

Original Investigation

Association of Posttraumatic Stress Disorder With Reduced In Vivo Norepinephrine Transporter Availability in the Locus Coeruleus

Robert H. Pietrzak, PhD, MPH; Jean-Dominique Gallezot, PhD; Yu-Shin Ding, PhD; Shannan Henry, BS; Marc N. Potenza, MD, PhD; Steven M. Southwick, MD; John H. Krystal, MD; Richard E. Carson, PhD; Alexander Neumeister, MD

IMPORTANCE Animal data suggest that chronic stress is associated with a reduction in norepinephrine transporter (NET) availability in the locus coeruleus. However, it is unclear whether such models are relevant to posttraumatic stress disorder (PTSD), which has been linked to noradrenergic dysfunction in humans.

OBJECTIVES To use positron emission tomography and the radioligand [¹¹C]methylreboxetine to examine in vivo NET availability in the locus coeruleus in the following 3 groups of individuals: healthy adults (HC group), adults exposed to trauma who did not develop PTSD (TC group), and adults exposed to trauma who developed PTSD (PTSD group) and to evaluate the relationship between NET availability in the locus coeruleus and a contemporary phenotypic model of PTSD symptoms.

DESIGN, SETTING, AND PARTICIPANTS Cross-sectional positron emission tomography study under resting conditions at academic and Veterans Affairs medical centers among 56 individuals in the following 3 study groups: HC (n = 18), TC (n = 16), and PTSD (n = 22).

MAIN OUTCOMES AND MEASURES The [¹¹C]methylreboxetine-binding potential of NET availability in the locus coeruleus and the severity of PTSD symptoms assessed using the Clinician-Administered PTSD Scale.

RESULTS The PTSD group had significantly lower NET availability than the HC group (41% lower, Cohen *d* = 1.07). NET availability did not differ significantly between the TC and HC groups (31% difference, Cohen *d* = 0.79) or between the TC and PTSD groups (15% difference, Cohen *d* = 0.28). In the PTSD group, NET availability in the locus coeruleus was independently positively associated with the severity of anxious arousal (ie, hypervigilance) symptoms (*r* = 0.52) but not with any of the other PTSD symptom clusters.

CONCLUSIONS AND RELEVANCE These results suggest that PTSD is associated with significantly reduced NET availability in the locus coeruleus and that greater NET availability in this brain region is associated with increased severity of anxious arousal symptoms in individuals with PTSD.

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Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Author: Alexander Neumeister, MD, Departments of Psychiatry and Radiology, New York University School of Medicine, One Park Ave, Eighth Floor, Room 225, New York, NY 10016 (alexander.neumeister@nyumc.org).

Posttraumatic stress disorder (PTSD) is an anxiety disorder that may arise in response to a traumatic event.¹ Recently, a 5-factor model composed of reexperiencing (ie, intrusive memories and nightmares), avoidance (ie, avoiding reminders of trauma), numbing (ie, detachment and loss of interest), dysphoric arousal (ie, sleep difficulties, irritability or anger, and concentration problems), and anxious arousal (ie, hypervigilance and exaggerated startle) symptoms has been demonstrated to provide a precise phenotypic representation of PTSD symptom structure.²⁻⁵ Although research on the symptom structure of PTSD has advanced its phenotypic characterization, only one study⁶ to date has examined neurobiological factors associated with this model and could not, as expected, fully explain the phenotypic heterogeneity of this disorder.

The norepinephrine transporter (NET) is a potential target for studying the pathogenesis of PTSD. The NET is part of the family of sodium chloride neurotransmitter transporters,⁷ has the highest concentration in the locus coeruleus, and has moderate levels within cortical and subcortical regions, including the frontal cortex, hippocampus, amygdala, thalamus, and cerebellar cortex.⁸ The human NET attenuates neuronal signaling by promoting rapid norepinephrine (NE) clearance from the synaptic cleft,⁹ thereby maintaining pre-synaptic NE storage.¹⁰

Characterizing NET availability following the healthy human adaptation of stress and the development of PTSD would shed light on noradrenergic contributions to the human stress response. Although acute stress does not alter NET density, evidence from rodent investigations shows that repeated exposure to stress decreases NET availability in the locus coeruleus and limbic brain regions.¹¹ This work has led to the idea that lower NET density may be related to the development of mood and anxiety disorders.¹²⁻¹⁵ However, human in vivo studies of the NET are lacking to date. The development of radiolabeled carbon 11 (¹¹C) reboxetine derivatives, which show specific localization and highly favorable binding kinetics in rats, nonhuman primates, and humans, makes it feasible to conduct in vivo studies of the NET¹⁶⁻¹⁹ using positron emission tomography (PET). Among the different reboxetine derivatives that have been tested, (*S,S*)-methylreboxetine (MRB) has a half-maximal inhibitory concentration of 2.5nM and is considered a promising PET ligand for studying the brain NET system.²⁰ Work conducted to date has found that the highest brain concentrations of (*S,S*)-[¹¹C]O-methylreboxetine ([¹¹C]MRB) were in midbrain regions, followed by the thalamus, while the lowest concentrations were observed in basal ganglia and occipital cortex. This is consistent with the known distribution of the NET in brain.^{17,21} This PET tracer has been shown to be useful in NET occupancy studies^{22,23} of atomoxetine hydrochloride and methylphenidate, which have demonstrated its use in measuring NET availability in vivo.

The objective of the present study was 2-fold. First, we sought to examine whether PTSD would be associated with lower NET availability in the locus coeruleus. We evaluated this hypothesis in the following 3 groups of individuals: healthy adults without exposure to trauma (HC group), adults exposed to trauma who did not develop PTSD or other lifetime

psychiatric illness (TC group), and adults exposed to trauma who developed PTSD (PTSD group). A trauma-exposed group without PTSD was included to assess the relationship between trauma exposure alone and NET availability. Relative to control subjects, we hypothesized that PTSD would be associated with decreased NET availability in the locus coeruleus. Second, we sought to evaluate whether NET availability in the locus coeruleus would be differentially associated with PTSD symptom dimensions of a contemporary, 5-factor phenotypic model of PTSD symptoms among individuals with PTSD. We predicted that NET availability in the locus coeruleus would be independently positively associated with the severity of anxious arousal (ie, hypervigilance) symptoms but not with any of the other PTSD symptom clusters.

Methods

Participants

Fifty-six participants were recruited into 3 groups using public advertisements, and they provided written informed consent. We recruited 22 adults with PTSD (hereafter referred to as the PTSD group), 16 adults who had been exposed to trauma but did not have PTSD (hereafter referred to as the trauma control [TC] group), and 18 healthy adult control subjects (hereafter referred to as the healthy control [HC] group). This study was approved by the Yale University School of Medicine Human Investigation Committee, the Human Subjects Subcommittee of the Veterans Affairs Connecticut Healthcare System, the Yale University Magnetic Resonance Research Center, and the Yale-New Haven Hospital Radiation Safety Committee.

All participants were evaluated by physical examination, electrocardiography, standard blood chemistry, hematology laboratory values, toxicology testing, and urinalysis. Excluded from the study were individuals with significant medical or neurologic conditions, those with a history of head injury that involved loss of consciousness, or those with substance abuse within 12 months of the imaging or a lifetime history of substance dependence. The absence of substance use was determined by self-report and was confirmed by the results of urine toxicology and breathalyzer tests at screening and on the days when magnetic resonance (MR) imaging and PET were conducted.

Lifetime traumatic events were assessed using the Traumatic Life Events Questionnaire.²⁴ Only traumatic events that met criteria A1 and A2 for a *DSM-IV-TR*-based diagnosis of PTSD were counted toward participants' trauma histories in this study. The severity and diagnoses of PTSD were assessed using the Clinician-Administered PTSD Scale (CAPS)²⁵ for *DSM-IV*. Additional measures included the Hamilton Rating Scale for Anxiety (HAM-A),²⁶ the Montgomery-Asberg Depression Rating Scale (MADRS),²⁷ and the Fagerström Test for Nicotine Dependence.²⁸ Psychiatric diagnoses were established using *DSM-IV-TR* criteria and the Structured Clinical Interview for *DSM-IV*,²⁹ which was administered by an experienced psychiatric clinician. Participants in the PTSD group were free of comorbid psychiatric disorders except for major depressive dis-

order (MDD) or alcohol abuse or dependence. The primary diagnosis in this group was PTSD, which was defined by PTSD being the dominant clinical syndrome, as well as that the onset of MDD or alcohol abuse or dependence occurred after the onset of PTSD. All but one participant in the PTSD group was treatment naive; this individual had a history of treatment with a selective serotonin reuptake inhibitor and had not been taking medication for more than 4 weeks before the imaging. None of the participants were undergoing psychotherapy at the time of imaging. After providing written informed consent, participants underwent a thorough medical and psychiatric evaluation, followed by MR imaging and resting-state PET on a high-resolution research tomograph PET imaging system (CTI; Siemens Medical Systems) with the NET radiotracer [^{11}C]MRB.

The inclusion criterion for the TC group was exposure to at least 1 potentially traumatic event that met *DSM-IV-TR* criteria A1 and A2, but that none of these events were associated with meeting lifetime criteria for PTSD or any other Axis I diagnosis. Inclusion criteria for the HC group were the absence of any trauma meeting the above criteria, no evidence of a psychiatric diagnosis among first-degree relatives, and a lack of any lifetime psychiatric diagnosis, including substance abuse or dependence, or nicotine dependence.

PET and MR Imaging Acquisition and Modeling

Positron emission tomography (PET) imaging was performed using high-resolution research tomography with its spatial resolution of up to 2.5 to 3.4 mm,³⁰ which allows us to measure NET availability in small brain regions (ie, the locus coeruleus,³¹ which has a volume of approximately 35 mm³ and has been previously described³²). Participants wore a swim cap to which a rigid optical tracking tool was attached to record head motion with an infrared detector (Vicra; NDI Systems). Following a transmission image, [^{11}C]MRB was injected intravenously, and PET data were acquired in list mode for 120 minutes. Dynamic list mode data were reconstructed, and motion was corrected as previously described.²³ To apply the regions of interest defined in the standard Montreal Neurological Institute space³³ to the PET data, 2 transformations were estimated. First, a linear affine coregistration (12 parameters) was estimated between the template MR image in Montreal Neurological Institute space and each participant's MR image, which was acquired on a 3-T imaging system (Trio; Siemens Medical Systems) as previously described.²³ Second, a summed image (0-10 minutes after injection) was created from the motion-corrected PET dynamic image and registered to the participant's MR image using 6-parameter rigid coregistration. All coregistrations were estimated using a mutual information algorithm (FLIRT, FSL 3.2; FMRIB Analysis Group). The occipital cortex, as defined in the automated anatomical labeling template,³⁴ was used as a reference region to compute multilinear reference tissue model parametric images³⁵ as follows: the original dynamic images were smoothed using a gaussian filter (with a full-width at half maximum of 5 voxels), the starting time for the multilinear fit was set to 20 minutes, and the parameter k_2' was set to the population average value (0.021 minute⁻¹). This value for k_2' was computed as the average k_2' value estimated with multilinear analysis

($k_2' = -1 / b, b$) as in equation 2 in the study by Ichise et al³⁶ from 24 HC participants whose arterial input function was also measured (data not shown). Third, the regional average value of the multilinear reference tissue model 2 binding potential (BP_{ND}) parametric images in the locus coeruleus was computed using a region of interest defined in the template MR space, as described elsewhere.³²

Data Analysis

Data distributions of all study variables were assessed for normality using the Shapiro-Wilk tests. Nonnormally distributed variables (eg, BP_{ND} values in the PTSD group) were transformed using logarithmic base 10 transformations. Continuously distributed demographic and clinical variables of the HC, TC, and PTSD groups were compared using analysis of variance; χ^2 tests were used to compare categorical variables. Analysis of covariance was conducted to test for group differences in BP_{ND} values in the locus coeruleus by group. In this analysis, the type of group (HC, TC, and PTSD) was entered as an independent variable, and BP_{ND} values in the locus coeruleus were entered as the dependent variable. Body mass index, which differed between groups, was entered as a covariate in this analysis. Pairwise comparisons were computed to compare each of the 3 groups on BP_{ND} values in the locus coeruleus, with $P < .01$ used to indicate significant group differences. This level of significance was selected to reduce the probability of making a type I error when evaluating group differences. Effect sizes of group differences in BP_{ND} values were computed using Cohen d ($(M_{\text{group 1}} - M_{\text{group 2}}) / SD_{\text{pooled}}$), where $M_{\text{group 1}}$ and $M_{\text{group 2}}$ represent the mean of group 1 and mean of group 2, respectively.³⁷ Scores on each of the PTSD symptom clusters that comprise the 5-factor model were computed by summing CAPS scores as follows: for reexperiencing, the sum of *DSM-IV-TR* symptoms B1 to B5; for avoidance, the sum of symptoms C1 and C2; for numbing, the sum of symptoms C3 to C7; for dysphoric arousal, the sum of symptoms D1 to D3; and for anxious arousal, the sum of symptoms D4 and D5. To evaluate the relationship between BP_{ND} values in the locus coeruleus and the 5-factor phenotypic model of PTSD symptom clusters among individuals with PTSD, Pearson product moment correlations (2-sided, $\alpha = .05$) of standardized BP_{ND} values and scores on each of these symptom clusters were computed. When a significant correlation between BP_{ND} values and a PTSD symptom cluster was observed, we conducted additional correlations to ascertain specific PTSD symptoms associated with BP_{ND} values.

Results

The **Table** gives demographic and clinical characteristics of the HC, TC, and PTSD groups. Unadjusted [^{11}C]MRB BP_{ND} values differed by group, with pairwise comparisons revealing that the PTSD group had significantly lower values than the HC group ($P = .009$). Age, sex, and race/ethnicity did not differ among the groups. The PTSD group was significantly more likely than the HC and TC groups to meet criteria for MDD and alcohol abuse or dependence and to report a greater number

Table. Demographic and Clinical Characteristics of the Study Groups

Characteristic	HC (n = 18)	TC (n = 16)	PTSD (n = 22)	Test of Difference	P Value	Pairwise Comparisons
(S,S)-methylreboxetine dose, mean (SD), MBq	651.2 (128.8)	631.1 (115.0)	651.3 (144.5)	$F_{2,53} = 0.16$.85	...
Unadjusted (S,S)-[¹¹ C]O-methylreboxetine BP_{ND} value in the locus coeruleus, mean (SD)	0.294 (0.145)	0.230 (0.109)	0.194 (0.096)	$F_{2,53} = 3.64$.03	PTSD < HC
Age, mean (SD), y	31.7 (8.8)	30.8 (8.4)	32.6 (8.9)	$F_{2,53} = 0.19$.82	...
Sex, No. (%)	9 (50)	12 (75)	11 (50)	$\chi^2_2 = 2.92$.23	...
White race/ethnicity, No. (%)	13 (72)	8 (50)	16 (73)	$\chi^2_2 = 2.58$.28	...
Body mass index, mean (SD) ^a	23.7 (1.7)	28.1 (5.2)	27.5 (3.8)	$F_{2,53} = 7.39$.001	PTSD, TC > HC
Current smoker, No. (%)	2 (11)	2 (13)	2 (9)	$\chi^2_2 = 0.12$.94	...
Age at first trauma, mean (SD), y	...	16.7 (8.1)	14.3 (5.3)	$F_{1,36} = 1.42$.24	...
No. of traumas, mean (SD)	...	3.4 (2.7)	5.5 (2.3)	$F_{1,36} = 7.56$.009	PTSD > TC
Clinician-Administered PTSD Scale score, mean (SD)	...	2.9 (5.7)	71.1 (16.5)	$F_{1,36} = 219.85$	<.001	PTSD > TC
Reexperiencing symptoms	...	1.1 (2.1)	18.5 (6.6)	$F_{1,36} = 98.48$	<.001	PTSD > TC
Avoidance symptoms	...	0.1 (0.5)	8.9 (3.3)	$F_{1,36} = 101.77$	<.001	PTSD > TC
Numbing symptoms	...	0.3 (0.9)	20.9 (6.6)	$F_{1,36} = 144.55$	<.001	PTSD > TC
Dysphoric arousal symptoms	...	1.0 (1.9)	14.6 (4.4)	$F_{1,36} = 123.92$	<.001	PTSD > TC
Anxious arousal symptoms	...	1.3 (1.8)	8.1 (3.7)	$F_{1,36} = 43.84$	<.001	PTSD > TC
Montgomery-Asberg Depression Rating Scale score, mean (SD)	4.0 (4.9)	2.9 (2.2)	26.1 (9.3)	$F_{2,51} = 73.78$	<.001	PTSD > HC, TC
Hamilton Anxiety Rating Scale score, mean (SD)	1.8 (2.6)	1.6 (2.1)	20.4 (7.4)	$F_{2,51} = 88.16$	<.001	PTSD > HC, TC
Major depression, No. (%)	0	0	9 (41)	$\chi^2_2 = 16.57$	<.001	PTSD > HC, TC
Alcohol abuse or dependence, No. (%)	0	0	5 (23)	$\chi^2_2 = 8.48$.01	PTSD > HC, TC

Abbreviations: HC, healthy adults; PTSD, adults exposed to trauma who developed posttraumatic stress disorder; TC, adults exposed to trauma who did not develop posttraumatic stress disorder. Empty cells are denoted by an ellipsis because an omnibus between-group difference was not observed;

thus, pairwise comparisons were not conducted.

^a Calculated as weight in kilograms divided by height in meters squared.

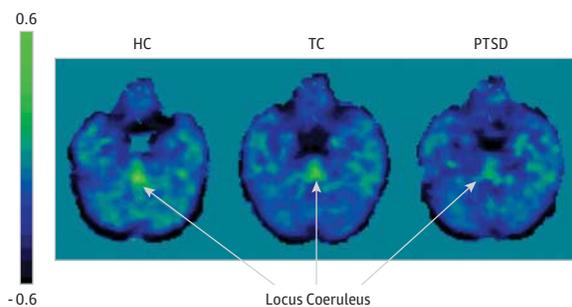
of traumatic life events compared with the TC group. The TC and PTSD groups had higher body mass index than the HC group. The PTSD group had higher CAPS scores than the TC group and had higher MADRS and HAM-A scores than the HC and TC groups. Groups did not differ for injection dose, which was determined by the difference in the injection syringe before and after injection (decay corrected), nor did they differ by current smoking status. Smoking status was not related to BP_{ND} values in the locus coeruleus; the mean (SD) values were 0.237 (0.126) for nonsmokers and 0.228 (0.096) for smokers ($F_{1,54} = 0.03$, $P = .86$). The CAPS, MADRS, and HAM-A scores did not differ between individuals having PTSD with vs those without a comorbid diagnosis of MDD. The mean (SD) CAPS scores were 70.8 (16.9) for PTSD without MDD and 71.6 (16.8) for PTSD with MDD ($F_{1,20} = 0.01$, $P = .92$). The mean (SD) MADRS scores were 27.5 (9.4) for PTSD without MDD and 24.1 (9.3) for PTSD with MDD ($F_{1,20} = 0.70$, $P = .41$). The mean (SD) HAM-A scores were 20.8 (7.6) for PTSD without MDD and 19.8 (7.6) for PTSD with MDD ($F_{1,20} = 0.11$, $P = .75$). The most common index traumas in the PTSD group were sexual abuse (7 participants [32%]), domestic violence (5 participants [23%]), and combat (5 participants [23%]). The most common index traumas in the TC group were domestic violence (6 participants [38%]), violence or robbery (4 participants [25%]), and combat (3 participants [19%]). Comparison of the TC and PTSD groups with respect to index traumas dichotomized by sexual or physical abuse vs other trauma did not reveal a significant

difference between groups; 9 participants (41%) in the PTSD group and 3 participants (19%) in the TC group reported sexual or physical abuse as their index trauma ($\chi^2_1 = 2.10$, $P = .15$).

Analysis of covariance examining BP_{ND} values in the locus coeruleus in the HC, TC, and PTSD groups revealed a significant effect of group ($F_{2,52} = 5.02$, $P = .01$); body mass index was not significant in this analysis ($F_{1,52} = 2.63$, $P = .11$). Specifically, the mean (SE) BP_{ND} values were 0.313 (0.030) in the HC group, 0.218 (0.030) in the TC group, and 0.186 (0.025) in PTSD group. Pairwise comparisons revealed that the PTSD group had significantly ($P < .01$) lower BP_{ND} values than the HC group (41% lower, $P = .003$). The differences between BP_{ND} values in the TC and HC groups (31% difference, $P = .04$) and in the TC and PTSD groups (15% difference, $P = .40$) did not achieve statistical significance for pairwise comparisons. The effect size for the difference between the HC and PTSD groups was large (Cohen $d = 1.07$; 95% CI, 0.40-1.74), while it was moderate for the difference between the HC and TC groups (Cohen $d = 0.79$; 95% CI, 0.09-1.49). **Figure 1** shows PET images of NET availability in the locus coeruleus in 3 representative participants from the HC, TC, and PTSD groups.

The mean (SE) BP_{ND} values did not differ between 9 participants having PTSD with MDD (0.191 [0.027]) and 13 participants having PTSD without MDD (0.197 [0.033]) ($F_{1,20} = 0.02$, $P = .89$) or between 5 participants having PTSD with alcohol abuse or dependence (0.246 [0.042]) and 17 participants having PTSD without alcohol abuse or dependence (0.178 [0.023])

Figure 1. Positron Emission Tomography Images of Norepinephrine Transporter Availability in the Locus Coeruleus of Participants in the Study Groups



Three representative participants were chosen with binding potential (BP_{ND}) values similar to the mean of each study group. Positron emission tomography images are in Montreal Neurological Institute space. HC indicates healthy adults; PTSD, adults exposed to trauma who developed posttraumatic stress disorder; and TC, adults exposed to trauma who did not develop posttraumatic stress disorder.

($F_{1,20} = 2.03, P = .17$). In analyses limited to the 2 trauma-exposed groups (ie, TC and PTSD), age at onset of the first trauma, the number of traumas, and the nature of the index trauma (ie, sexual or physical abuse vs other traumas) were not related to BP_{ND} values ($F_{1,31} < 1.14$ for all, $P > .29$ for all).

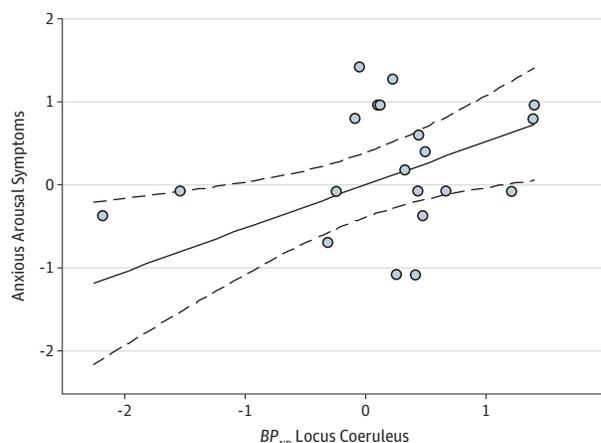
In the PTSD group, BP_{ND} values in the locus coeruleus were independently significantly positively associated with the severity of anxious arousal (ie, hypervigilance) symptoms ($r = 0.52, P = .01$) (Figure 2) but not with reexperiencing ($r = 0.03, P = .88$), avoidance ($r = 0.03, P = .90$), numbing ($r = 0.23, P = .29$), or dysphoric arousal ($r = 0.18, P = .43$) symptoms. Correlations between BP_{ND} values in the locus coeruleus and scores on the 2 individual anxious arousal symptoms revealed that this association was significant for the severity of hypervigilance ($r = 0.47, P = .03$) but not exaggerated startle ($r = 0.21, P = .34$) symptoms.

Discussion

Two key findings emerged from this study. First, consistent with preclinical studies, we found that PTSD was associated with significantly reduced NET availability in the locus coeruleus, with inspection of effect sizes suggesting that this difference was large (ie, >1 SD). Second, among individuals with PTSD, NET availability in the locus coeruleus was independently and positively associated with anxious arousal symptoms, most notably hypervigilance, using a contemporary, 5-factor model of PTSD symptoms.²⁻⁵

This latter finding agrees with the National Institute of Mental Health's Research Domain Criteria (www.nimh.nih.gov/research-funding/rdoc/index.shtml) dimensional approach to classifying mental disorders. It provides support for a putative neurobiological abnormality that underlies anxious arousal or hypervigilance in PTSD.

Figure 2. Scatterplot of the Association Between Standardized (S,S)-[¹¹C]O-methylreboxetine BP_{ND} Values in the Locus Coeruleus and Anxious Arousal Symptoms Among Individuals With Posttraumatic Stress Disorder



Values represent SDs; dashed lines represent 95% CIs. BP_{ND} indicates binding potential.

Our data help in refining a model of NE dysregulation in PTSD. The results are in accord with animal investigations demonstrating that chronic stress is associated with a reduction in NET availability in the locus coeruleus,³⁸ which may, in turn, result in exaggerated synaptic availability of NE in projection areas, such as the cortex. This work has shown that most NE axons in the prefrontal cortex have an unrecognized latent capacity to enhance the synthesis and recovery of NE,¹⁴ which could be an important mechanism in the capacity of adapting to stress. Given that reuptake of NE after its release terminates the neural signal, reduced reuptake results in high concentrations of synaptic NE and could lead to increased tonic firing of NE neurons in the locus coeruleus, consequently resulting in a hyperaroused state in which phasic activity of these neurons is impeded.³⁹ Our data in the PTSD group showing that NET availability in the locus coeruleus was independently positively associated with anxious arousal symptoms, most notably hypervigilance, suggest that this presumably compensatory mechanism in PTSD may serve to clear elevated synaptic NE in an attempt to maintain the normal availability of synaptic NE.

The results of the present study provide support for the validity of the 5-factor model of PTSD symptom dimensionality⁴ because NET availability in the locus coeruleus was significantly associated with the severity of anxious arousal (but not dysphoric arousal) symptoms. Therefore, this finding suggests greater specificity of an association between NET availability in the locus coeruleus and PTSD-related hypervigilance in individuals with PTSD. This approach to linking brain-phenotype associations provides a more refined understanding of how neurobiological factors associated with PTSD may be linked to the phenotypic heterogeneity of this disorder.

One challenging aspect of any PET study with the NET is that in the brain, NET levels are lower than those of other receptors, such as dopamine transporters and serotonin

transporters.⁴⁰ Furthermore, several NET reuptake inhibitors that have been tested as radioligands have shown high nonspecific binding.¹⁶ This can introduce great intersubject variability, requiring a large sample size for a PET imaging study. Nevertheless, the locus coeruleus has the highest concentration of the NET,⁸ which is why we specifically focused on this region. In addition, the locus coeruleus is a small region, which may add more variability to the results. The ability to quantify these small regions depends on high-resolution PET data and careful methods. In the present study, the locus coeruleus region was defined based on the registration of each participant's MR image to an atlas to avoid observer bias. We have also optimized the method for BP_{ND} quantification with [¹¹C]MRB (see the Methods section) to balance accuracy and noise.

Although this study is limited by the small sample size and ligand properties, it is the first to date to evaluate NET availability in the locus coeruleus in well-characterized groups of trauma-exposed adults with and without PTSD relative to HCs.

Additional research will be useful in confirming the results of this study and in evaluating NET availability in the locus coeruleus in other psychiatric conditions characterized by noradrenergic abnormalities, such as major depression and addictive disorders, both of which are often comorbid with PTSD.

Ultimately, our study addresses a concern that there has been limited progress in the development of truly innovative novel neurobiology-based treatment models for patients with PTSD. Because chronic stress often alters brain monoamine levels (eg, NE) and consequently results in dysregulation of stress circuits,⁴¹ the administration of drugs that block NE reuptake have been shown to have anxiolytic effects by directly influencing sympathetic nervous system function.⁴² These preclinical models are supported by preliminary human studies^{43,44} in PTSD, demonstrating that antidepressants with a noradrenergic mechanism of action may be effective in PTSD, particularly in addressing hypervigilance, although conclusive clinical trial results have not been reported to date.

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Author Affiliations: Clinical Neurosciences Division, National Center for Posttraumatic Stress Disorder, Veterans Affairs Connecticut Healthcare System, West Haven (Pietrzak, Southwick, Krystal); Department of Psychiatry, Yale University School of Medicine, New Haven, Connecticut (Pietrzak, Potenza, Southwick, Krystal); Department of Diagnostic Radiology, Yale University School of Medicine, New Haven, Connecticut (Gallezot, Henry, Carson); Departments of Psychiatry and Radiology, New York University School of Medicine, New York (Ding, Neumeister); Steven and Alexandra Cohen Veterans Center for the Study of Posttraumatic Stress and Traumatic Brain Injury, Department of Psychiatry, New York University Langone Medical Center, New York, New York (Neumeister).

Author Contributions: *Study concept and design:* Ding, Krystal, Neumeister.

Acquisition of data: Ding, Neumeister.

Analysis and interpretation of data: All authors.

Drafting of the manuscript: Pietrzak, Neumeister.

Critical revision of the manuscript for important intellectual content: All authors.

Statistical analysis: Pietrzak.

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Study supervision: Ding, Potenza, Carson, Neumeister.

Conflict of Interest Disclosures: Dr Pietrzak is a scientific consultant to CogState Ltd. Dr Potenza has consulted for Boehringer Ingelheim, Somaxon, gambling businesses and organizations, law offices, and the federal defender's office in issues regarding impulse-control disorders. He has received research support from the Mohegan Sun Casino, the National Center for Responsible Gaming, and the following pharmaceutical companies: Psyadon, Forest Laboratories, Ortho-McNeil,

Oy-Control/Biotie, and GlaxoSmithKline. Dr Krystal has been a consultant to the following companies: Aisling Capital LLC, AstraZeneca Pharmaceuticals, Brintnall & Nicolini Inc, Easton Associates, Gilead Sciences Inc, GlaxoSmithKline, Janssen Pharmaceuticals, Lundbeck Research US, Merz Pharmaceuticals, MK Medical Communications, Pfizer Pharmaceuticals, F. Hoffmann-La Roche Ltd, SK Holdings Co Ltd, Takeda Industries, Teva Pharmaceutical Industries Ltd, and Transcept Pharmaceuticals. He has the following patents and inventions: Seibyl JP, Krystal JH, Charney DS. Dopamine and noradrenergic reuptake inhibitors in treatment of schizophrenia. Patent 5,447,948. September 5, 1995. He is a coinventor on a filed patent application by Yale University related to targeting the glutamatergic system for the treatment of neuropsychiatric disorders (PCTW006108055A).

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