td>
<td></td>
</tr>
<tr>
<td></td>
<td>50% African-American</td>
<td></td>
</tr>
<tr>
<td></td>
<td>6% Other</td>
<td></td>
</tr>
<tr>
<td>Marital Status</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>19% married</td>
<td></td>
</tr>
<tr>
<td></td>
<td>25% divorced</td>
<td></td>
</tr>
<tr>
<td></td>
<td>19% separated</td>
<td></td>
</tr>
<tr>
<td></td>
<td>38% never married</td>
<td></td>
</tr>
<tr>
<td>Education</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>6% not graduate high school</td>
<td></td>
</tr>
<tr>
<td></td>
<td>38% graduate high school or GED</td>
<td></td>
</tr>
<tr>
<td></td>
<td>38% some college</td>
<td></td>
</tr>
<tr>
<td></td>
<td>18% graduate 2 year college</td>
<td></td>
</tr>
<tr>
<td></td>
<td>or more education</td>
<td></td>
</tr>
<tr>
<td>Current job</td>
<td>44% unemployed</td>
<td></td>
</tr>
<tr>
<td>Ever sought mental health services</td>
<td>75% yes</td>
<td></td>
</tr>
<tr>
<td></td>
<td>38% yes</td>
<td></td>
</tr>
<tr>
<td>Ever been hospitalized</td>
<td>38% yes</td>
<td></td>
</tr>
<tr>
<td></td>
<td>for psychiatric reason</td>
<td></td>
</tr>
<tr>
<td>PCL score</td>
<td>62.3</td>
<td>13.5</td>
</tr>
<tr>
<td>BDI-II score</td>
<td>24</td>
<td>11.7</td>
</tr>
<tr>
<td>Number of total direct assaults</td>
<td>7.6</td>
<td>2.4</td>
</tr>
<tr>
<td></td>
<td>3.0</td>
<td>1.2</td>
</tr>
<tr>
<td>from non-caregiver</td>
<td>1.6</td>
<td>1.2</td>
</tr>
<tr>
<td>Number of sexual assaults</td>
<td>2.9</td>
<td>1.4</td>
</tr>
<tr>
<td></td>
<td>44%</td>
<td></td>
</tr>
<tr>
<td>Current major depressive disorder</td>
<td>44%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>56%</td>
<td></td>
</tr>
<tr>
<td>Current panic disorder</td>
<td>44%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>56%</td>
<td></td>
</tr>
<tr>
<td>Current generalized anxiety disorder</td>
<td>100%</td>
<td></td>
</tr>
<tr>
<td>Current PTSD</td>
<td>25%</td>
<td></td>
</tr>
<tr>
<td>Current substance use disorder</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note. PCL = Posttraumatic Checklist — civilian version; BDI-II – Beck Depression Inventory-II.
parameters of the anxiety ratings during the trauma exposure (to control for the relationships between individual differences in PTSD symptoms and anxiety ratings during the trauma exposure). We again controlled for multiple comparisons with cluster-level thresholds of 16 contiguous voxels surviving an uncorrected \( p < .005 \).

2. Results

2.1. Behavioral

As can be seen in Table 2, mean anxiety ratings (collapsed across exposure epochs) were significantly higher during the trauma exposure relative to the neutral exposure (\( t = 6.4, p < .001 \). By contrast, mean dissociation and vividness ratings did not significantly differ between the trauma and neutral exposures (\( p s > .2 \)). The slope for the change in anxiety ratings during the trauma exposure across the 5 exposures was significantly positive (\( t = 2.5, p = .024 \)), indicating increased emotional engagement with the trauma memory.

2.2. Imaging

Functional connectivity with the right amygdala significantly increased across the imaginal trauma exposures versus the neutral exposures for the bilateral anterior insula and right hippocampus (Fig. 1), and also with right inferior frontal gyrus, and ventral visual cortex (whole-brain statistical map provided in Supplementary Fig. 2). Functional connectivity with the left amygdala significantly increased across the imaginal trauma exposures versus the neutral exposures for the right anterior insula and decreased with the right superior frontal gyrus (Fig. 2; whole-brain statistical map provided in Supplementary Fig. 3). Trauma exposure-related functional connectivity with the right hippocampus significantly increased for the right putamen and dorsomedial PFC/dorsal anterior cingulate cortex (ACC) (Fig. 3; whole-brain statistical map provided in Supplementary Fig. 4). Trauma exposure-related functional connectivity with the left hippocampus significantly increased for the right putamen and right orbitofrontal gyrus (Fig. 4; whole-brain statistical map provided in Supplementary Fig. 5). Finally, functional connectivity with the medial PFC significantly increased for the bilateral anterior insula (Fig. 5) as well as right inferior frontal gyrus, right parietal cortex, and portions of the ventral visual stream across imaginal trauma exposures (whole-brain statistical map provided in Supplementary Fig. 6).

Given that the analyses are based on contrasts of changes in functional connectivity during trauma versus neutral exposures, the direction of the observed changes in connectivity are equivocal (e.g., a positive contrast value could indicate that connectivity increased during the trauma exposures or that connectivity did not change during the trauma exposures but decreased during the neutral exposures). Therefore, we also plotted the mean functional connectivity values across the trauma and neutral exposures for the main regions identified in the above contrasts (Supplementary Figs. 7—11). As can be seen, in each case, the observed fcMRI changes are represented by the direction of the contrast effect: that is, a positive contrast value indicates increasing connectivity during the trauma exposures and decreasing or static connectivity during the neutral exposures.

Correlations between PTSD symptom severity and functional connectivity changes related to trauma exposures. As indicated in Fig. 6, we found an overlapping region in the right anterior insula/ inferior frontal gyrus where greater PTSD symptoms were associated with less strengthening of functional connectivity across trauma exposures with both the right hippocampus (Fig. 6A) and right amygdala (Fig. 6B). Similarly, there was a region in the right

### Table 2

Mean (SD) subjective ratings during the trauma and neutral memory exposures.

<table>
<thead>
<tr>
<th>Exposure epoch</th>
<th>Anxiety ratings</th>
<th>Vividness ratings</th>
<th>Dissociation ratings</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Trauma</td>
<td>Neutral</td>
<td>Trauma</td>
</tr>
<tr>
<td>1</td>
<td>6.6 (2.6)</td>
<td>3.3 (2.6)</td>
<td>7.4 (3.1)</td>
</tr>
<tr>
<td>2</td>
<td>7.6 (2.5)</td>
<td>2.7 (2.5)</td>
<td>8.2 (2.7)</td>
</tr>
<tr>
<td>3</td>
<td>7.3 (2.3)</td>
<td>2.5 (2.4)</td>
<td>8.1 (1.7)</td>
</tr>
<tr>
<td>4</td>
<td>7.4 (2.4)</td>
<td>2.2 (2.8)</td>
<td>8.6 (1.5)</td>
</tr>
<tr>
<td>5</td>
<td>7.4 (2.4)</td>
<td>2.4 (3)</td>
<td>8.4 (1.8)</td>
</tr>
</tbody>
</table>

Fig. 1. Neural Regions where connectivity with the right amygdala significantly changes across the trauma exposures relative to the neutral exposures. Thresholded at \( p < .05 \) using cluster-level thresholds of 16 contiguous voxels surviving an uncorrected \( p < .005 \) based on Monte Carlo simulations.
posterior insula/inferior frontal gyrus (Fig. 6c) where greater PTSD symptoms were associated with less trauma exposure-related strengthening of functional connectivity with the mPFC.

2.3. Comorbidity

Finally, given the comorbidity in the present sample, we also conducted exploratory tests of whether the observed functional connectivity results differed as a function of comorbidity with major depressive disorder, panic disorder, and generalized anxiety disorder. We observed that the presence of these comorbidities (versus their absence) did not significantly affect the degree of observed functional connectivity changes during RETM nor did it alter the direction of the observed effects (results available upon request from first author).

3. Discussion

The results of this initial exploratory study suggest that functional connectivity of the key nodes implicated in fear extinction changes with repeated exposure to a traumatic memory. There was consistency in the brain regions whose functional connectivity with these nodes changed, such that strengthening of functional connectivity with the striatum was observed for both the right and left hippocampus, and strengthening of functional connectivity with the anterior insular cortices was observed for both left and right amygdala as well as mPFC. These findings implicate the integration of the striatum and anterior insula with key nodes implicated in fear extinction as a core process occurring during repeated exposure to the traumatic memory. Given the role of both the striatum and anterior insular cortices in reward learning and,
more specifically, in tracking prediction errors during learning (Bossaerts, 2010; Oyama et al., 2010; Preuschoff et al., 2008; Schultz and Dickinson, 2000; Stalnaker et al., 2012), one hypothesis explaining the observed findings is that fear extinction induced through repeated exposure to a traumatic memory draws heavily on tracking prediction errors to facilitate therapeutic learning processes. That is, from a fear conditioning perspective, trauma reminders (CS+) signal the occurrence of the traumatic event (US). Repeated presentation of the CS+ in the absence of the US would therefore be expected to generate prediction errors, and recent evidence among humans indeed suggests that striatal activity tracks prediction errors during fear extinction learning (Li et al., 2011). Accordingly, the observed increased functional connectivity with the striatum and anterior insular cortices suggests that the tracking of prediction errors becomes increasingly integrated into the fear extinction neural network during repeated exposure to the traumatic memory and that this influence underlies the learning that the CS + no longer predicts the US. While this is one plausible hypothesis explaining the observed changes in functional connectivity, it should be emphasized that this hypothesis is based on patterns of observed brain data (i.e., reverse inference) and more data is needed to corroborate this tentative hypothesis.

We also found evidence that greater severity of baseline PTSD symptoms was associated with less functional integration of the right insular cortex and neighboring inferior frontal gyrus into the fear extinction network across trauma exposures. As individual differences in anxiety responses to the trauma exposure were controlled in the analysis, the observed relationship with baseline PTSD symptoms cannot be attributed to differences in emotional responses to the trauma exposures. One hypothesis explaining this finding is that those individuals with more severe PTSD symptoms may generate less prediction errors during the fear extinction process, which might be expected to confer risk for poorer treatment outcomes. Prior research has found that more severe pre-treatment PTSD symptoms are associated with worse treatment outcomes (Karatzias et al., 2007), and the present finding suggests a possible neural mechanism mediating the worse outcomes associated with more severe PTSD symptoms. If this explanation is valid, then it might be expected that supplemental therapeutic procedures that can potentiate connectivity between the fear extinction network and right insular cortex/inferior frontal gyrus may lead to better treatment outcomes among individuals with greater PTSD symptom severity.

In addition to finding increased integration of neural regions associated with tracking prediction errors into the fear extinction network, we also observed several other changes in functional connectivity with regions of theoretical interest. Functional connectivity between the right amygdala and right hippocampus was found to increase across the trauma exposure. Given the role of the hippocampus in memory consolidation and contextual retrieval during extinction (Myers and Davis, 2007), it seems possible that

Fig. 4. Neural Regions where connectivity with the left hippocampus significantly changes across the trauma exposures relative to the neutral exposures. Thresholded at \( p < .05 \) using cluster-level thresholds of 16 contiguous voxels surviving an uncorrected \( p < .005 \) based on Monte Carlo simulations.

Fig. 5. Neural Regions where connectivity with the medial PFC significantly changes across the trauma exposures relative to the neutral exposures. Thresholded at \( p < .05 \) using cluster-level thresholds of 16 contiguous voxels surviving an uncorrected \( p < .005 \) based on Monte Carlo simulations.
the increasing functional connectivity between these regions is indicative of encoding of the new association that, in a certain context, trauma reminders (CS+) do not signal the occurrence of the US. We also observed strengthening of functional connectivity between the right hippocampus and a region extending from the dorsomedial PFC into the dorsal anterior cingulate cortex (ACC). Given the role of this region in conflict monitoring (Botvinick et al., 2001; Kerns et al., 2004), this observation may reflect the integration of conflict monitoring processes during fear extinction. Indeed, the dACC is also implicated in tracking prediction errors and volatility of expected outcomes (Behrens et al., 2007; Rushworth and Behrens, 2008); thus, the ‘conflict’ during fear extinction to traumatic memories may involve changes in the discrepancy between actual and expected threat outcomes. Again, these hypotheses about cognitive functions are based on observed patterns of brain activity (i.e., reverse inferences), and it must be emphasized that these are hypotheses in need of further corroboration.

Finally, we did not observe changes in connectivity between the amygdala and mPFC. Given the hypothesized role of the mPFC in fear extinction learning (Maren et al., 2013; Milad et al., 2007; Myers and Davis, 2007; Orsini et al., 2011; Quirk and Beer, 2006), it may have been expected that we would observe increasing modular relationships (i.e., negative functional connectivity) between the regions, such that more mPFC activity is associated with less amygdala activity. One possible explanation for the failure to observe this relationship in the present data is that it may require more than 5 repeated exposures for sufficient learning to occur that would facilitate mPFC inhibition of the amygdala. The failure to observe this finding also highlights the need to continue studying the in vivo neural mechanisms of change that occur during actual therapies in order to better inform how to implement and improve them.

Several study limitations of this study should temper conclusions. First, a single truncated session of RETM is unlikely to be therapeutic, as is seen clinically when PTSD patients actually sometimes show a transient increase in PTSD symptoms during the early stages of RETM (Foa et al., 2002). Future research is also necessary to determine the functional connectivity changes during RETM that scale with symptom reductions. Second, our sample was limited to adult women with PTSD related to assaultive violence exposure. While this increased the homogeneity of the sample, the degree to which these results generalize to more heterogeneous populations is unknown. Third, the inferences regarding increased integration of prediction error tracking during fear extinction learning need to be further corroborated with future research. Fourth, the lack of a control group limits inferences regarding whether the observed results are specific to RETM for PTSD populations specifically, to trauma exposed populations generally, or simply to exposure to stressful memories. Fifth, there was a high degree of comorbidity in the present sample, which limits inferences regarding generalizability to PTSD populations specifically.

**Funding sources**

Portions of this work were supported through grants 1R21MH097784-01 and T32 DA022981-02. The content is solely the responsibility of the authors and does not necessarily represent the official views of National Institute for Mental Health or the National Institutes of Health.

**Financial disclosures**

All authors report no financial conflicts of interest.

**Role of funding**

Portions of this project were supported by Award Number UL1RR029884 and KL2RR029883 from the National Center for Research Resources, and RO1DA019999, R21DA025243, T32DA022981 from the National Institute on Drug Abuse, and R21MH097784 from the National Institute of Mental Health. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Center For Research Resources or the National Institutes of Health.
Contributions
Josh Cisler was involved in study design, analysis, interpretation, and manuscript writing. Sonet Smitherman was involved in study design and analysis. Scott Steele was involved in analysis and interpretation. Jennifer Lenow was involved in analysis, interpretation, and manuscript writing. Clint Kilts was involved in study design, interpretation, and manuscript writing. Betty Everett was involved in study design, interpretation, and manuscript writing. Erick Messias was involved in study design, interpretation, and manuscript writing.

Acknowledgements
We thank Cindy Mosley, Andi Ham, Shanti Tripathi, and George Andrew James for help with recruitment, analysis, and administration.

Appendix A. Supplementary data
Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.jpsychires.2013.09.013.

References

