

Altered resting state functional connectivity of fear and reward circuitry in comorbid PTSD and major depression

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Background: Individuals with comorbid posttraumatic stress disorder and major depressive disorder (PTSD-MDD) often exhibit greater functional impairment and poorer treatment response than individuals with PTSD alone. Research has not determined whether PTSD-MDD is associated with different network connectivity abnormalities than PTSD alone.

Methods: We used functional magnetic resonance imaging (fMRI) to measure resting state functional connectivity (rs-FC) patterns of brain regions involved in fear and reward processing in three groups: patients with PTSD-alone ($n = 27$), PTSD-MDD ($n = 21$), and trauma-exposed healthy controls (TEHCs, $n = 34$). Based on previous research, seeds included basolateral amygdala (BLA), centromedial amygdala (CMA), and nucleus accumbens (NAcc).

Results: Regardless of MDD comorbidity, PTSD was associated with decreased connectivity of BLA-orbitalfrontal cortex (OFC) and CMA-thalamus pathways, key to fear processing, and fear expression, respectively. PTSD-MDD, compared to PTSD-alone and TEHC, was associated with decreased connectivity across multiple amygdala and striatal-subcortical pathways: BLA-OFC, NAcc-thalamus, and NAcc-hippocampus. Further, while both the BLA-OFC and the NAcc-thalamus pathways were correlated with MDD symptoms, PTSD symptoms correlated with the amygdala pathways (BLA-OFC; CMA-thalamus) only.

Conclusions: Comorbid PTSD-MDD may be associated with multifaceted functional connectivity alterations in both fear and reward systems. Clinical implications are discussed.

KEY WORDS

amygdala, depression, fear processing, MDD, nucleus accumbens, PTSD, resting state functional connectivity, reward processing

1 | INTRODUCTION

Almost half of individuals with posttraumatic stress disorder (PTSD) have comorbid major depressive disorder (MDD) (Kessler et al., 1995). Although individuals with PTSD-MDD have greater functional impairment, more chronic course, and poorer treatment response than those with PTSD alone (Kessler et al., 2005), research has never

addressed whether they exhibit different alterations of network synchronicity. We used resting state functional connectivity (rs-FC) to investigate whether PTSD-MDD has a different underlying neural basis compared to PTSD alone and to trauma-exposed healthy controls (TEHCs).

Most PTSD neuroimaging research has focused on fear circuitry, primarily linking the amygdala to PTSD neural dysfunction (Shin, Rauch, & Pitman, 2006). While early magnetic resonance imaging (MRI) identified reduced amygdala volume in PTSD (Depue et al., 2014; Morey et al., 2012), recent discoveries of the functional heterogeneity of the amygdala (Roy et al., 2009) and the multiple roles its subregions play in fear processing and response (Phelps, Delgado, Nearing, & LeDoux, 2004)

Abbreviations: BLA, basolateral amygdala; CMA, centromedial amygdala; CSF, cerebrospinal fluid; fMRI, functional magnetic resonance imaging; Ham-D, Hamilton Depression Rating Scale; NAcc, nucleus accumbens; OFC, orbitalfrontal cortex; PTSD-MDD, posttraumatic stress disorder and major depressive disorder; rs-FC, resting state functional connectivity; SCID, Structured Clinical Interview for DSM-IV Axis I Disorders; sgACC, subgenual ACC; TEHCs, trauma-exposed healthy controls

pose the first question guiding this investigation: namely, whether people with comorbid PTSD-MDD exhibit different connectivity patterns of amygdala subregions than people with PTSD alone. Particularly important to PTSD are the basolateral amygdala (BLA) and centromedial amygdala (CMA). The BLA is regulated by prefrontal cortex inhibition, which modulates fear acquisition and evaluation of sensory information (Jovanovic & Ressler, 2010). The CMA has a likely role in fear expression via connections with the thalamus, striatum, forebrain, and brainstem (including periaqueductal gray) (Duvarci & Pare, 2014; LeDoux, 1998).

Several studies have examined rs-FC alterations in amygdala and its subregions in PTSD (Aghajani et al., 2016; Nicholson et al., 2015). For example, Brown et al. (2014) reported altered rs-FC in BLA and CMA among adults with PTSD, suggesting that the BLA and CMA may play markedly different roles in patients with PTSD than controls. To our knowledge, no research has compared adults with PTSD to those with PTSD-MDD.

Several fMRI studies of MDD have shown increased amygdala activation and decreased PFC activation (Lee et al., 2008; Siegle et al., 2007). Furthermore, studies examining prefrontal-limbic connectivity in MDD reported similar alterations to those found in PTSD. For example, Kong et al. (2013) investigated amygdala-PFC functional connectivity during emotional face processing in medication-naïve patients with MDD, the finding of decreased amygdala-rostral PFC may reflect emotional dysregulation. A resting state study further demonstrated decreased amygdala-PFC rs-FC in patients with MDD compared to healthy controls (Tang et al., 2013). These studies provide evidence of potentially comparable dysfunction in the prefrontal-limbic circuitry among patients with PTSD and those with MDD.

Beyond fear circuit dysfunction, a few studies indicate that PTSD may entail reward-processing deficits (Elman et al., 2009). Indeed, patients with PTSD often report anhedonic symptoms: reduced motivational approach behavior and lack of pleasure in rewarding activities. Compared to trauma-exposed controls, patients with PTSD reported lower satisfaction with monetary reward and diminished task motivation, and exerted less effort to obtain rewards (Sailer et al., 2008). Anhedonia has links to deficits in reward processing in a brain network centered on the nucleus accumbens (NAcc), which is part of the ventral striatal regions that receive excitatory input from cortical areas and project output to the thalamus and brainstem. Previous work found less activation in ventral striatum to positive feedback in a decision-making task and monetary reward task in PTSD patients (Elman et al., 2009; Sailer et al., 2008). Similarly, in depression, for which reward system deficits are considered a key feature, research has described abnormal striatal activity in a reward decision-making task, monetary reward task, and reward-learning task (Forbes et al., 2009), and functional connectivity studies found decreased reward network connectivity proportional to depression severity (Satterthwaite et al., 2015).

Only one study to date (Kennis et al., 2013) has examined differences in functional connectivity between PTSD-alone and PTSD-MDD. This study focused on the insula and ACC as seed regions, not addressing potential alterations in pathways involving the NAcc. Thus the contribution of NAcc func-

tional connectivity patterns to the pathophysiology of PTSD-MDD relative to PTSD alone remains unclear. Identifying the underlying network connectivity of PTSD with and without MDD might inform future clinical interventions. Addressing whether PTSD-MDD involves alterations in both fear and reward processing might guide future targets of PTSD interventions, which currently focus primarily on fear network function (e.g., prolonged exposure (PE) (Foa et al., 2005; Helpman et al., 2016b).

Confronting these gaps in knowledge, the current study examined rs-FC of amygdala (BLA and CMA) and striatal-subcortical (NAcc) regions as seed regions of known involvement in fear and reward processing. We addressed four questions: (1) whether subjects with PTSD (with or without comorbid MDD), compared to TEHCs, exhibit differential functional connectivity patterns in the amygdala BLA and CMA subregions; (2) whether PTSD is associated with fear processing alterations regardless of depression comorbidity; (3) whether comorbid PTSD-MDD displays different functional connectivity patterns of striatal-subcortical (NAcc) pathways compared to PTSD-alone; and (4) whether the amygdala and NAcc connectivity pathways are differentially associated with PTSD and MDD symptoms. We hypothesized that: (1) compared to TEHCs, subjects with PTSD will show distinctive amygdala BLA and CMA functional connectivity patterns; (2) PTSD-alone and PTSD-MDD subjects will show similar alterations in frontal-amamygdala connectivity; (3) subjects with PTSD-MDD will show greater striatal-subcortical connectivity abnormalities than PTSD-alone and TEHC subjects; (4) frontal-amamygdala connectivity will be negatively associated with PTSD symptoms; and striatal-subcortical connectivity will be negatively associated with MDD symptoms.

2 | METHODS

2.1 | Participants

Resting state fMRI was conducted in 82 subjects: 21 with PTSD-MDD, 27 with PTSD-alone (PTSD), and 34 TEHCs, as part of a multimodal imaging study in PTSD (Helpman et al., 2016a). Briefly, PTSD subjects, with and without MDD, and TEHCs matched on age, sex, trauma type, and race/ethnicity were recruited via online advertisement and fliers. All participants met DSM-IV-TR (American Psychiatric Association 2000) PTSD criterion A1 for adult traumatic events, including vehicular accidents, sexual or physical assaults, and witnessing serious injuries or deaths. A psychiatrist determined medical exclusions by history and physical examination. An independent clinical evaluator administered the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID) (First, Spitzer, Gibbon, & Williams, 1996) and Clinician-Administered PTSD Scale (CAPS) (Weathers, Keane, & Davidson, 2001) to assess psychiatric diagnoses and PTSD severity. Subjects with PTSD were required to have at least moderate severity, operationalized by a CAPS total score of ≥ 50 . MDD diagnosis was determined by SCID DSM-IV criteria for a major depressive episode. Exclusion criteria for subjects with PTSD included history of Axis I psychiatric diagnosis other than comorbid current MDD, substance

or alcohol dependence within the past 6 months or abuse within the past 2 months, any psychotropic medication within 4 weeks prior to participation (six weeks for fluoxetine). Severe depression (score ≥ 25 on the 17-item Hamilton Depression Rating Scale (Ham-D, (Hamilton, 1960)) was an exclusion criterion due to concerns about research delaying treatment. Control subject exclusion criteria were current or past Axis I disorders including substance use disorders, and CAPS score > 20 . The New York State Psychiatric Institute Institutional Review Board approved all procedures, and all participants provided written informed consent after receiving explanation of the procedures in accordance with the World Medical Association Code of Ethics.

2.2 | Image acquisition

A 1.5 T GE Twin Speed MR Scanner operating on the Excite 3 12.0 M4 HD platform equipped with an 8-channel gradient head coil was used. A high-resolution T1-weighted 3D MPRAGE sequence was acquired for each subject (repetition time = 7.25 ms, echo time = 3 ms, Flip angle = 7°, field of view = 25.6 cm, 256 × 256 pixel matrix, slice thickness = 1 mm). Five-minute functional resting-state images (i.e., blood oxygenation level dependent, BOLD) were acquired using a gradient echo T2*-weighted sequence (repetition time = 3 s, echo time = 30 ms, flip angle = 90°, field of view = 22.4 cm, 64 × 64 pixel matrix, slice thickness = 2.2 mm). Subjects were instructed to relax, remain awake, and lie still with their eyes open.

2.3 | Preprocessing of imaging data

All fMRI images were preprocessed using MATLAB version R2012b (The MathWorks, Inc., Natick, MA, USA) and statistical parametric mapping software (SPM12; Wellcome Trust Centre for Neuroimaging, UCL, London, UK). All functional images were slice time corrected, motion corrected using a six-parameter rigid body transformation, then co-registered to each participant's T1-weighted structural image. Coregistered images were normalized to the Montreal Neurological Institute (MNI) canonical template and smoothed with an 8 mm full-width-at-half-maximum (FWHM) Gaussian kernel. Functional connectivity analyses were performed on the smoothed images.

2.4 | Seed-based functional connectivity analyses

rs-FC analyses were carried out using a seed-based approach implemented in the CONN-fMRI Functional Connectivity toolbox v13 (Whitfield-Gabrieli & Nieto-Castanon, 2012). Prior to correlation analysis, band-pass filtering with a frequency window of 0.01 to 0.09 Hz was performed. Artifact detection tools implemented in CONN was used for outlier detection (Whitfield-Gabrieli & Nieto-Castanon, 2012). The principal component-based noise-correction "CompCor" method in this toolbox was used for additional control of physiological noise and head motion effects. Outlier volumes for each subject identified as having large spiking artifacts (i.e., volumes >3 standard deviations from the mean image intensity), or large motion (i.e., 0.5 mm for scan-to-scan head-motion composite changes

in x, y, or z direction). Anatomical images were segmented into gray matter, white matter, and cerebrospinal fluid (CSF) regions. Covariates corresponding to head motion (six realignment parameters and their derivatives), outliers (one covariate per outlier consisting of 0's everywhere and a one for the outlier time point), and the BOLD time series from the subject-specific white matter and CSF masks were used in the connectivity analysis as predictors of no interest and removed from the BOLD functional time series using linear regression.

From the original total of 54 PTSD and 35 TEHC, seven participants (6 PTSD, 1 TEHC) were excluded from further analysis due to movement exceeding ± 1.5 mm, and more than 20% of each subject's data points having been detected as outliers. Consequently, the final analysis included 82 participants: 48 PTSD, 34 TEHC. Sum of root mean square (RMS) of six relative head motion parameters (movement from this time point to next time point) was calculated for each subject in all groups (TEHC, PTSD-alone, and PTSD-MDD). No significant difference of head motion was found between each pair of groups ($P > .5$). Linear regression was performed to study the linear relationship between the dependent variable (sum of head motion) and independent variable (groups). Regression analysis results showed that total head motion could not predict groups ($R^2 = 0.029$, $t = 1.5$, $P = .119$).

Between-ROI connectivity analysis was performed using several ROIs previously identified as important in PTSD and MDD, including CMA, BLA (Fig. 1), NAcc, orbitofrontal cortex (OFC), thalamus (THA), hippocampus (HIP), and subgenual ACC (sgACC). Amygdala subregion ROIs were derived from the Juelich Histological Atlas, and other cortical and subcortical ROIs from the FSL Harvard-Oxford Atlas maximum likelihood cortical and subcortical atlases (Desikan et al., 2006). A 70% threshold was applied to these atlases. The mean BOLD time series was computed across all voxels within each ROI. Bivariate-regression analyses were used to determine the linear association of the BOLD time series between each pair of regions for each subject. Both positive and negative correlations were examined. The resultant correlation coefficients were transformed into z-scores using Fisher's transformation to satisfy normality assumptions.

To clarify the direction of significant results from ROI-to-ROI analysis, we extracted β -weights of functional connectivity and averaged across all voxels within each ROI.

To investigate group differences outside the predefined ROIs, exploratory whole brain group analyses were performed on BLA, CMA, and NAcc seeds. The resulting maps were initially tested for significance at threshold of $P < .005$, 20 voxels cluster, as we did not have specific hypotheses in regions outside of our a priori ROIs. Voxel-wise FDR corrections were conducted on the whole brain maps. Both results are presented in Supporting Information Tables S1–S3.

2.5 | Statistical analyses

Statistical analyses employed SPSS software (SPSS Inc. Chicago, IL, USA). T-tests were used to test differences in clinical symptoms, age, and years of education between groups. Chi-square test was used to analyze differences in sex and race.

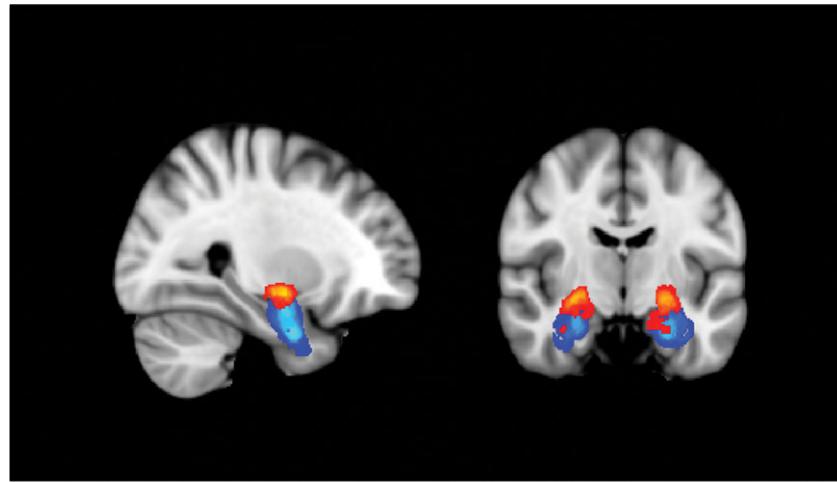


FIGURE 1 Centromedial amygdala (CMA) (right and left, Red) and basolateral amygdala (BLA) (right and left, blue) seed ROIs. The underlying brain template is from FSL MNI152 standard-space T1-weighted average structural template image

Baseline FC differences between all PTSD and TEHC subjects were tested using univariate analysis of covariance (ANCOVA) controlling for effects of age, sex, and education. As age and sex did not differ between the two groups, separate analysis without age and sex covariates was tested. Exclusion of age and sex as covariates at the group level did not substantially change the findings.

Group differences of FC in TEHC, PTSD-alone, and PTSD-MDD were further tested using ANCOVA with group as the fixed factor and functional connectivity as dependent variables. The between-group factor (fixed factor) comprised three levels: PTSD-MDD, PTSD-alone, and TEHC. Age, sex, and years of education were used as covariates. FDR correction was performed across each connectivity pair between seed-ROIs and target-ROIs. Post hoc ANCOVA analysis was examined for each seed region, comparing both PTSD patient groups, and each patient group to the control group. Age, sex, and years of education were used as covariates when comparing patient groups to the control group. As the PTSD subgroups (PTSD-alone and PTSD-MDD) differed on CAPS score levels, and to ensure that between-group differences in FC were attributable to MDD comorbidity as opposed to greater severity in PTSD-MDD relative to PTSD-alone, we used baseline CAPS scores as covariates in this analysis.

Linear regression analyses were performed to investigate the relationship between the strength of rs-FC and symptom severity (CAPS) and depressive symptoms (HAM-D) in all subjects. The significance level for tests for the four connectivity pathways of interest (BLA-OFC, CMA-THA, NAcc-THA, and NAcc-HIP) was established at $P \leq .012$ (Bonferroni-corrected).

3 | RESULTS

3.1 | Demographics and clinical variables

Table 1 presents the demographic and clinical characteristics of the subjects. First, all patients with PTSD were compared with TEHCs.

Patients with PTSD did not differ from TEHC in age ($p = .67$) or sex ($\chi^2 p = .45$). As expected, PTSD subjects had significantly higher depression symptom severity (on HAM-D) and PTSD symptom severity (CAPS) than TEHC ($p < .001$). Second, PTSD-MDD was compared with PTSD-alone. PTSD-MDD subjects did not differ from PTSD-alone in age ($p = .98$), sex ($p = .61$) or years of education ($p = .85$). PTSD-MDD subjects had higher depression symptom severity ($p < .001$) and PTSD symptom severity ($p = .005$) than PTSD-alone subjects.

3.2 | Functional connectivity analysis

3.2.1 | Comparing PTSD and TEHC subjects on rs-FC of amygdala subregions

Between-ROI connectivity analysis was performed on a priori defined ROIs. PTSD subjects had significantly decreased BLA-OFC ($t = 2.64$, $df = 82$, $p_{FDR} < .05$) and CMA-THA connectivity compared with TEHC ($t = 2.60$, $df = 82$, $p_{FDR} < .05$) (Fig. 2). No difference was observed between PTSD and TEHC using the NAcc as seed ($p_{FDR} > .05$). Whole brain exploratory analysis using BLA and CMA as seeds appear in Supporting Information Tables S1 and S2.

3.2.2 | Comparing PTSD-alone, PTSD-MDD, and TEHC subjects on rs-FC of amygdala and striatal-subcortical regions

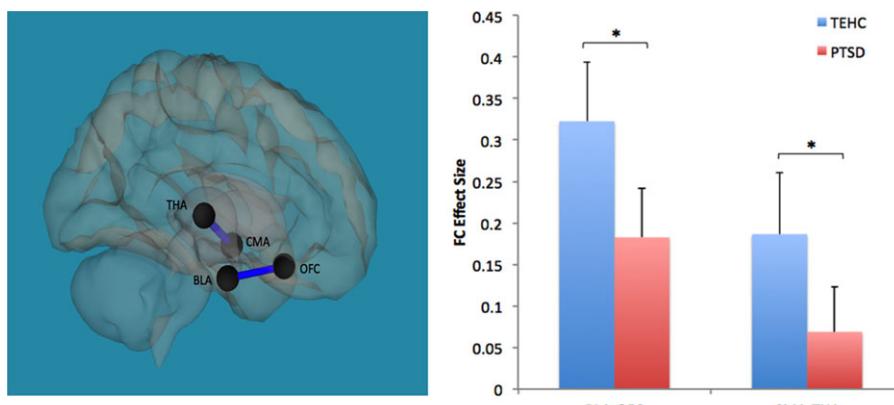
ANCOVA revealed significant differences among the three groups in NAcc-THA ($F(2,81) = 5.5$, $p_{FDR} < .05$), and NAcc-HIP ($F(2,81) = 3.9$, $p_{FDR} < .05$) connectivity, but not BLA-OFC and CMA-THA connectivity. Post hoc ANCOVA tests on the two pathways revealed significantly more decreased rs-FC in PTSD-MDD than PTSD-alone group in NAcc-THA ($F(1,47) = 10.8$, $p = .002$) and NAcc-HIP ($F(1,47) = 8.04$, $p = .007$) pathways, and decreased rs-FC in PTSD-MDD relative to TEHC group in NAcc-THA ($F(1,54) = 4.4$, $p = .04$) and NAcc-HIP ($F(1,54) = 4.1$, $p = .045$) pathways. Post hoc ANCOVA tests also revealed differences between PTSD-alone and PTSD-MDD ($F(1,47) = 4.29$, $p = .044$), and between TEHCs and PTSD-MDD ($F(1,54) = 4.4$, $p = .04$) in the

TABLE 1 Demographic and clinical characteristics of the sample ($n = 82$)

	PTSD all ($n = 48$)	TEHC ($n = 34$)	P (PTSD vs. TEHC)	PTSD-MDD ($n = 21$)	PTSD-alone ($n = 27$)	P (MDD vs. PTSD-a)
Sex, N (%)			.45			.61
Male	19 (39.6)	11 (32.4)		7 (33.3)	12 (44.4)	
Female	29 (60.4)	23 (67.6)		14 (66.7)	15 (55.6)	
Race, N (%) ^a			.70			.66
Caucasian	14 (29.2)	11 (32.4)		6 (28.6)	8 (29.6)	
African-American	12 (25.0)	11 (32.4)		7 (33.3)	5 (18.5)	
Hispanic	17 (35.4)	11 (32.4)		6 (28.6)	11 (40.7)	
Others	4 (8.3)	1 (2.9)		2 (9.5)	2 (7.4)	
Age, mean years (SD)	36.1 (8.8)	35.1 (10.6)	.67	36.1 (8.2)	36.0 (9.1)	.98
Education, mean years (SD)	14.2 (2.0)	16.1 (1.9)	<.001	14.2 (2.0)	14.1 (2.0)	.85
HAM-D, mean (SD)	16.2 (5.5)	2.0 (2.1)	<.001	19.2 (5.0)	13.8 (4.6)	<.001
CAPS-total, mean (SD)	81.3 (15.5)	3.9 (4.7)	<.001	88.6 (15.8)	75.7 (12.5)	.005

HAM-D, Hamilton Depression Scale; CAPS, Clinician-Administered PTSD Scale; PTSD, posttraumatic stress disorder; PTSD-a: posttraumatic stress disorder-alone; TEHC, trauma-exposed healthy controls; MDD, major depressive disorder

^aOne PTSD-alone subject lacked ethnicity information.

**FIGURE 2** Decreased BLA-OFC, CMA-THA connectivity were found in PTSD, when compared with TEHC ($p < .05$, FDR-corrected)

BLA-OFC pathway (Fig. 3). No other group difference was observed in post hoc ANCOVA tests.

3.3 | Relationship between functional connectivity and clinical measures

Post hoc correlation analysis of the functional connectivity pathways and PTSD (CAPS) and depressive (HAM-D) symptoms were performed for all PTSD patients. Amygdala pathway connectivity negatively correlated with PTSD symptom severity (BLA-OFC, $r = -0.288$, $p \leq .006$; CMA-THA, $r = -0.234$, $p \leq .012$), suggesting decreased connectivity is associated with greater PTSD severity (Fig. 4). No significant relationships were found between any NAcc pathways and PTSD symptoms. MDD symptoms, however, were negatively associated with the BLA-OFC pathway ($r = -0.324$, $p \leq .006$) in all PTSD patients, suggesting an association of depressive symptoms severity with decreased top-down frontal control; and with NAcc-THA pathway ($r = -0.342$, $p \leq .006$), suggesting impaired affect regulation function (Fig. 5). No significant relationships were found between any of the pathways and PTSD and MDD symptoms in the two PTSD subgroups (PTSD-alone, PTSD-MDD). Results are presented in Supporting Information.

4 | DISCUSSION

The study results directly support our hypotheses. First, consistent with previous animal and human research, amygdala BLA and CMA subregions showed differences in functional connectivity between participants with PTSD and TEHCs. Specifically, whereas TEHC exhibited intact amygdala connectivity, PTSD participants had decreased functional connectivity in two distinct pathways: the BLA-OFC, involved in fear processing (Jovanovic & Ressler, 2010); and the CMA-thalamus, involved in fear response (Duvarci & Pare, 2014). Second, the PTSD-MDD group exhibited greater decrease in BLA-OFC pathway functional connectivity than either PTSD-alone or healthy control subjects, suggesting deficient frontal control of amygdala among patients with comorbid PTSD-MDD. Third, reward system-related striatal-subcortical connectivity was reduced for PTSD-MDD in two pathways, NAcc-thalamus and NAcc-hippocampus, relative to PTSD-alone or controls. Lastly, differential relationships emerged between PTSD and MDD clinical symptom severity and connectivity in fear and reward pathways. Whereas PTSD symptoms were only associated with amygdala subregions' connectivity pathways, MDD symptoms were associated with both fear and reward pathway connectivity.

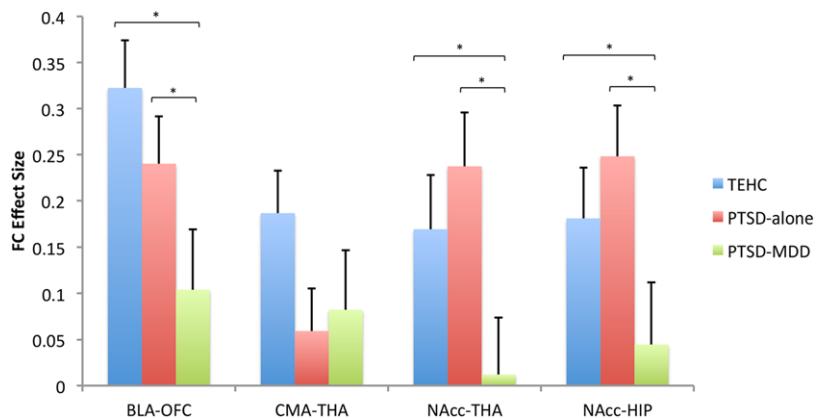


FIGURE 3 Rs-FC of BLA-OFC, CMA-THA, NAcc-THA, and NAcc-HIP for PTSD-MDD, PTSD-alone, and TEHC groups. ANCOVA revealed significant differences among the three groups in NAcc-THA ($F(2,81) = 5.5, p_{FDR} < .05$), and NAcc-HIP ($F(2,81) = 3.9, p_{FDR} < .05$) connections. Significant connectivity revealed by post hoc ANCOVA tests were marked as asterisk (*)

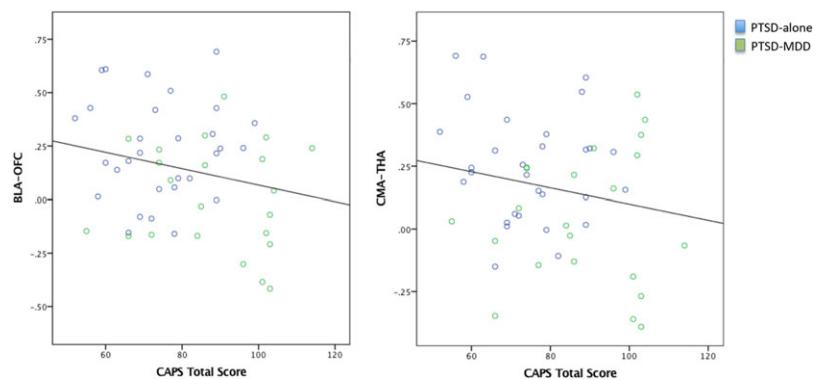


FIGURE 4 Correlations between CAPS scores and rs-FC of BLA-OFC ($r = -0.288, p \leq .006$) (left) and CMA-THA ($r = -0.234, p \leq .006$) (right) in all PTSD participants (PTSD-alone and PTSD-MDD combined). NAcc-THA ($r = -0.12$) and NAcc-HIP ($r = -0.078$) were not correlated with CAPS total score in all PTSD participants. Blue dot: PTSD-alone, green dot: PTSD-MDD

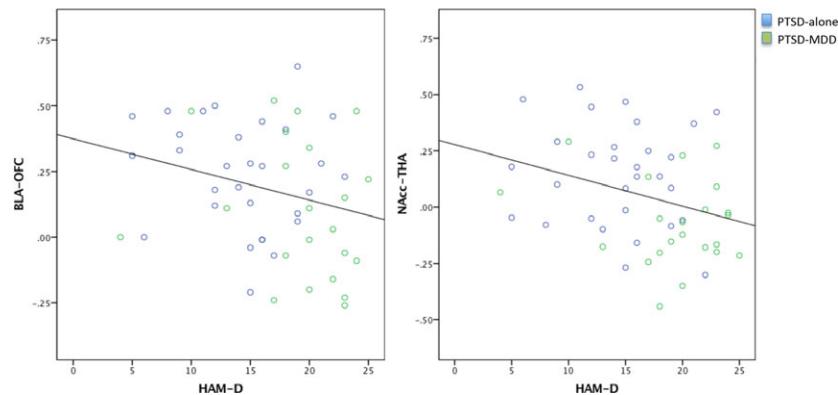


FIGURE 5 Correlations between HAMD total and FC of BLA-OFC ($r = -0.324, p \leq .006$) (left) and NAcc-THA ($r = -0.342, p \leq .006$) (right) in all PTSD participants (PTSD-alone and PTSD-MDD combined). NAcc-HIP ($r = -0.213, p = .056$) and CMA-THA ($r = -0.061, p = .589$) did not reach significant. Blue dot: PTSD-alone, Green dot: PTSD-MDD

Our first set of findings confirmed that amygdala subregions of BLA and CMA may have distinct roles in PTSD, supporting previous research that the BLA connects with cortical regions and CMA connects with subcortical regions (Brown et al., 2014; Etkin et al., 2009). The OFC is implicated in various functions, particularly higher-order executive functions involving inhibition of emotional responses and decision-making (Milad & Rauch, 2007).

Several animal and human neuroimaging studies have implicated the OFC and adjacent ventromedial PFC in the extinction of conditioned fear (Milad, Rauch, Pitman, & Quirk, 2006). Indeed, inadequate top-down control over the amygdala by the OFC may be associated with exaggerated fear response and anxious behaviors (Koenigs & Grafman, 2009), and several PTSD studies have shown that diminished PFC activation is manifested in exaggerated amygdala

activity as well as impaired amygdala-PFC coupling (Shvil, Rusch, Sullivan, & Neria, 2013), which in turn may result in heightened hyperarousal (Sadeh et al., 2014). Our findings further suggest decreased OFC functional connectivity to BLA among subjects with PTSD compared to non-PTSD trauma exposed controls. This finding is consistent with previous studies demonstrating that amygdala modulation of fear conditioning is localized in the BLA (McGaugh, 2004, Roozenboom et al., 2006), and that a BLA-OFC pathway malfunction may impair conditioned fear response (Baxter et al., 2000). We found that BLA-OFC functional connectivity negatively correlates with PTSD and MDD symptoms, suggesting that diminished BLA-OFC coupling, representing altered top down control, is associated with greater clinical severity of both PTSD and MDD.

We also found reduced rs-FC between the CMA and thalamus among PTSD subjects, reflecting impaired behavioral and physiological responses in PTSD (Greco & Liberzon, 2016). Our results further indicated negative correlation of CMA-THA functional connectivity with PTSD symptoms, suggesting that diminished CMA-THA coupling is associated with greater clinical severity of PTSD. Our findings, however, are inconsistent with the report of Brown et al. (2014). They found that PTSD associated with stronger BLA connectivity with the pregenual ACC, dorsomedial PFC, and dorsal ACC compared to TEHC, and no difference in CMA connectivity between PTSD and controls. Whereas our study excluded medicated patients, Brown and colleagues included them, with treatment potentially affecting functional connectivity.

Testing frontal-amamygdala connectivity patterns between PTSD alone, PTSD-MDD, and TEHCs, our findings showed that although the difference between PTSD-alone and TEHCs did not reach statistical significance, PTSD-MDD subjects manifested greater decrease in BLA-OFC connectivity than either PTSD-alone or TEHC. These findings support that a combination of PTSD-MDD symptoms increased impairment in the frontal-limbic pathway in our sample. While previous task-based work provided preliminary evidence of reduced amygdala and mPFC activation among patients with PTSD-MDD relative to those without depression during fear processing (Kemp et al., 2007), our findings of top-down control functional connectivity impairments separately in PTSD-alone and in PTSD-MDD groups are the first to demonstrate comparable abnormalities in rs-FC.

Our next findings focused on reward-related pathways. Striatal-subcortical connectivity was mainly altered among subjects with PTSD-MDD, and the NAcc-THA pathway negatively correlated with MDD symptoms. The NAcc has been consistently reported as the key reward network region affected in MDD during reward processing (Misaki et al., 2016), and has been a target of deep brain stimulation for treatment-resistant MDD patients (Nauczytel et al., 2013). The NAcc receives massive projections directly from the thalamus, and the NAcc-thalamus circuit is involved in regulating affective and motivational function (Haber & Calzavara, 2009). Reduced NAcc-THA connectivity may underlie the more severe problems with motivational function prevalent in PTSD-MDD. Furthermore, our finding that functional connectivity of the NAcc-THA negatively correlates with depressive symptoms, but not with PTSD symptoms, may suggest

such abnormality as a marker for comorbid PTSD-MDD within a PTSD sample.

Reward network impairments, long associated with depression (Zhang et al., 2013), were also discovered in PTSD (Elman et al., 2005), yet their characterization remains uncertain (Nawijn et al., 2015). Our data may illuminate potential impairments associated with MDD among patients diagnosed with PTSD. While low level depressive symptoms in the PTSD-only group were not associated with identifiable alterations in NAcc functional connectivity, more severe MDD and PTSD symptoms in the PTSD-MDD group were associated with greater alterations in both the NAcc and amygdala pathways.

Interestingly, our findings suggest reduced connectivity between the NAcc and hippocampus in PTSD-MDD versus PTSD-alone subjects. Animal studies reveal that an interaction between the hippocampus and NAcc may play a role in spatial context conditioning (Ito, Robbins, Pennartz, & Everitt, 2008). More recent neuroimaging studies in humans have begun to explore interactions between hippocampus and NAcc (Shohamy & Adcock, 2010), suggesting that reward modulates hippocampal memory formation. Other studies have shown that individuals with MDD exhibit potentiated NAcc, caudate, and putamen activation as well as disturbed ventral striatum-hippocampus connectivity in response to negative stimuli (Admon et al., 2015), and a large resting state fMRI study ($n = 994$) revealed convergent connectivity between hippocampus and NAcc, indicating the effects of motivation and reward processing on memory formation (Kahn & Shohamy, 2013).

In summary, our data confirmed alterations in functional connectivity of amygdala subregions involved in fear processing (BLA-OFC) and fear expression (CMA-THA), and also have begun to identify potential markers of altered reward processing in PTSD-MDD that might primarily relate to MDD rather than to PTSD. Future studies may clarify whether causal or temporal relationships may exist between PTSD and MDD, with possible "spillover" of corticolimbic dysregulation into the reward network. Although unable to address these temporal or causal relations, our results suggest that altered rs-FC in both fear and reward networks might be a marker for PTSD-MDD, potentially informing both diagnosis and treatment of this comorbidity.

5 | CLINICAL IMPLICATIONS

Although most PTSD treatments to date have focused on normalizing fear network deficits (Foa et al., 2005, Helpman et al., 2016b), our findings suggest that when PTSD patients have comorbid MDD, as is common (Neria & Bromet, 2000), they may benefit from a more comprehensive treatment approach addressing impairments in both fear and reward processing. Previous treatment studies have demonstrated efficacy in depression for treatments that putatively address reward dysfunction, such as behavioral activation (Dimidjian et al., 2006) and dopaminergic drugs (Soskin, Holt, Sacco, & Fava, 2013). PTSD treatments using such approaches have yet to be fully examined (Acierno et al., 2016). A recent study found that interpersonal psychotherapy (IPT), originally designed to treat depression, showed similar efficacy to PE for patients with chronic PTSD, and with a trend toward greater efficacy than PE for patients with comorbid

PTSD-MDD (Markowitz et al., 2015). This may reflect an IPT effect on reward processing, via relationship enhancement, pleasure seeking, and facilitating problem solving. Future neuroimaging research may inform whether highly targeted treatments for PTSD-MDD, addressing both fear and reward processing impairments when needed, can normalize altered connectivity, and in turn improve associated clinical symptoms.

6 | LIMITATIONS

This study lacked an MDD-only group, making it impossible to evaluate whether subjects with MDD but not PTSD have different functional connectivity compared with PTSD-MDD. Including MDD-only patients in future research can elucidate specific effects of MDD. Our approach also used subregions of amygdala and NAcc as seeds and other ROIs as targets. However, the cross-sectional, correlational techniques we applied preclude examination of causal relationships among the ROIs. Third, 62% of PTSD and 68% of TEHC subjects were female. Previous studies have shown significant sex-related differences in functional connectivity between amygdala and prefrontal regions (Kilpatrick, Zald, Pardo, & Cahill, 2006). Although we controlled for sex effects in all functional connectivity analyses, sex difference might still skew our results. Fourth, the two PTSD subgroups differed in CAPS score levels. Although the CAPS score was corrected for when we compared functional connectivity between subjects with PTSD-alone and those with PTSD-MDD, our results may be still somewhat biased by a symptom overlap (e.g., numbing and dysphoria) between PTSD and depression (Gros, Price, Magruder, & Frueh, 2012). Fifth, our data showed no relationships between any of the connectivity pathways and symptom severity in the two PTSD subgroups. Future studies with larger and more heterogeneous samples may clarify better these relationships. Sixth, the current study only provided baseline, group-level network connectivity biomarkers for PTSD with and without MDD. Individual-level data will ultimately be needed to provide information that can guide optimal treatment for individuals. Identifying brain biomarkers at the individual level using machine-learning techniques that predict treatment response may help achieve this goal. Sixth, as all our subjects were trauma exposed, our study was not designed to distinguish trauma-exposed from nontrauma-exposed subjects. Future studies should consider adding nontrauma-exposed subjects. Lastly, we collected our data using a 1.5 T scanner with relatively short resting-state scan time. Although a 1.5 T MRI is still completely adequate for most fMRI scans (Wardlaw et al., 2012), our data warrant replication in higher resolution scanners with eye-tracking systems, larger samples, and longer scan time.

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CONFLICT OF INTEREST

Drs. Zhu, Helpman, Van Meter, Lindquist, Wager, and Mr. Papini, report no biomedical financial interests or potential conflicts of interest.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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