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Diagnostic and Predictive Neuroimaging Biomarkers for Posttraumatic Stress Disorder

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ABSTRACT

BACKGROUND: Comorbidity between posttraumatic stress disorder (PTSD) and major depressive disorder (MDD) has been commonly overlooked by studies examining resting-state functional connectivity patterns in PTSD. The current study used a data-driven approach to identify resting-state functional connectivity biomarkers to 1) differentiate individuals with PTSD (with or without MDD) from trauma-exposed healthy control subjects (TEHCs), 2) compare individuals with PTSD alone with those with comorbid PTSD+MDD, and 3) explore the clinical utility of the identified biomarkers by testing their associations with clinical symptoms and treatment response.

METHODS: Resting-state magnetic resonance images were obtained from 51 individuals with PTSD alone, 52 individuals with PTSD+MDD, and 76 TEHCs. Of the 103 individuals with PTSD, 55 were enrolled in prolonged exposure treatment. A support vector machine model was used to identify resting-state functional connectivity biomarkers differentiating individuals with PTSD (with or without MDD) from TEHCs and differentiating individuals with PTSD alone from those with PTSD+MDD. The associations between the identified features and symptomatology were tested with Pearson correlations.

RESULTS: The support vector machine model achieved 70.6% accuracy in discriminating between individuals with PTSD and TEHCs and achieved 76.7% accuracy in discriminating between individuals with PTSD alone and those with PTSD+MDD for out-of-sample prediction. Within-network connectivity in the executive control network, prefrontal network, and salience network discriminated individuals with PTSD from TEHCs. The basal ganglia network played an important role in differentiating individuals with PTSD alone from those with PTSD+MDD. PTSD scores were inversely correlated with within–executive control network connectivity ($p < .001$), and executive control network connectivity was positively correlated with treatment response ($p < .001$).

CONCLUSIONS: Results suggest that unique brain-based abnormalities differentiate individuals with PTSD from TEHCs, differentiate individuals with PTSD from those with PTSD+MDD, and demonstrate clinical utility in predicting levels of symptomatology and treatment response.

Keywords: fMRI classification, Machine learning, Major depressive disorder, Posttraumatic stress disorder, Resting-state functional MRI, Support vector machine, Treatment outcome

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Posttraumatic stress disorder (PTSD) is a debilitating condition commonly observed in individuals following traumatic exposure, with estimated lifetime prevalence of 6.8% (1). PTSD is highly heterogeneous (2) and frequently comorbid with major depressive disorder (MDD) (3), complicating our ability to identify its brain mechanisms and identify novel therapeutic targets. Accumulating resting-state functional connectivity (rsFC) studies implicate altered within-network connectivity in the salience network (SN), default mode network (DMN), and executive control network (ECN) as well as between these networks (4,5). Within the SN, which typically includes the anterior cingulate cortex (ACC) and anterior insula, studies have found enhanced connectivity between the amygdala and insula nodes in individuals with PTSD relative to trauma-exposed healthy control subjects (TEHCs) and non-trauma–exposed healthy control subjects (HCs) (5–7). It was hypothesized that such enhanced connectivity attests to hypervigilance (6,7), whereas decreased connectivity between DMN nodes (e.g., posterior parietal cortex [PPC], precuneus, ventromedial prefrontal cortex [PFC], hippocampus) in individuals with PTSD (5,8,9) reflects depersonalization/derealization symptoms (10). It has been further suggested that these altered rsFC patterns may represent neurobiological correlates of increased salience processing and hypervigilance at the cost of awareness of internal thoughts and autobiographical memory in PTSD (4). Individuals with PTSD also showed decreased connectivity within the ECN (or frontal parietal network, which includes portions of the lateral PFC and PPC),

potentially representing diminished emotion regulation abilities (i.e., inability to downregulate negative emotions) (11,12).

Although the preponderance of data supports a view of PTSD as being associated with altered within- and between-network connectivity in the SN, DMN, and ECN, divergent findings have also been reported (4). Within the SN, connectivity between the amygdala and dorsal ACC has been shown in various studies to be higher (13), lower (6), or unaltered (7) in individuals with PTSD compared with control subjects (TEHCs and HCs). Both higher (5,14) and lower (8) between-network connectivity of DMN nodes, such as the PCC/precuneus and SN, have been demonstrated in individuals with PTSD compared with control subjects. Some studies have reported reduced connectivity between the amygdala and the inferior frontal gyrus, ventromedial PFC, and middle frontal cortex (6,13,14), whereas others have found no differences in connectivity between the amygdala and ventromedial PFC pathway (7,15).

A potential reason for these divergent findings might be the high comorbidity rates between PTSD and MDD, which have been largely overlooked by existing connectivity data analyses. PTSD and MDD co-occur in as many as 52% of cases (16,17), and this comorbidity is associated with significantly greater subjective distress and impairment than either condition alone [e.g., (7–10)], demonstrating a more chronic course of impairment (18). These clinical differences suggest that corresponding underlying neurobiological differences may be present as well. Meta-analyses on connectivity abnormalities in MDD (19–22) suggest that MDD is characterized by hypoconnectivity within the ECN and between frontoparietal systems and parietal regions of the dorsal attention network (DAN). MDD was also associated with hyperconnectivity within the DMN and with hyperconnectivity between ECN control systems and regions of the DMN. It is an open question whether individuals with PTSD+MDD show more connectivity abnormalities that are similar to those documented among individuals with MDD than do individuals with PTSD without MDD comorbidity.

To date, only a few studies (23,24) have assessed whether individuals with PTSD+MDD exhibit connectivity differences relative to individuals with PTSD alone. Kennis *et al.* (23) found in PTSD+MDD, versus PTSD alone, increased connectivity between the subgenual and perigenual ACC as well as decreased connectivity of the subgenual ACC with the thalamus. Yet this study focused on the insula and ACC as seed regions and did not address potential alterations in pathways involving the nucleus accumbens (NAcc). Zhu *et al.* (24) found that PTSD+MDD, compared with PTSD alone, was associated with multifaceted functional connectivity alterations, including decreased connectivity across multiple amygdala and striatal-subcortical pathways. These findings suggest that individuals with comorbid PTSD+MDD may show dysfunctions that characterize both individuals with PTSD and those with MDD, but it was not possible to draw definitive conclusions because of the small sample size.

Little is known about the clinical utility of the altered within- and between-networks connectivity identified so far in the literature on PTSD. The few available findings suggest that rsFC of the PCC with the perigenual anterior cingulate and the right amygdala is associated with current PTSD symptoms and that correlation with the right amygdala predicts future PTSD symptoms, but no treatment effect has been studied (25). Another study showed that neural circuitry changes may be associated with treatment response but did not investigate the ability of baseline biomarkers to predict treatment response (26). Closing this gap in the literature by investigating the clinical utility of identified biomarkers is of critical importance in the progress toward personalized PTSD treatments (27).

To address these gaps in knowledge, the current study had four aims, namely to 1) identify network connectivity differences distinguishing individuals with PTSD (with and without comorbid MDD) from TEHCs, 2) identify network connectivity differences distinguishing individuals with PTSD without MDD from those with PTSD+MDD, 3) examine the clinical utility of the features identified through aims 1 and 2 by examining their associations with MDD and PTSD symptomatology, and 4) test the utility of the identified network connectivity features in predicting subsequent treatment outcome in a subsample receiving prolonged exposure (PE) therapy. These four aims are critical for developing a better understanding of the unique neuropathology of patients with PTSD and to identify novel therapeutic targets.

To identify the network connectivity features (aims 1 and 2 above), the current study used a support vector machine (SVM) model, which is a multivariate pattern recognition machine learning (ML) technique especially well suited for discriminating high-dimensional rsFC functional magnetic resonance imaging (fMRI) data. ML approaches have two main advantages over standard univariate analytical methods that are typically used in neuroimaging. First, the traditional approaches are based on average estimates of differences at the group level. By contrast, ML approaches make possible inferences at the level of the individual rather than the group. In an effort to increase the translational applicability of the results to clinical practice where decisions are made about individual patients and not groups, there has been a recent shift toward the use of multivariate ML techniques (28–32). Findings based on ML approaches are expected to have higher translational applicability to everyday decision making in clinical practice. Second, ML approaches are more sensitive to differences that are subtle and spatially distributed by taking interregional correlations into account. Such spatially distributed patterns in the brain might be undetectable using group comparisons. Thus, ML approaches provide an optimal framework for investigating psychiatric disorders that affect a distributed network of regions (29–32).

Previous studies comparing traditional and ML approaches with group classification based on resting-state data suggest that ML approaches are more sensitive to the subtle and spatially diffuse alterations typically observed in psychiatric disorders and therefore may be better suited to the development of real-world clinical diagnostic tools than are standard mass-univariate techniques (28). Previous studies suggest SVM's ability to discriminate between trauma-exposed individuals with and without PTSD (67.57%–91%) and between TEHCs and HCs with high levels of accuracy (33,34). Studies further suggest SVM's ability to predict long-term response to antidepressant medication (21).

METHODS AND MATERIALS

Participants

We combined data from three studies conducted at the New York State Psychiatric Institute. The studies were approved by the Institutional Review Board of the New York State Psychiatric Institute, and all participants provided written informed consent after receiving an explanation of the procedures. rsFC fMRI was conducted in a total of 179 individuals (51 with PTSD alone, 52 with PTSD+MDD, and 76 TEHCs). Detailed inclusion and exclusion criteria for each study appear in Table S1. Briefly, all participants met the DSM-IV-TR criteria A1 and A2 (35) or the DSM-5 PTSD criterion A (36) for adult traumatic events. Clinical evaluators administered the Structured Clinical Interview for DSM-IV Axis I Disorders (37) and the Clinician-Administered PTSD Scale (CAPS) (38) to establish psychiatric diagnoses and assess PTSD severity. All participants in the PTSD+MDD group, but not in the PTSD-alone and TEHC groups, also met Structured Clinical Interview for DSM Disorders DSM-IV or DSM-5 criteria for a major depressive episode (35). Exclusion criteria for participants in the TEHC group consisted of current or past Axis I disorders, including substance use disorders and the use of any psychotropic medications. Exclusion criteria for all groups included any condition that would rule out MRI administration.

A subsample of 55 patients with PTSD (33 PTSD alone and 22 PTSD+MDD) underwent PE treatment conducted by one of two trained therapists adhering to a 10-week standard PE protocol (39). The detailed PE treatment protocol was described in Helpman *et al.* (40) and Zhu *et al.* (24).

Seed-Based Functional Connectivity Analyses

Neuroimaging data acquisition, preprocessing of imaging data, and seed-based functional connectivity analyses appear in the Supplement. rsFC analyses were carried out using a seed-based approach implemented in the CONN fMRI functional connectivity toolbox version 13 (41). Region of interest (ROI)-to-ROI connectivity analysis was performed using 43 ROIs previously identified as important in PTSD and MDD (see Supplement). The mean blood oxygen level–dependent time series was computed across all voxels within each ROI. Bivariate regression analyses were used to determine the linear association of the blood oxygen level–dependent time series between each pair of regions for each individual. The resultant correlation coefficients were transformed into *z* scores using Fisher's transformation to satisfy normality assumptions.

Statistical Analyses

Clinical Variables. We used SPSS software, version 23 (IBM Corp., Armonk, NY) for statistical analyses. *t* tests were used to test the differences in clinical symptoms and age between groups. Chi-square tests were used to analyze differences in gender and race.

ML Analysis: SVM. Linear kernel SVM has emerged as one of the most popular supervised ML methods, with learning algorithms aimed at classification used in neuroimaging (42) and psychiatry (43) studies. SVM uses a well-defined dataset to create a decision function or hyperplane that can best distinguish between categories, which can then be used to predict to which predefined group a new observation belongs. SVM can effectively handle high-dimensional data and is less prone to overfitting of the data (44). SVM classifies data points by maximizing the margin between classes in a high-dimensional space (45). It constructs an optimal classifier through a training phase in which key brain features are identified to distinguish between two groups (such as patients vs. control subjects), which is then applied to categorize new unseen data in the testing phase. Comparison studies between multivariate pattern recognition methods showed that SVM reduces the effect of noisy features that are highly correlated with each other in the presence of a large number of features (45). SVM can be combined with different methods for dimensionality reduction and feature selection to improve diagnostic accuracy (45). SVM was applied using the Statistics and Machine Learning Toolbox in MATLAB (The MathWorks, Inc., Natick, MA). The main steps of the SVM method included 1) preprocessing of features (regressing out age, gender, and dataset and normalizing each feature to [−1 1]), 2) feature extraction and selection within each cross-validation (using an embedded feature selection method, which combines filter- and wrapper-based approaches, to select the most discriminative features), 3) training the SVM classifier model by 10-fold cross-validation using the training data, and 4) evaluating the performance of the SVM model using the 10% holdout evaluation data (46). For more information regarding each of the steps, see the Supplement.

Correlation Analysis. We used SPSS software to calculate the correlations between identified features and clinical symptoms. Because some of the studies used CAPS-IV and others used CAPS-5, we used the index developed by Powers *et al.* (47) to convert the two versions of the CAPS into a common one for analysis. To correct for multiple correlations, we used an alpha of .0028 (0.05/18) for the 18 network connectivities identified based on the SVM implementation for the first comparison (individuals with PTSD with and without MDD vs. TEHCs) and used an alpha of .0025 (0.05/20) for the 20 network connectivities for the second comparison (individuals with PTSD alone vs. individuals with PTSD+MDD). We regressed out age, gender, and sites/scanners as covariates during the feature preprocessing, so no covariate was used during the correlation analysis. Combining data from different scanners with different scanning parameters and field strengths is common in the neuroimaging literature (48) and can yield reliable data (49) as long as the data are regressed out for scanner type. To examine associations between the identified features and treatment outcome in the subsample receiving PE, we also tested the correlations between pretreatment rsFC features and reduction in PTSD symptoms from pretreatment to posttreatment in both the CAPS and Hamilton Depression Rating Scale (HAM-D).

RESULTS

Demographics and Clinical Characteristics of the Participants

The PTSD and TEHC groups were not significantly different in gender (58 male subjects for the PTSD group; 36 male subjects

Table 1. Demographic and Clinical Characteristics of the Three Groups

	TEHC Group (n = 76)	PTSD Alone Group (n = 51)	PTSD+MDD Group (n = 52)
Gender, n (%)			
Male	36 (47.36%)	29 (56.86%)	29 (55.76%)
Female	40 (52.64%)	22 (43.14%)	23 (44.24%)
Race, n (%)			
Caucasian	21 (27.63%)	12 (23.52%)	17 (32.69%)
African American	23 (30.26%)	27 (52.94%)	22 (42.30%)
Hispanic	26 (34.21%)	0 (0%)	5 (9.61%)
Other	6 (7.89%)	12 (23.52%)	8 (15.38%)
Age, Years, Mean (SD)	40.8 (15.8)	40.6 (13.8)	43.9 (14.7)
HAM-D, Mean (SD)	2.97 (3.5)	12.8 (6.2)	18.7 (6.1)
Total CAPS, Mean (SD)	6.3 (6.8)	56.8 (23.5)	57.2 (28.9)

CAPS, Clinician-Administered PTSD Scale; HAM-D, Hamilton Depression Rating Scale; MDD, major depressive disorder; PTSD, posttraumatic stress disorder; TEHC, trauma-exposed healthy control subject.

for the control group; $\chi^2_1 = 1.40$, $p = .23$) or age (42.22 years for the PTSD group; 40.80 years for the control group; $t_{177} = -0.63$, $p = .53$). Patients with PTSD showed a significantly higher total CAPS score than TEHCs ($t = -15.92$, $p < .0001$). We repeated the analyses to test potential differences between the PTSD groups with and without MDD comorbidity. No significant differences were found for age ($t_{101} = -1.17$, $p = .24$), CAPS ($t_{101} = -0.79$, $p = .93$), or gender ($\chi^2_1 = 0.013$, $p = .91$) between the two groups. As expected, the PTSD+MDD group had higher HAM-D scores than the PTSD without MDD group (means = 18.67 and 12.82, respectively; $t_{101} = -4.80$, $p < .0001$). Detailed demographic and clinical data are shown in Table 1.

Discrimination Between Individuals With PTSD With and Without MDD and TEHCs

The PTSD versus TEHC classification revealed 18 final features (for the full list, see Figure 1) as the final selected subset based on the SVM implementation (area under the curve = 0.87, loss = 0.16; validation testing set: accuracy = 70.6%). The most discriminative features differentiating individuals with PTSD from TEHCs included within-network connectivity in the ECN, including ECN.LPFCr–ECN.PPCr and ECN.LPFCl–ECN.PPCl, and within the SN (SN.ACC–SN.AInsular and CMA–SN.AInsular) (see Table 2 for network abbreviations). Compared with individuals with PTSD, TEHCs showed stronger connectivity in the within-ECN and within-SN networks. All abbreviations appear in Table 2.

Discriminative features also emerged between network connectivity among SN–DAN, SN–DMN, DMN–DAN, and DMN–ECN. Compared with patients with PTSD, TEHCs showed lower connectivity in the DMN–DAN and SN–DMN but showed higher connectivity in the SN–DAN, SN–DMN, and DMN–ECN. For a full list of areas, see Table S2.

Discrimination of Individuals With PTSD+MDD From Those With PTSD Alone

The PTSD-alone versus PTSD+MDD classification revealed 20 final features (for the full list, see Figure 2) as the final selected subset based on the SVM implementation (training set area under the curve = 0.85, loss = 0.15; validation testing set: accuracy = 76.7%). The most discriminative features differentiating individuals with PTSD alone from those with PTSD+MDD included within-network connectivity in the basal ganglia network (BGN) (NAcc-THA), within the DAN (DAN.FEFl–DAN.IPSr), and within the SN (CMA-SN.RPFCl). Individuals with PTSD alone showed higher within connectivity than individuals with PTSD+MDD in the BGN but showed lower within connectivity in the ECN, SN, and DAN.

In addition, discriminative features emerged between the BGN and other related networks, including BGN–DAN

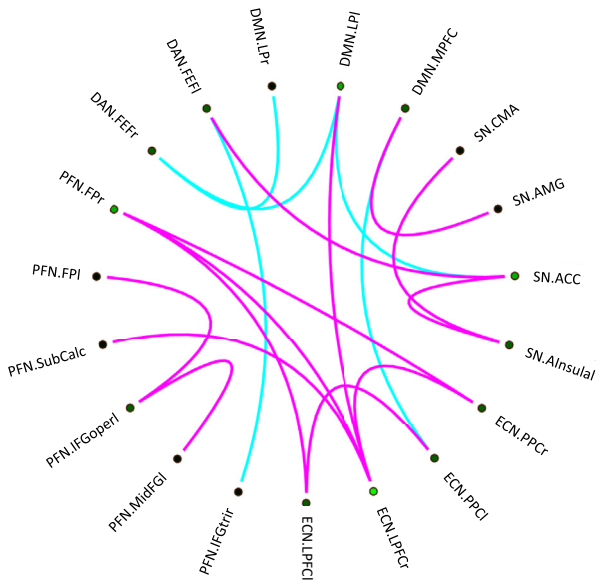

Figure 1. The most discriminative networks from differentiating all individuals with posttraumatic stress disorder (PTSD) from trauma-exposed healthy control subjects (TEHCs). Purple: TEHCs > PTSD; blue: TEHCs < PTSD. The figure represents the connectogram of the most discriminative multivariate features (spatial functional connectivity). The abbreviations are listed in Table 2.

Table 2. Abbreviations of Network Names

Network	Seed Names	Abbreviation	Coordinates (x, y, z)
ECN	Networks.Executive Control.Lateral Prefrontal Cortex left	ECN.LPFCl	−43, 33, 28
	Networks.Executive Control.Lateral Prefrontal Cortex right	ECN.LPFCr	41, 38, 30
	Networks.Executive Control.Posterior Parietal Cortex left	ECN.PPCl	−46, −58, 49
	Networks.Executive Control.Posterior Parietal Cortex right	ECN.PPCr	52, −52, 45
SN	Networks.Salience.Anterior Cingulate Cortex	SN.ACC	0, 22, 35
	Networks.Salience.AInsula left	SN.Insulal	−44, 13, 1
	Networks.Salience.AInsula right	SN.Insular	47, 14, 0
	Networks.Salience.Rostral Prefrontal left	SN.RPFCl	−32, 45, 27
	Networks.Salience.Rostral Prefrontal right	SN.RPFCr	32, 46, 27
	Networks.Salience.Supramarginal Gyrus left	SN.SMGl	−60, −39, 31
	Networks.Salience.Supramarginal Gyrus right	SN.SMGr	62, −35, 32
	Atlas.Amygdala	AMG	±23, −4 , −18
	Atlas.Basolateral Amygdala	BLA	±27, −7, −10
	Atlas.Central Medial Amygdala	CMA	±23, −6, −20
DMN	Networks.DefaultMode.Medial Prefrontal Cortex	DMN.MPFC	1, 55, −3
	Networks.DefaultMode.Lateral Parietal left	DMN.LPl	−39, −77, 33
	Networks.DefaultMode.Lateral Parietal right	DMN.LPr	47, −67, 29
	Networks.DefaultMode.Posterior Cingulate Cortex	DMN.PCC	1, −61, 38
	Atlas.Anterior Hippocampus	HIPA	±30, −15, −18
	Atlas.Posterior Hippocampus	HIPP	±29, −38, 2
	Atlas.Precuneus Cortex	Precuneus	0, −65, 41
BGN	Atlas.Nucleus Accumbens	NAcc	10, 12, −7
	Atlas.Thalamus	THA	±10, −17, 9
DAN	Networks.DorsalAttention.Frontal Eye Fields left	DAN.FEFl	−27, −9, 64
	Networks.DorsalAttention.Frontal Eye Fields right	DAN.FEFr	30, −6, 64
	Networks.DorsalAttention.Intraparietal Sulcus left	DAN.IPSl	−39, −43, 52
	Networks.DorsalAttention.Intraparietal Sulcus right	DAN.IPSr	39, −42, 54
PFN	Atlas.Superior Frontal Gyrus right	SFGr	16, 18, 61
	Atlas.Superior Frontal Gyrus left	SFGl	−16, 18, 61
	Atlas.Middle Frontal Gyrus right	MidFGr	43, 18, 45
	Atlas.Middle Frontal Gyrus left	MidFGl	−43, 18, 45
	Atlas.Inferior Frontal Gyrus, Pars Triangularis right	IFGtrir	46, 27, 27
	Atlas.Inferior Frontal Gyrus, Pars Triangularis left	IFGtril	−46, 27, 27
	Atlas.Inferior Frontal Gyrus, Pars Opercularis right	IFGoperr	54, 16, 19
	Atlas.Inferior Frontal Gyrus, Pars Opercularis left	IFGoperl	−54, 16, 19
	Atlas.Frontal Pole right	FPr	31, 59, 13
	Atlas.Frontal Pole left	FPl	−31, 59, 13
	Atlas.Subcallosal Cortex	SubCalC	0, 21, −13
	Atlas.Orbital Frontal Cortex right	OFCr	32, 24, −15
	Atlas.Orbital Frontal Cortex left	OFCl	−32, 24, −15
SMN	Networks.SensoriMotor.Lateral left	SMN.Ll	−55, −12, 29
	Networks.SensoriMotor.Lateral right	SMN.Lr	56, −10, 29
	Networks.SensoriMotor.Superior	SMN.S	0, −31, 67

BGN, basal ganglia network; DAN, dorsal attention network; DMN, default mode network; ECN, executive control network; PFN, prefrontal network; SMN, sensorimotor network; SN, salience network.

and BGN–SN, as well as other between-network connectivity, including SN–DMN, DAN–ECN, and SMN–DMN. Individuals with PTSD alone showed higher connectivity in BGN-other networks, SN–DMN, DAN–ECN, and SMN–other networks. For a full list of areas, see Table S3.

Associations Between the Identified Biomarkers at Baseline and PTSD and MDD Symptomatology at Baseline

We examined the correlations between rsFC features identified above and CAPS and HAM-D symptom severity at baseline.

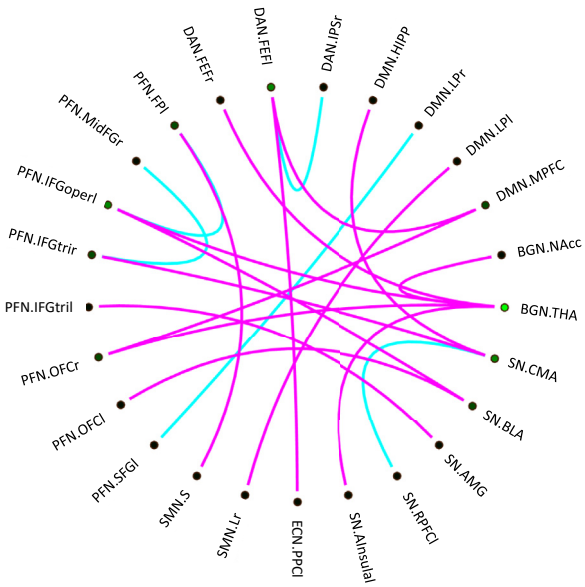

Figure 2. The most discriminative networks from differentiating individuals with posttraumatic stress disorder (PTSD) alone from individuals with PTSD + major depressive disorder (MDD). Purple: PTSD alone > PTSD+MDD; blue: PTSD alone < PTSD+MDD. The figure represents the connectogram of the most discriminative multivariate features (spatial functional connectivity). The abbreviations are listed in Table 2.

Associations Between Identified Biomarkers From PTSD-All and TEHC Classification and Symptomatology. For the CAPS, significant negative correlation was found between baseline CAPS scores and within-ECN connectivity with $p < .001$ (ECN.LPFCR–ECN.PPCR: $r = -.302$; FPr-ECN.PPC: $r = -.248$; ECN.LPFCL–ECN.PPCL: $r = -.237$). For the HAM-D, significant negative correlation was found between baseline HAM-D scores and within-ECN connectivity with $p < .001$ (FPr-ECN.LPFCR: $r = -.239$, $p = .002$).

Associations Between Identified Biomarkers From PTSD+MDD and PTSD-Alone Classification and Symptomatology. For the CAPS, no significant correlation was found in any networks. For the HAM-D, no significant correlation was found in any networks.

The Utility of Baseline Biomarkers in Predicting PE Treatment Outcome, Calculated as Changes in Symptoms From Pretreatment to Posttreatment

We examined the correlations between the baseline rsFC features identified above and the changes in CAPS and HAM-D symptom severity from baseline to posttreatment.

Features Identified From PTSD-All and TEHC Classification. For the CAPS, higher within-ECN connectivity (ECN.LPFCr–ECN.PPCr: $r = .455$, $p < .001$; FPr-ECN.LPFCr: $r = .415$, $p = .002$) correlated with greater PTSD CAPS symptom reduction. For the HAM-D, no significant correlation was found.

Features Identified From PTSD-Alone and PTSD-MDD Classification. For the CAPS, no significant association was found. For the HAM-D, no significant association was found.

Trend-Level Findings: Associations With Symptomatology at Baseline. For individuals with PTSD-all versus TEHCs, a trending negative correlation was found between baseline CAPS scores and within-SN connectivity (SN.ACC–SN.Insular: $r = -.205$, $p = .007$). A trending positive correlation was found between baseline CAPS scores and within-DMN-DAN connectivity (DMN.LPR–DAN.FEFr: $r = .207$, $p = .007$). For individuals with PTSD+MDD versus those with PTSD alone, a trending negative correlation was found between baseline CAPS scores and NAcc-THA ($r = -.203$, $p = .041$). A trending negative correlation was also found between baseline HAM-D scores and THA-DAN.FEFr connectivity ($r = -.182$, $p = .066$).

Trend-Level Findings: Associations With Treatment Response. A trending positive correlation was found between greater PTSD CAPS symptom reduction and within-ECN connectivity (FPr-ECN.PPCr: $r = .365$, $p = .006$) and within-SN connectivity (SN.ACC–SN.Ainsular: $r = .284$, $p = .035$). For correlations with specific clusters of the CAPS, see Tables S4 to S7.

DISCUSSION

The current study identified functional connectivity biomarkers differentiating individuals with PTSD, individuals with PTSD+MDD, and TEHCs and demonstrated their clinical utility. An SVM model was able to discriminate with a high level of accuracy between individuals with PTSD and TEHCs and between individuals with PTSD alone and those with comorbid PTSD+MDD. Specifically, we achieved 70.6% accuracy in discriminating between individuals with PTSD and TEHCs and achieved 76.7% accuracy in discriminating between individuals with PTSD and those with PTSD+MDD for out-of-sample prediction. Within-networks and between-networks connectivity features differentiating individuals with PTSD from TEHCs (Figure 1) and differentiating individuals with PTSD alone from those with PTSD+MDD (Figure 2) were consistent with at least some of the previous reports characterizing connectivity abnormalities in PTSD and attest to the importance of MDD-related abnormalities in differentiating between PTSD alone and PTSD+MDD. The identified altered connectivity features characterizing individuals with PTSD (with or without MDD comorbidity) compared with TEHCs demonstrated clinical utility, as evident by the associations between these features and symptomatology and by the ability to predict treatment response.

The findings attest to the ability to differentiate between individuals with PTSD and TEHCs with a relatively high level of accuracy. Consistent with at least some of the literature, among the most discriminative features were altered within-network connectivity in the SN and the ECN as well as altered SN–DMN between-network connectivity (4,5). The findings are consistent with some previous reports suggesting enhanced connectivity between amygdala and insula nodes

within the SN (6,7) but not with some other studies (4,50). In addition to the networks described in the literature on PTSD, the current findings also demonstrate the role of the triple network alteration consisting of the ECN, the SN, and the DMN. It has been suggested that the SN integrates sensory, emotional, and cognitive information, acts as an interface between the DMN and the ECN to integrate and balance internal mental processes with external stimulus-driven cognitive and affective processes (51,52), and may be useful in differentiating individuals with PTSD from control subjects (53). Individuals with PTSD showed higher DMN–DAN network connectivity, which may reflect the abnormal cognitive function associated with PTSD. Currently, the diagnosis of PTSD relies on subjective reporting of symptoms. The altered network connectivities identified here may eventually be used to develop objective biomarkers for PTSD to help clinicians improve the accuracy of PTSD diagnosis.

The findings further demonstrated the ability to differentiate between individuals with PTSD+MDD and those with PTSD alone with 76.7% accuracy. Among the most discriminative rsFC abnormalities in PTSD+MDD versus PTSD alone were those related to reward dysfunctions, which are typical of patients with MDD (54). Individuals with PTSD+MDD versus those with PTSD alone showed rsFC abnormalities within the BGN, which has been found to underlie reward behavior in prior reports (55). The BGN comprises the striatum (subdivided into the caudate nucleus and putamen), globus pallidus, and thalamus (56). Altered BGN connectivity in individuals with PTSD+MDD, as opposed to those with PTSD alone, may underlie impaired motivation and a high prevalence of addictions and substance use in this subpopulation (57). The findings also attest to the importance of identifying not only within-network but also between-network impairments, indicating both altered BGN within-network connectivity and altered connectivity between the BGN and other related networks (BGN–DAN and BGN–SN) in PTSD+MDD versus PTSD alone.

Unique brain-based biomarkers differentiating PTSD alone from PTSD+MDD may help to explain divergent findings in PTSD connectivity studies enrolling heterogeneous populations, mixing individuals with PTSD alone and those with PTSD+MDD. Including different proportions of individuals with PTSD alone and those with PTSD+MDD may influence which networks show the most altered connectivity. Moreover, features differentiating PTSD+MDD from PTSD alone may be useful in identifying novel therapeutic targets, which are much needed in this comorbid subgroup that is frequently nonresponsive to treatment and shows poor prognosis (18). Currently, targets of intervention for PTSD include fear processing pathways but do not address MDD-related deficits. Potentially distinct patterns of brain regions may be involved in fear and reward processing in individuals with PTSD alone and in those with comorbid PTSD+MDD. PTSD may be associated with decreased connectivity of pathways that are key to fear processing and fear expression such as the basolateral amygdala–orbital frontal cortex and cingulate motor area–thalamus, respectively (58). PTSD comorbidity with MDD may be associated with decreased connectivity of pathways, which are key to the reward system, for example, decreased connectivity across multiple amygdala and striatal–subcortical pathways: basolateral amygdala–orbital frontal cortex, NAcc–thalamus, and NAcc–hippocampus (59). Thus, it has been suggested that comorbid PTSD+MDD is associated with multifaceted functional connectivity alterations in both fear and reward systems (24). The current findings support this suggestion. The fact that available treatments do not focus on the specific patterns of alteration that characterize individuals with PTSD+MDD may explain the poor prognosis of currently available treatments for this subpopulation compared with that of patients with PTSD alone (24). Given the importance of the BGN and reward-related abnormalities in PTSD+MDD versus PTSD alone, new therapeutic solutions for individuals with PTSD+MDD are needed that target the altered BGN such as those focusing on dopaminergic targets.

Several post hoc explanations may be suggested for why classification accuracy for PTSD versus PTSD+MDD was higher than that for PTSD versus non-PTSD. One explanation is that the NAcc may play a critical role in differentiating between those with and without MDD comorbidity, resulting in higher heterogeneity within the PTSD diagnosis (i.e., between PTSD+MDD and PTSD alone) than between individuals who were exposed to trauma and developed PTSD and those who did not develop PTSD (24). This and other post hoc explanations should be considered with caution, however, because the difference between the clarification accuracy of individuals with PTSD versus TEHCs and that of individuals with PTSD alone versus Those with PTSD+MDD was only 6.1% (70.6% and 76.7%, respectively).

Findings demonstrate the clinical utility of the identified biomarkers discriminating individuals with PTSD-all from TEHCs. Specifically, significant associations were found between alteration in within-ECN connectivity and PTSD and MDD symptoms, such that higher connectivity was associated with more severe symptoms. The identified biomarkers were also capable of predicting treatment response; lower within-ECN connectivity was associated with greater PTSD symptom reduction. This finding is consistent with a previous report demonstrating decreased connectivity within the ECN in patients with PTSD, potentially representing diminished emotion regulation abilities (i.e., inability to downregulate negative emotions) (4). Interestingly, the identified biomarkers discriminating PTSD alone from PTSD+MDD were not significantly associated with symptomatology and treatment response. One potential post hoc explanation is that the received treatment focused on PTSD and that treatment focusing on MDD may have yielded different results.

Several limitations should be noted. First, the current study combined data from three separate trials to increase sample size, with some differences among the trials in their inclusion and exclusion criteria as well as differences between scanners in spatial and temporal signal-to-noise ratios. In addition, we relied exclusively on differences between DSM disorders despite the potential interest in within-disorder variance, including categorization options that transcend the boundaries of clinical diagnosis. Future studies should implement unsupervised ML approaches that can complement the current findings by determining the extent to which the biomarkers identified here for PTSD+MDD and PTSD are indeed those that create distinct subpopulations of patients. This could determine whether the identified data-driven biotypes of homogeneous patterns of dysfunctional connectivity match those found in the current study. Future studies with larger samples should also explore

the association between the different clusters of PTSD symptoms and the identified resting-state features. Finally, it should be noted that because a trauma-unexposed subgroup was not included, the effect of trauma exposure could not be tested.

These caveats notwithstanding, the current findings suggest that unique sets of brain-based biomarkers differentiate between individuals with PTSD (with and without comorbid MDD) and TEHCs as well as between individuals with PTSD alone and those with PTSD+MDD. Certain connectivity alterations in the PTSD+MDD comorbid population versus the PTSD-alone population may explain inconsistencies between previous studies that enrolled diverse participant populations. The current findings suggest that brain function abnormalities observed in PTSD+MDD versus PTSD alone during fMRI resting state were those related to corticolimbic dysregulation, which are the basis of MDD etiology and describe altered connections. The findings also stress the importance of the triple network in PTSD. The findings further demonstrate the clinical utility of the identified connectivity alterations, especially within the ECN, by demonstrating its associations with PTSD and MDD symptoms and its ability to predict subsequent treatment response. Taken together, the findings support the potential of resting-state fMRI to inform accurate future clinical assessment of psychopathology in individuals at high risk for developing PTSD following exposure to trauma by the development of objective biomarkers indicative of the diagnostic heterogeneity of psychopathology and of treatment prognosis. Such objective biomarkers may facilitate the early identification of heterogeneous subtypes of illness. Neuroimaging techniques hold the promise to aid in the clinical assessment of individual psychiatric patients, particularly in cases where a clear differential diagnosis is difficult to establish because of comorbidity. If these findings are replicated in future research, they can make an important contribution to accurate diagnosis and help to identify precise targets for maximally efficient treatment of PTSD+MDD and PTSD alone.

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