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The Effect of Early Trauma Exposure on Serotonin Type 1B Receptor Expression Revealed by Reduced Selective Radioligand Binding

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Abstract

Context—Serotonergic dysfunction is implicated in the pathogenesis of posttraumatic stress disorder (PTSD), and recent animal models suggest that disturbances in serotonin type 1B receptor function, in particular, may contribute to chronic anxiety. However, the specific role of the serotonin type 1B receptor has not been studied in patients with PTSD.

Objective—To investigate in vivo serotonin type 1B receptor expression in individuals with PTSD, trauma-exposed control participants without PTSD (TC), and healthy (non–trauma-exposed) control participants (HC) using positron emission tomography and the recently developed serotonin type 1B receptor selective radiotracer [¹¹C]P943.

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Design—Cross-sectional positron emission tomography study under resting conditions.

Setting—Academic and Veterans Affairs medical centers.

Participants—Ninety-six individuals in 3 study groups: PTSD (n=49), TC (n=20), and HC (n=27).

Main Outcome Measure—Regional [¹¹C]P943 binding potential (BP_{ND}) values in an a priori-defined limbic corticostriatal circuit investigated using multivariate analysis of variance and multiple regression analysis.

Results—A history of severe trauma exposure in the PTSD and TC groups was associated with marked reductions in [¹¹C]P943 BP_{ND} in the caudate, the amygdala, and the anterior cingulate cortex. Participant age at first trauma exposure was strongly associated with low [¹¹C]P943 BP_{ND} . Developmentally earlier trauma exposure also was associated with greater PTSD symptom severity and major depression comorbidity.

Conclusions—These data suggest an enduring effect of trauma history on brain function and the phenotype of PTSD. The association of early age at first trauma and more pronounced neurobiological and behavioral alterations in PTSD suggests a developmental component in the cause of PTSD.

Traumatic events and extreme stress exposure can elicit a variety of psychiatric syndromes.¹ However, relatively little is known regarding the human neurobiological mechanisms that underlie adaptive or pathologic responses to traumatic stress.^{2,3} A subset of individuals exposed to trauma¹ develop posttraumatic stress disorder (PTSD), a disabling clinical syndrome characterized by recurrent intrusive memories of a traumatic event, repeated avoidance of reminders of the trauma, and high levels of arousal and anxiety.⁴ The neurobiological mechanisms through which specific features of stress, including the number, severity, and duration of stress exposure or the developmental timing of traumatization, modulate PTSD risk and severity are unknown.⁵⁻⁹ Consequently, treatment options for these often chronically symptomatic patients remain limited.^{10,11}

The serotonin system plays a critical role in behavioral and emotional regulation,¹²⁻¹⁴ and serotonin dysfunction has been implicated repeatedly in the neurobiological processes of PTSD.^{3,15-17} Administration of *m*-chlorophenylpiperazine, a serotonin agonist, can evoke specific symptoms of PTSD, but these effects are not observed when *m*-chlorophenylpiperazine is administered to patients with other psychiatric disorders.¹⁸⁻²⁰ Also, the serotonin system is the target of the only 2 medications approved by the US Food and Drug Administration for the treatment of PTSD.²¹⁻²⁴ However, defining the specific role of the serotonin system in PTSD has been challenging in the face of a wide and complex diversity of receptor subtypes and their functions.²⁵ To date, relatively few in vivo molecular imaging studies of the serotonin system in PTSD have been undertaken. A small study²⁶ of the serotonin type 1A receptor in a heterogeneous sample of patients with PTSD found no regional binding differences compared with a control group, and no other serotonin receptors or the serotonin transporter have been studied in PTSD. Recent studies²⁷⁻³³ have begun to highlight the role of the serotonin type 1B receptor subtype specifically in anxious and depressive phenotypes in animals. Of particular relevance to PTSD, the serotonin type 1B receptor is stress responsive such that stress exposure reduces receptor function in animals, resulting in behaviors that resemble aspects of chronic anxiety.^{34,35}

Functional neuroimaging research³⁶⁻³⁸ has identified a circuit of cortical and subcortical brain regions that regulates stress-related behaviors that may be dysfunctional in individuals with PTSD. This circuit includes the anterior cingulate cortex (ACC), the striatum, the amygdala, and the hippocampus^{36,39,40} and is innervated extensively by serotonin-containing neurons arising from raphe nuclei in the brainstem.¹⁴ Maladaptive behavioral

responses to trauma exposure and clinical symptoms of PTSD are believed to emerge from neurochemical and neurophysiologic dysfunction of this circuit; evidence suggests that serotonergic mechanisms play a key role in this process.^{38,41}

The recent development of the serotonin type 1B receptor selective radiotracer, designated [¹¹C]P943,⁴² now makes it possible to conduct an in vivo assessment of serotonin type 1B receptors in humans in brain regions associated with stress regulation and PTSD. Following the animal models, we predicted that individuals with PTSD would have lower levels of regional [¹¹C]P943 binding potential (BP_{ND}) in the limbic corticostriatal circuit compared with non-trauma-exposed control participants. In light of the clinical and epidemiologic data suggesting a more severe clinical course of PTSD and higher rates of comorbid depression with PTSD after higher levels of traumatic stress exposure and early onset of stress exposure (eg, trauma exposure in adolescence),^{5-9,43} we specifically investigated the effect of these variables on [¹¹C]P943 BP_{ND} . To test the hypotheses, we studied patients with PTSD, trauma-exposed control participants free of lifetime psychiatric illness (TC), and healthy (ie, non-trauma-exposed) control participants (HC). We included the TC group to assess the effects of trauma exposure per se on [¹¹C]P943 BP_{ND} , independent of PTSD symptoms, to clarify whether serotonin type 1B receptor alterations are explained by a history of trauma exposure or whether they result from the presence of PTSD symptoms.

METHODS

PARTICIPANTS

Ninety-six participants in 3 study groups (PTSD, n=49; TC, n=20; and HC, n=27) were recruited through public advertisements. Participants with PTSD were free of comorbid psychiatric disorders except for major depressive disorder (MDD) if the primary diagnosis was determined to be PTSD (which was defined by PTSD being the dominant clinical syndrome) and if the onset of MDD occurred after the onset of PTSD. Participants with PTSD were largely treatment naive (ie, 1 of 49 participants had a history of treatment with a serotonin-selective reuptake inhibitor and was not taking medication for >4 weeks before the scan via positron emission tomography [PET]). None of the participants were undergoing psychotherapy at the time of scanning. After providing written informed consent, participants underwent a thorough medical and psychiatric evaluation followed by magnetic resonance imaging (MRI) and a resting-state scan via PET with the serotonin type 1B receptor antagonist radiotracer [¹¹C]P943. Psychiatric diagnoses were made using *DSM-IV-TR* criteria and the Structured Clinical Interview for *DSM-IV* administered by an experienced physician.^{4,44} Symptom severity of PTSD was measured using the Clinician-Administered PTSD Scale for *DSM-IV* (CAPS),⁴⁵ and trauma history was quantified using the Traumatic Life Events Questionnaire.⁴⁶ Only traumatic events that met *DSM-IV-TR* PTSD criterion A1 for trauma exposure and criterion A2, which confirms the emotional response to the trauma, were counted toward participants' trauma history in this study. Additional measurements included the Hamilton Rating Scale for Anxiety (HAM-A),⁴⁷ the Montgomery-Asberg Depression Rating Scale (MADRS),⁴⁸ the Fagerström Test for Nicotine Dependence,⁴⁹ and the Wechsler Abbreviated Scale of Intelligence.⁵⁰ To meet the TC inclusion criteria, individuals must have been exposed to at least 1 potentially traumatic event that met *DSM-IV-TR* criteria A1 and A2 but have no lifetime PTSD or other Axis I diagnosis.

All the participants were evaluated by physical examination; electrocardiographic, standard blood chemistry, hematology laboratory, and toxicologic testing; and urinalysis. Participants with significant medical or neurologic conditions, with substance abuse within 12 months of the scan via PET or a lifetime history of substance dependence, or with history of head injury with loss of consciousness were excluded from the study. The absence of substance

use was determined by self-report and confirmed by the results of urine toxicologic and breathalyzer tests at screening and on the days when scans via MRI and PET were administered. This study was approved by the Yale University School of Medicine Human Investigation Committee, the Mount Sinai School of Medicine Institutional Review Board, 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.

ACQUISITION AND ANALYSIS OF SCANS VIA [¹¹C]P943 PET

Participant preparation for the scan via PET consisted of indwelling venous catheter placement across all diagnostic groups. Also, radial arterial catheter placement was performed in an initial subgroup of individuals (n=39) for arterial blood collection and blood input function establishment to validate the kinetic modeling method. After a robust analysis method was established, placement of the arterial catheter was discontinued. A transmission scan using a ¹³⁷Cs point source was obtained before the emission scan. The scans via PET were acquired for 120 minutes at rest using a single intravenous injection of the high-specific activity selective serotonin type 1B receptor antagonist radiotracer [¹¹C]P943⁴² and a high-resolution research PET scanner (207 slices, resolution <3-mm full-width at half maximum in 3-dimensional acquisition mode). Dynamic scan data were reconstructed with corrections (ie, attenuation, normalization, scatter, randoms, and dead time). Motion correction of data obtained via PET was performed by coregistering each reconstructed frame to an early summed image (0–10 minutes after injection) using a 6-parameter mutual information algorithm and Functional Magnetic Resonance Imaging of the Brain (FMRIB)'s Linear Image Registration Tool (FLIRT, FSL 3.2; FMRIB Analysis Group, Oxford, United Kingdom).

The MRI results were obtained for each participant using a Siemens 3T Trio system (Siemens Medical Solutions USA, Inc, Malvern, Pennsylvania) to exclude individuals with anatomical abnormalities and for coregistration. A second summed image (0–10 minutes after injection) was created from the motion-corrected scan via PET and registered to the participant's MRI results, which, in turn, was registered (via 12-parameter affine transformation) to an MRI template (a Montreal Neurological Institute space). The regions of interest (ROIs) were taken from the template for SPM2 (via anatomical automatic labeling) and applied to the image obtained via PET to produce time-activity curves for each ROI in reference to the cerebellum.⁵¹ Pixel-by-pixel analysis was performed using the multilinear reference tissue model MRTM2⁵² to produce images of BP_{ND} .⁵³ The interpretation of BP_{ND} is $f_{ND} * B_{avail} / K_d$, in which f_{ND} is the tracer-free fraction in a region without specific binding, B_{avail} is the unoccupied receptor concentration, and K_d is the dissociation equilibrium constant of the tracer. The cerebellum was used as the reference region because it is essentially devoid of serotonin type 1B receptors.⁵⁴ Assuming that no change is observed in affinity or nonspecific binding between participant groups, changes in BP_{ND} were interpreted as changes in receptor concentration. The BP_{ND} values from MRTM2 have provided highly comparable results ($R^2=0.83-0.94$ across the ROIs) with those obtained with arterial input functions.⁵⁵ Mean (SD) cerebellum distribution volume data collected in the initial subgroup of study participants were not different among the 3 diagnostic groups (HC: 4.48 [1.09]; TC: 4.89 [0.52]; and PTSD: 4.47 [0.46]; HC vs TC: $P=.43$; HC vs PTSD: $P=.98$; and TC vs PTSD: $P=.34$), validating its use as a reference region in modeling analysis.

The [¹¹C]P943 BP_{ND} values were measured in a prespecified limbic corticostriatal circuit that includes the amygdala, the hippocampus, the ACC, the caudate, and the globus pallidus. These regions constitute a neural circuit consistently implicated in the pathogenesis of PTSD^{36,39,40} and are known to contain high levels of serotonin type 1B receptors.⁵⁴

STATISTICAL ANALYSIS

Analyses of variance (ANOVAs) were used to compare continuous clinical and demographic variables of the PTSD, TC, and HC groups. Continuous variables were examined for normality using normal probability plots and Kolmogorov-Smirnov test statistics by group and region. No transformations were necessary. In the case of dichotomous variables, χ^2 tests were used. Multivariate ANOVA (MANOVA) of [^{11}C]P943 BP_{ND} values from the 5 ROIs in the a priori limbic corticostriatal circuit model across the 3 groups was used to test for group differences in [^{11}C]P943 BP_{ND} in the circuit. Subsequently, separate ANOVAs for each region were used to determine the location of between-group differences in [^{11}C]P943 BP_{ND} , followed by post hoc Tukey honestly significant difference t tests among groups. Also, MANOVA was used to assess the effects of age, sex, race, body mass index, and injected dose of [^{11}C]P943 BP_{ND} .

Associations among continuous demographic, clinical, and [^{11}C]P943 BP_{ND} variables were assessed using Pearson product-moment correlations using a 2-sided .05 significance threshold. Follow-up stepwise multiple regression was performed to further clarify the effect of demographic and clinical variables on [^{11}C]P943 BP_{ND} . In the stepwise regression, we evaluated the following variables for entry into the model: age, age at first traumatic experience, number of traumatic experiences, MADRS score, CAPS score, sex, and body mass index. The variable associated with the lowest P value below the threshold of .05 was entered into the model first. Then, we attempted to add additional variables 1 at a time using a significance level of .05 until no more variables could be added. We used R^2 to assess what percentage of the variability in the serotonin type 1B measures the predictors of the model explained. We also performed an additional stepwise regression in which group was entered into the model regardless of significance and additional predictors were added as indicated. Each of the potentially influential variables was considered 1 at a time, and at each inclusion step, the predictor with the lowest significance level less than .05 was entered. The model building stopped when no more predictors could be entered into the model. In the last step, we reexamined the significance of the group effect to assess whether group was a significant predictor of [^{11}C]P943 BP_{ND} after accounting for the other significant variables.

Mean (SD) is reported unless otherwise noted, and significance was set at 2-tailed $\alpha = .05$. Statistical analyses were conducted using commercially available software programs (SPSS, version 16.0; SPSS, Inc, Chicago, Illinois, and SAS, version 9.1.31; SAS Institute, Inc, Cary, North Carolina).

RESULTS

DEMOGRAPHIC AND CLINICAL CHARACTERISTICS OF THE SAMPLE

Participants with PTSD experienced clinically significant symptoms of PTSD (mean [SD] CAPS score: 66.5 [19.7]; range, 27.0–97.0), anxiety (mean [SD] HAM-A score: 19.3 [7.2]; range, 13.0–31.0), and depression (mean [SD] MADRS score: 25.6 [8.2]; range, 14.0–41.0). In comparison, participants in the TC group had very low scores on the CAPS (mean [SD], 3.3 [5.2]; range, 0–17.0), HAM-A (2.5 [3.1]; 0–10.0), and MADRS (3.7 [3.2]; 0–11.0). Both trauma-exposed groups experienced multiple lifetime traumas (PTSD: mean [SD], 4.7 [2.5]; range, 1.0–11.0; TC: 3.6 [2.5]; 1.0–11.0), and the numbers did not differ between groups ($t_{67} = -1.6$, $P = .11$). The mean (SD) age of participants at their first trauma exposure was 15.1 (5.5) years (range, 8.0–25.0 years) in the PTSD group and 16.5 (7.0) years (range, 3.0–27.0 years) in the TC group ($t_{67} = 0.86$, $P = .39$) (Table 1). In the PTSD group, 15 patients met the criteria for current MDD at the time of scanning via PET and 34 were free of lifetime or current MDD.

MEASURES OF [¹¹C]P943 *BP_{ND}* VIA PET

Analysis of [¹¹C]P943 *BP_{ND}* in a Limbic Corticostriatal Circuit—The full factorial group×ROI MANOVA was significant, indicating [¹¹C]P943 *BP_{ND}* differences between groups in the proposed limbic corticostriatal circuit ($F_{10,178}=2.18, P=.02$). Univariate tests of between-group differences in each ROI yielded significant regional effects in the caudate ($F_{2,93}=7.23, P=.001$), the amygdala ($F_{2,93}=4.12, P=.02$), and the ACC ($F_{2,93}=3.34, P=.04$). The hippocampus and globus pallidus ANOVAs were not significant (Table 2).

Primary Hypothesis Testing: [¹¹C]P943 *BP_{ND}* Comparison Between PTSD and HC—To test the primary hypothesis of serotonin type 1B receptor dysfunction in PTSD, we performed Tukey honestly significant difference post hoc *t* tests on [¹¹C]P943 *BP_{ND}* values between the PTSD and HC groups in each of the 3 ROIs that demonstrated significance by NOVA (ie, the caudate, the amygdala, and the ACC) after the primary MANOVA. In the caudate, [¹¹C]P943 *BP_{ND}* was reduced by 18.8% in the PTSD group compared with the HC group ($P=.006$) (Figure 1). In the amygdala, [¹¹C]P943 *BP_{ND}* was reduced by 10.9% in the PTSD group compared with the HC group ($P=.047$). In the ACC, [¹¹C]P943 *BP_{ND}* was reduced by 9.1% in the PTSD group compared with the HC group ($P=.048$) (Table 2). These results were driven by the PTSD+MDD subgroup, which, in these regions, differed significantly from the group with PTSD only, as will be described in detail herein.

Effects of Trauma on [¹¹C]P943 *BP_{ND}* in the TC Group—We compared [¹¹C]P943 *BP_{ND}* values between the TC and HC groups and between the TC and PTSD groups. Again, we restricted the analysis to the 3 brain regions that demonstrated group significances by ANOVA (ie, the caudate, the amygdala, and the ACC) after the primary MANOVA. In the caudate, [¹¹C]P943 *BP_{ND}* was reduced by 25.8% in the TC group compared with the HC group (post hoc Tukey comparison, $P=.002$); the PTSD and TC groups did not differ (post hoc Tukey comparison, $P=.56$). In the amygdala, [¹¹C]P943 *BP_{ND}* was reduced by 14.7% in the TC group compared with the HC group (post hoc Tukey comparison, $P=.03$); the PTSD and TC groups did not differ (post hoc Tukey comparison, $P=.74$). In the ACC, [¹¹C]P943 *BP_{ND}* values were not significantly different between the TC and HC groups (post hoc Tukey comparison, $P=.10$) (Table 2).

Associations Among [¹¹C]P943 *BP_{ND}*, Trauma History, and Clinical Characteristics—To further characterize the relationship between [¹¹C]P943 *BP_{ND}* and trauma history, we first performed bivariate correlation analyses between [¹¹C]P943 *BP_{ND}* values and trauma history variables in each significant ROI (ie, the caudate, the amygdala, and the ACC) in the PTSD and TC groups. In the PTSD group, [¹¹C]P943 *BP_{ND}* was correlated with participant age at first trauma in the caudate ($r=0.49, P<.001$) and the ACC ($r=0.42, P=.003$) such that the earlier the first trauma exposure, the lower the [¹¹C]P943 *BP_{ND}* (Figure 2). This association was not found in the amygdala. Participant age at first trauma was negatively correlated with CAPS score ($r=-0.36, P=.02$) (but not with HAM-A or MADRS scores) such that the younger the participant age at first trauma, the higher the level of PTSD symptom severity. Also, the total number of lifetime traumatic experiences was positively correlated with the CAPS score ($r=0.32, P=.04$). In the TC group, [¹¹C]P943 *BP_{ND}* values were similarly correlated with age at first trauma in the caudate ($r=0.75, P<.001$) and the amygdala ($r=0.47, P=.04$).

To determine the effects of MDD comorbidity on [¹¹C]P943 *BP_{ND}*, we first divided the participants with PTSD into those with ($n=15$) and those without ($n=34$) lifetime or current MDD. Participants with PTSD+MDD were older than were participants with PTSD only (mean [SD] age, 36.7 [9.6] vs 29.8 [8.3] years; $t_{46}=-2.54; P=.02$), had greater PTSD symptom severity (mean [SD] CAPS score, 75.3 [16.1] vs 62.2 [20.1]; $t_{41}=-2.13; P=.04$),

had a significantly earlier onset of trauma (9.9 [4.1] vs 17.4 [4.4] years; $t_{47}=5.62$; $P < .001$), and had a significantly greater number of lifetime traumatic experiences (5.9 [1.9] vs 4.1 [2.5]; $t_{47}=-2.52$; $P = .02$). The [^{11}C]P943 BP_{ND} was significantly reduced in the caudate in the PTSD+MDD group compared with the group with PTSD only (27.0% reduction, $t_{47}=3.27$, $P = .002$); the same was true in the ACC (11.0% reduction, $t_{47}=2.44$, $P = .02$), and the hippocampus (15.4% reduction, $t_{47}=2.19$, $P = .03$).

To clarify the effects of trauma history, symptom severity, and MDD comorbidity on [^{11}C]P943 BP_{ND} , we performed stepwise multiple regression analysis. In the PTSD group, only participant age at first trauma was significantly associated with the caudate [^{11}C]P943 BP_{ND} ($F_{1,40}=15.44$, $P < .001$), explaining 28.0% of the variance, and ACC [^{11}C]P943 BP_{ND} ($F_{1,40}=9.71$, $P = .003$), explaining 20.0% of the variance. The [^{11}C]P943 BP_{ND} difference between the PTSD and PTSD+MDD subgroups was no longer statistically significant after entering age at first trauma into the model, indicating that age at first trauma accounts for the observed reductions in [^{11}C]P943 BP_{ND} . Neither the group nor any of the other variables was significantly associated with amygdala [^{11}C]P943 BP_{ND} .

Regression analysis performed in the combined sample of all trauma-exposed participants (PTSD and TC, $n=67$) further confirmed that only participant age at first trauma was significantly associated with caudate [^{11}C]P943 BP_{ND} ($F_{1,58}=17.09$, $P < .001$), explaining 23.0% of the variance, and amygdala [^{11}C]P943 BP_{ND} ($F_{1,58}=8.72$, $P = .005$), explaining 13.0% of the variance.

COMMENT

In this study, we demonstrated a robust association between *in vivo* regional reductions in [^{11}C]P943 BP_{ND} , a measure of serotonin type 1B receptor expression, and trauma history in patients with PTSD and in TC participants. Lower [^{11}C]P943 BP_{ND} in PTSD was associated with an earlier age at first trauma exposure, a greater number of lifetime trauma exposures, more severe PTSD symptoms, and comorbidity with MDD. Regression analyses clarified that participant age at onset of the first trauma was the strongest predictor of [^{11}C]P943 BP_{ND} reductions in individuals with a history of severe trauma.

The findings that low serotonin type 1B receptor expression is associated with greater symptom severity, co-morbidity with MDD, earlier onset of trauma exposure, and greater total lifetime trauma burden are consistent with the results of numerous epidemiologic studies documenting elevated risk of PTSD and more severe symptoms associated with childhood trauma and higher trauma load.^{5-9,43} In particular, early life stress has been repeatedly implicated as a risk factor for adult trauma exposure^{56,57} and for the development of PTSD.^{7,58,59} Although most research has focused on neuroendocrine function and the hypothalamic-pituitary-adrenal axis as mediating biological factors between early trauma and risk of PTSD,^{43,60} the findings of the present study highlight the serotonin system as being potentially important as well. The present findings are consistent with the lasting behavioral effects resulting from early perturbations of the serotonin system leading to anxiety-related phenotypes in animals.^{61,62}

The strong association between trauma exposure and reduced serotonin type 1B receptor level found in the trauma control group further demonstrates the specific effects of trauma on molecular adaptations in neuronal networks that are dysfunctional in PTSD. However, low [^{11}C]P943 BP_{ND} in the PTSD and TC groups suggests that abnormal serotonin type 1B receptor expression does not sufficiently explain the phenotype of PTSD. Thus, the data more strongly support the hypothesis that the extent of serotonin type 1B receptor alteration reflects features of trauma exposure (eg, age at exposure and the intensity, number, or

perhaps other features of the trauma history) rather than the nature of the response to the trauma (eg, whether the individual did or did not develop PTSD). Individuals who proceed to develop PTSD would be expected to possess an additional vulnerability factor resulting from genetic or environmental factors or to lack a protective factor that may characterize resistance to the pathologic effects of trauma.

Autoradiographic studies demonstrate high levels of serotonin type 1B receptors localized to the basal ganglia,^{27,63–66} with somewhat lower levels localized to the neocortex and the amygdala,^{27,67} consistent with the findings of the present study. The observed [¹¹C]P943 BP_{ND} reductions in the trauma-exposed cohorts were in the amygdala, the ACC, and the caudate, in line with current neurocircuitry hypotheses of PTSD.^{36,39,40} The largest [¹¹C]P943 BP_{ND} reductions were in the caudate, a region that has been implicated in normal emotional behavior and emotional disorders^{68–70}; however, it has received relatively little attention in neurobiological studies of PTSD (although several studies^{71–74} do address it). Of note, Cohen et al⁷³ reported volumetric reductions in the caudate and the ACC in adults with a history of high levels of early life stress in the absence of psychiatric illness. The researchers found that higher levels of childhood and adolescent stress were associated with a larger magnitude of volumetric reduction, paralleling the findings of the present study. However, the [¹¹C]P943 BP_{ND} data reported in the present study are corrected for any volumetric variation in the sample so that our serotonin type 1B receptor findings represent an additional neurobiological abnormality rather than being explained by any potential volumetric variations.

Functionally, serotonin type 1B receptors are G proteins negatively coupled to adenylyl cyclase that seem to regulate limbic corticostriatal signaling primarily as axon terminal heteroreceptors on nonserotonergic neurons (eg, γ -aminobutyric acid-, glutamate-, and dopamine-containing neurons).^{75–78} Although the behavioral functions of this receptor are incompletely understood, numerous preclinical studies^{30–35,79–81} implicate the receptor in emotional behavior, stress reactivity, and anxiety states. The present findings of in vivo reductions in serotonin type 1B receptors associated with trauma are consistent with those of animal studies^{34,35} demonstrating reductions in serotonin type 1B receptor messenger RNA transcription after stress exposure. A study³³ of serotonin type 1B receptor overexpression in the dorsal raphe nucleus demonstrates decreased anxiety in animals (ie, fear-potentiated startle) in a stress-dependent manner. Loss of serotonin type 1B receptor-mediated regulation of glutamate and γ -aminobutyric acid systems has the potential to lead to downstream reductions in neurotrophic signaling and neurogenesis and loss of dendritic spines and branches in neurocircuitry relevant to PTSD.⁸²

The serotonin system likely plays a role in multiple psychiatric disorders, and the degree of specificity of the observed [¹¹C]P943 BP_{ND} reductions related to trauma exposure in the present study remains uncertain. Some of us recently reported reduced ventral striatal [¹¹C]P943 BP_{ND} in individuals with MDD compared with HC participants.⁸³ In a second study,⁸⁴ some of us found elevated ventral striatal [¹¹C]P943 BP_{ND} in individuals with alcohol dependence. Notably, MDD and alcohol dependence are often comorbid with PTSD. However, no ventral striatal between-group differences were observed in the present study. Instead, we found reduced [¹¹C]P943 BP_{ND} in the caudate in trauma-exposed individuals. Although the causative implications of these differential binding patterns are not yet fully understood, these initial data suggest potential diagnostic specificity.

Some difficulty can occur in interpreting BP_{ND} data from human neuroimaging studies. Between-group differences in ligand binding could represent differences in receptor number as a result of true downregulation, which requires receptor degradation and perhaps decreased synthesis. Alternately, increased serotonin release, enhanced neuronal activity in

the dorsal raphe nuclei, and increased serotonin synthesis and turnover in response to stress^{85,86} could lead to agonist-induced internalization of serotonin type 1B receptors.⁸⁷ Finally, assuming a displacement model, differences in ligand binding could be explained by changes in transmitter release in which serotonin and the radioligand may compete directly for occupancy of the same receptor binding site,⁸⁸ although this possibility has not yet been sufficiently addressed in human studies.

Several limitations to the present study deserve comment. Inherent limitations exist regarding the reliance on retrospective participant reports of trauma history. We also chose to include a broad range of trauma histories and individuals who had experienced multiple different trauma types. Therefore, the specific contribution of different types of trauma cannot be evaluated reliably in this study owing to the presence of multiple traumas of mixed types in many individuals in the cohort. However, the inclusion of a range of trauma histories allowed for observations of correlations between the developmental timing of trauma, trauma load, and serotonin type 1B receptor measures. The present study design does not address the important question of whether trauma exposure directly reduces serotonin type 1B receptor expression. Preclinical data suggest serotonin type 1B receptor modulation by environmental stress. However, other explanations for the observed findings include premorbid low levels of serotonin type 1B receptor expression resulting from genetic or environmental factors in individuals predisposed to trauma exposure or to the development of PTSD. Perhaps most important, this study did not allow us to fully clarify the potential pathologic role of reduced serotonin type 1B receptor expression in PTSD.

The findings of the present study are consistent with the premise that exposure to early trauma produces long-lasting neurobiological changes in the human brain and suggests a potential neurodevelopmental component in the cause of PTSD. Future studies are needed to clarify molecular factors in addition to the serotonin type 1B receptor that may characterize individuals who are vulnerable to the potentially pathogenic effects of trauma.

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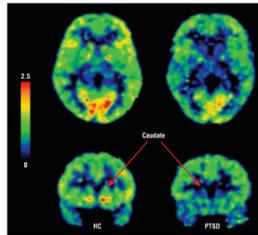


Figure 1. Regional [^{11}C]P943 MRTM2 binding potential (BP_{ND}) scans via positron emission tomography coregistered to magnetic resonance images illustrate reduced caudate BP_{ND} in the posttraumatic stress disorder (PTSD) group (right) relative to the healthy control (HC) group (left). The color scale represents relative BP_{ND} values (as reported in the Results section of the text). The caudate region of interest is outlined in the axial section and is indicated by an arrow in the corresponding coronal view.

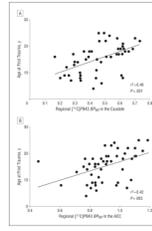


Figure 2.

Association between participant age at first trauma exposure and regional [^{11}C]P943 binding potential (BP_{ND}) in the caudate (A) and the anterior cingulate cortex (ACC) (B) in posttraumatic stress disorder. The younger the age at first trauma exposure, the lower the [^{11}C]P943 BP_{ND} in the caudate and the ACC.

Table 1

Demographic, Clinical, and Positron Emission Tomographic Procedural Characteristics of the 96 Study Participants

Characteristic	PTSD Group (n=49)	TC Group (n=20)	HC Group (n=27)	P Value ^a
Demographics				
Age, mean (SD) [range], y	32.0 (9.3) [19.0–54.0]	30.7 (9.6) [20.0–55.0]	30.4 (8.9) [18.0–54.0]	.74
Sex, M/F, No.	26/23	14/6	17/10	.39
Ethnicity, No.				
White	23	10	22	NA
African American	19	9	4	NA
Hispanic	7	1	1	NA
BMI, mean (SD)	28.4 (5.0)	27.2 (4.4)	24.2 (4.6)	.003 ^b
Smoking status, No.				.95
Yes	4	2	2	NA
No	45	18	25	NA
Description of index trauma, No. (%)				
Physical assault ^c	38 (77.6)	16 (80.0)	NA	NA
Combat related	9 (18.4)	4 (20.0)	NA	NA
MVC	2 (4.1)	0	NA	NA
Indices of lifetime trauma burden, mean (SD)				
Age at first trauma, y	15.1 (5.5)	16.5 (7.0)	NA	.39
No. of lifetime traumatic experiences ^d	4.7 (2.5)	3.6 (2.5)	NA	.11
Clinical measures, mean (SD)				
HAM-A score	19.3 (7.2)	2.5 (3.1)	3.3 (4.3)	<.001 ^e
MADRS score	25.6 (8.2)	3.7 (3.2)	4.1 (4.5)	<.001 ^e
CAPS total score	66.5 (19.7)	3.3 (5.2)	NA	<.001 ^e
CAPS reexperiencing cluster score	17.7 (7.4)	0.56 (1.4)	NA	<.001 ^e
CAPS avoidance cluster score	27.6 (9.9)	0.89 (1.9)	NA	<.001 ^e
CAPS hyperarousal cluster score	21.2 (6.7)	1.9 (3.1)	NA	<.001 ^e
Injection variables, mean (SD)				
Injected dose, MBq	596 (135.00)	637 (99.00)	625 (140.00)	.41
Specific activity, MBq/nmol	165 (69.08)	176 (83.00)	176 (67.00)	.77
Injected mass, µg	1.89 (1.35)	1.89 (1.02)	1.73 (0.77)	.83

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CAPS, Clinician-Administered PTSD Scale for *DSM-IV*; F, female; HAM-A, Hamilton Rating Scale for Anxiety; HC, healthy (ie, non-trauma-exposed) control participant; M, male; MADRS, Montgomery-Asberg Depression Rating Scale; MVC, motor vehicle crash; NA, not applicable; PTSD, posttraumatic stress disorder; TC, trauma-exposed control participant free of lifetime psychiatric illness.

^aDetermined by independent-samples *t* tests or analyses of variance followed by the Tukey post hoc test for continuous variables or by the χ^2 test for dichotomous variables.

^bPost hoc PTSD>HC, *P*=.002.

^cIncludes sexual assault, domestic violence, and other non-combat-related physical violence.

^dThose included meet *DSM-IV-TR* criterion A for PTSD.

^ePost hoc PTSD>HC, $P<.001$; PTSD>TC, $P<.001$.

Table 2

Regional [¹¹C]P943 *BP_{ND}* in the PTSD, TC, and HC Study Groups in a Limbic Corticostriatal Circuit^a

Region	¹¹ C]P943 <i>BP_{ND}</i> , Mean (SD)				<i>F</i> _{2,93}	<i>P</i> Value
	PTSD Group (n=49)	TC Group (n=20)	HC Group (n=27)			
ACC	0.909 (0.143)	0.902 (0.104)	1.00 (0.216)	3.34	.04	
Amygdala	0.692 (0.166)	0.663 (0.115)	0.777 (0.133)	4.12	.02	
Caudate	0.465 (0.147)	0.425 (0.156)	0.573 (0.130)	7.23	.001	
Hippocampus	0.395 (0.099)	0.366 (0.103)	0.401 (0.106)	0.94	.39	
Pallidum	1.583 (0.338)	1.579 (0.271)	1.722 (0.291)	1.96	.15	

Abbreviations: ACC, anterior cingulate cortex; *BP_{ND}*, binding potential; HC, healthy (ie, non-trauma-exposed) control participant; PTSD, posttraumatic stress disorder; TC, trauma-exposed control individual free of lifetime psychiatric illness.

^a Significant group differences in [¹¹C]P943 *BP_{ND}* in a limbic corticostriatal circuit initially established by multivariate analysis of variance, including the 5 a priori regions of interest (Wilks λ $F_{10,18}=2.18$; $P=.02$). The *F* statistics and *P* values were determined by subsequent 1-way analysis of variance for each region of interest. The Tukey honestly significant difference post hoc *t* tests and percentage differences were as follows: anterior cingulate cortex: PTSD<HC (9.1%, $P=.048$), TC=HC ($P=.10$), PTSD=TC ($P=.98$); amygdala: PTSD<HC (10.9%, $P=.047$), TC<HC (14.7%, $P=.027$), PTSD=TC ($P=.74$); and caudate: PTSD<HC (18.8%, $P=.006$), TC<HC (25.8%, $P=.002$), PTSD=TC ($P=.56$).