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HIGHER IN VIVO SEROTONIN-1A BINDING IN POSTTRAUMATIC STRESS DISORDER: A PET STUDY WITH [^{11}C]WAY-100635

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Abstract

Background—Brain serotonin-1A receptors (5-HT$_{1A}$) are implicated in anxiety. We compared regional brain 5-HT$_{1A}$ binding in medication-free participants with posttraumatic stress disorder (PTSD) and healthy volunteers using fully quantitative positron emission tomography (PET) methods.

Methods—Twenty patients with DSM-IV PTSD (13 with comorbid major depressive disorder, [MDD]) and 49 healthy volunteers underwent PET imaging with 5-HT$_{1A}$ antagonist radioligand [C-11]WAY100635. Arterial blood sampling provided a metabolite-corrected input function and the concentration of free ligand in plasma (f_P) for estimation of regional binding potential, BP_F (= $B_{available}$ /K_D). Linear mixed modeling compared BP_F between groups across regions of interest (ROIs).

Results—The PTSD group had higher 5-HT$_{1A}$ BP_F across brain ROIs (P = .0006). Post hoc comparisons showed higher 5-HT$_{1A}$ BP_F in PTSD in all cortical ROIs (26–33%), amygdala (34%), and brainstem raphe nuclei (43%), but not hippocampus. The subgroup of seven PTSD patients without comorbid MDD had higher 5-HT$_{1A}$ BP_F compared with healthy volunteers (P = .03).

Conclusions—This is the first report of higher brainstem and forebrain 5-HT$_{1A}$ binding in vivo in PTSD. The finding is independent of MDD. PTSD and MDD have in common an upregulation of 5-HT$_{1A}$ binding including midbrain autoreceptors that would favor less firing and serotonin release. This abnormality may represent a common biomarker of these stress-associated brain disorders.

Keywords

posttraumatic stress disorder (PTSD); serotonin-1A (5-HT1A); positron emission tomography; WAY100635; major depressive disorder

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INTRODUCTION

Posttraumatic stress disorder (PTSD) is a disabling[1] anxiety disorder that results from severe traumatic experiences with symptoms that persist months to years. These include reexperiencing phenomena (e.g. nightmares, intrusive images), pathological avoidance, emotional numbing, and hyperarousal. Some are more vulnerable to development of PTSD than others exposed to similar trauma; but degree of stress also contributes to risk, as in combat-related PTSD in which risk increases with each tour of duty.[2] Both genetic factors and early life adversity moderate future vulnerability to PTSD.[3,4]

The serotonin (5-HT) neurotransmitter system[5] has cell bodies in brainstem median and dorsal raphe nuclei that project widely in the brain, including to key fear circuitry loci such as amygdala, hippocampus, and ventromedial prefrontal cortex (PFC), mainly targeting GABAergic inhibitory neurons. The serotonin-1A receptor (5-HT_{1A}) in particular is related to anxiety expression in both rodents[6,7] and humans.[8–10] The 5-HT_{1A} receptor is both a somatodentritic autoreceptor on raphe nuclei serotonin neurons, inhibiting neuronal firing; and a terminal field postsynaptic receptor on nonserotonergic neurons in forebrain projection sites, where disruption of 5-HT_{1A} expression during development may lead to a lifelong anxious phenotype.[11]

Despite demonstration of, albeit modest, treatment efficacy for the serotonin selective reuptake inhibitors (SSRIs) in PTSD,[12] little is known about the role of the serotonin system in this disorder. Rodent data suggest 5-HT_{1A} alterations may account for bias toward threatening cues,[6] something observed clinically in PTSD. Moreover, attenuation of contextual fear appears to involve 5-HT_{1A} in the extended amygdala,[13] SSRIs administered concomitantly with extinction training in mice induce an enduring loss of conditioned fear memory; and in PTSD when administered with an extinction-based therapy, SSRIs produce greater improvement in PTSD symptoms and remission rates.[14] Such data suggest regional brain mapping of 5-HT_{1A} in individuals with PTSD is warranted.

Positron emission tomography (PET) employing the radioligand [carbonyl-C-11]WAY-100635 has allowed estimation of regional brain binding to the 5-HT_{1A} receptor in vivo, and regional brain differences in binding measures have been reported in major depressive disorder (MDD),[15–17] social anxiety disorder,[8] and panic disorder.[9,10] There has been one prior report regarding 5-HT_{1A} binding in PTSD by PET using the radioligand [F-18]FC-WAY, reporting no difference in the regional distribution volume (V_T) from healthy volunteers.[18] However, limitations of this radiotracer[19] as well as quantitative modeling issues[20] may account for this negative finding. Therefore, we compared regional 5-HT_{1A} binding potential ($BP_F = B_{available} / K_D$) using a metabolite-corrected arterial input function and free fraction in a sample of 20 medication-free PTSD participants and 49 healthy volunteers.

MATERIALS AND METHODS

PARTICIPANTS

Twenty participants met DSM-IV criteria for current PTSD. These patients were recruited concurrently with a healthy volunteer group ($N = 49$) previously reported in refs.[16, 21] Diagnoses were determined by experienced masters and PhD-level psychologists using the Structured Clinical Interview for DSM-IV (SCID);[22] and a team of experienced clinical research psychologists and psychiatrists generated best-estimate diagnoses. Inclusion criteria were assessed through psychiatric, chart review, SCID, review of systems, physical exam, routine blood tests, and urine toxicology. Eligibility criteria for PTSD patients included age 18–65 years old; current PTSD; absence of psychotropic medications for at least 2 weeks

prior to screening with exception for sedative/hypnotics (one PTSD participant had clonazepam >7 days before scan, and one PTSD participant had zolpidem >7 days before scan); no substance abuse within 2 months nor dependence within 6 months of screening; no lifetime exposure to 3,4-methylenedioxymethamphetamine; no history of psychotic disorder; no significant medical condition; and not pregnant. Criteria for healthy volunteer participants were similar except for a required absence of DSM-IV Axis I psychiatric disorders, and absence of mood or psychotic disorders in any first-degree relative. Beck Depression Inventory,[23] Hamilton Depression Rating Scale,[24] and Global Assessment Scale[25] assessed subjective and objective depression severity and functional impairment, respectively. Brown–Goodwin Aggression Inventory[26] measured lifetime aggression.

Index traumas in the PTSD group meeting DSM-IV-TR PTSD criterion A1 included 11 childhood physical and/or sexual abuse; one domestic abuse and childhood abuse; one domestic abuse; two sexual assault as adults; one physical assault as adult and childhood physical abuse; four with other severe traumatic events that occurred as adults. Of the healthy volunteers, three reported physical and/or sexual abuse, occurring before the age of 15 in each. Thirteen of the 20 PTSD patients also met DSM-IV criteria for a current major depressive episode (MDE) as part of MDD. Other Axis I disorders in the PTSD group included current ($n = 5$) or lifetime ($n = 1$) panic disorder, social anxiety disorder ($n = 3$), simple phobia ($n = 1$), and binge eating disorder ($n = 1$). Five PTSD participants had past histories of alcohol and/or substance abuse (one past alcohol dependence; one past alcohol, cannabis, stimulant, and cocaine abuse; one past alcohol abuse and cannabis dependence; one past alcohol abuse, and cannabis, and stimulant dependence; and one hypnotic/anxiolytic and cannabis abuse).

The protocol was approved by the Institutional Review Board of the New York State Psychiatric Institute, and participants gave written informed consent after explanation of the study.

RADIOCHEMISTRY AND INPUT FUNCTION MEASUREMENT

Preparation of [C-11]WAY100635 and measurement of arterial input function, metabolites, and plasma free fraction (f_P) has been described.[20,27] The mean ± *SD* injected dose of [C-11]WAY100635 was comparable between healthy volunteer (8.0 ±3.5 mCi) and PTSD (6.9 ± 2.5 mCi) groups ($t = 1.3$, $df = 67$, $P = .19$). Injected mass was higher (2.8 ± 1.8 versus 1.5 ± 0.8 μg; $t = 4.2$, $df = 67$, $P < .001$) and decay-corrected specific activity (1.6 ± 0.7 versus 2.3 ± 0.8 mCi/nmole; $t = -3.5$, $df = 67$, $P = .001$) was lower in the healthy volunteer group compared with the PTSD group. Later studies differed after our human dosimetry study[28] determined the injected dose (and consequently injected mass) needed to be lowered. No correlation within-groups between injected mass and BP_F was found in any region (data not shown). Main analyses were also performed covarying for injected mass and injected dose.

IMAGE ACQUISITION AND ANALYSIS

PET imaging was performed on an ECAT EXACT HR+ (Siemens/CTI, Knoxville, TN). After bolus infusion of [C-11]WAY100635 over 30 s, a 110-min emission scan was acquired in 3D mode as 20 successive frames of increasing duration (3 × 20 s, 3 × 1 min, 3×2 min, 2×5 min, 9×10 min). Automated arterial sampling was conducted every 5 s for first 2 min and then manually at longer intervals thereafter. Image analysis was performed using MATLAB 2006b (The Mathworks, Natick, MA) with extensions to the following: Functional Magnetic Imaging of the Brain's Linear Image Registration Tool (FLIRT) v 5.2.,[29] Brain Extraction Tool v1.2,[30] Statistical Parametric Mapping (SPM5) normalization,[31] and segmentation routines.[32] To correct for subject motion during PET

scan, denoising filter techniques were applied to all PET images starting at frame 5. All frames were aligned to the eighth frame using rigid body FLIRT. A mean of motion-corrected frames 8–18 was registered to the magnetic resonance imaging (MRI) using FLIRT.

Acquisition of T1-weighted MRI for co-registration of PET images and identification of regions of interest (ROIs) were performed for each participant as previously described using a 1.5T Signa Advantage or a 3T Signa HDx system (General Electric, Milwaukee, MI).[27] Twelve ROIs were hand drawn on left and right sides of brain on each subject's MRI by experienced technicians trained to reliably demarcate these regions using brain atlases[33, 34] and published reports.[35, 36] Test–retest variability between raters was less than 3% for each of the 12 ROIs. These ROIs included ventral, medial, dorsolateral PFC; anterior and posterior cingulate; insular, parietal, temporal, and occipital cortex; amygdala, hippocampus, and parahippocampal gyrus. As a more conservative approach, the ROIs for dorsolateral prefrontal, temporal, parietal, and occipital cortex were included in the main group comparisons despite no direct expected effects in PTSD, noting that our prior work on anxiety symptoms in MDD indicated associations with 5-HT_{1A} binding in these ROIs.[10] An ellipsoid (2 cm^3) was manually placed on the raphe nuclei of each individual's mean PET image, completely encompassing the high [C-11]WAY100635 binding region containing median and dorsal raphe nuclei. A cylindrical reference region was drawn in cerebellar white matter (CWM), a region virtually devoid of 5-HT_{1A}.[20] ROI contours of cortical ROIs were refined using the segmented MRI to reflect the gyral pattern and differences between PET and MRI fields of view.[21] Specifically, a gray matter probability mask was generated in SPM5 using each subject's segmented MRI. By multiplying all PET voxels within each cortical ROI by the voxel's corresponding gray matter probability mask value (range between 0 and 1), the cortical ROIs were modified to include only gray matter voxels.

DERIVATION OF REGIONAL OUTCOME MEASURE

Regional distribution volumes (V_T) of [C-11]WAY100635 were derived from kinetic analysis using the arterial input function and a two-tissue compartment (2T) model.[27] V_T is the sum of the nondisplaceable and specific compartments distribution volumes, noted as V_{ND} and V_S, respectively.[37] Time-activity curves were fit with a 2T model, with V_{ND} fixed to the V_T previously estimated in the CWM reference region using a one-tissue compartment model.[20] The main outcome measure of binding potential was BP_F (= $B_{available} / K_D$), the ratio at equilibrium of the concentration of specifically bound radioligand in tissue to the concentration of free radioligand in the tissue (with $B_{available}$ equal to concentration of unoccupied receptor, and K_D representing the dissociation constant); BP_F was calculated as $(V_{T(\mathrm{ROI})} - V_{ND}) / f_P$.[37]

GENOTYPING THE C(-1019)G POLYMORPHISM

Participants were genotyped for the C(-1019)G polymorphism of HTR1A, the 5-HT_{1A} receptor gene, to explore if biallelic genotype status has an effect on regional brain binding of 5-HT_{1A} in PTSD. Genotyping was performed as previously described in ref.[38] using allele-specific polymerase chain reaction (PCR) amplification.

STATISTICAL ANALYSIS

To borrow strength across all ROIs and to properly account for correlation among ROIs in the same participant, linear mixed-effects models[39] were fit to the ROI-level BP_F estimates with region and diagnostic group as fixed effects and participant as the random effect. This modeling strategy provides a way to partition the expected variability into two sources: the biological variability among subjects within the diagnostic groups and the variability in

estimating BP_F for each region within each subject, which will include noise in PET scanning, as well as in measures derived from blood samples. This also allows for a single hypothesis to test for a difference between groups that is manifested in each ROI, thus avoiding the multiple comparisons considerations that would arise if the regions were tested separately. To stabilize variance across regions, adjust for slight skewness in distribution of binding measures, and allow testing for a proportional change in binding across regions, we fit the model to log-transformed binding potentials as we[10, 21, 38, 40, 41] and others[15] have reported for PET data analyses. Demonstrating a difference in log(BP_F) is equivalent to demonstrating a difference in the same direction of raw BP_F, as the natural log is a monotone transformation. Estimated standard errors were computed using a bootstrap algorithm that takes into account errors in metabolite, plasma, and brain data,[42] with observations weighted accordingly. Models were fit using the "nlme" package in the R software environment (www.r-project.org). Post hoc pair-wise comparisons between groups for each individual ROI were also performed, and results are presented with no adjustment for multiple comparisons. Additional statistical analyses include Student's *t*-tests, χ^2 test, and Fisher's exact test performed in SPSS 18.0 (SPSS Statistics, 2010) or R.

RESULTS

Table 1 lists demographic and clinical characteristics of the sample. The healthy volunteer and PTSD groups had comparable age and sex distribution. The healthy volunteer group had about 2 years more of education than the PTSD group. Years of education were not related to 5-HT$_{1A}$ BP_F (data not shown).

The free fraction of [C-11]WAY100635 in plasma (f_p) was higher in healthy volunteers (8.1 ± 2.4%) compared with PTSD (6.1 ± 1.4%) group ($t = 6.9$, $df = 58.8$, $P < .0001$). The distribution volume of the reference region, V_{ND}, did not differ between healthy volunteers (0.29 ± 0.11) and PTSD group (0.27 ± 0.08%; $t = 0.69$, $df = 67$, $P = .49$).

A linear mixed-effects model of regional 5-HT$_{1A}$ BP_F, controlling for sex, age, and aggression,[43] demonstrated the PTSD group had higher 5-HT$_{1A}$ BP_F compared with healthy volunteers ($F_{1,64} = 12.9$, $P = .0006$). There was also higher binding in females compared with males ($F_{1,64} = 10.8$, $P = .0016$). Neither age ($F_{1,64} = 0.15$, $P = .69$) nor lifetime aggression severity score ($F_{1,64} = 0.35$, $P = .56$) were related to 5-HT$_{1A}$ BP_F in group comparison across all regions (although in the healthy volunteer group aggression severity was related to 5-HT$_{1A}$ BP_F) Years of education was also not related to 5-HT$_{1A}$ BP_F ($F_{1,63} = 1.0$, $P = .32$).

When controlling for between group differences in injected mass, the finding of higher 5-HT$_{1A}$ BP_F in the PTSD group remained significant ($F_{1,63} = 12.2$, $P = .0009$); and injected mass was not related to 5-HT$_{1A}$ BP_F ($F_{1,63} = 0.60$, $P = .44$). The main finding also remained significant ($F_{1,63} = 12.7$, $P = .0007$) when the model controlled for injected radioactivity of dose, which itself was also not related to 5-HT$_{1A}$ BP_F ($F_{1,63} = 0.054$, $P = .82$).

A significant diagnosis × region interaction ($F_{13,803} = 1.9$, $P = .03$) indicated that 5-HT$_{1A}$ BP_F differences between diagnostic groups varied between brain region. Post hoc differences in each ROI indicated significantly higher binding in the PTSD group in all ROIs except hippocampus (Table 2; ordered from largest to smallest difference). The greatest difference was seen in raphe nuclei (43% higher in PTSD) and the least in hippocampus (19% higher in PTSD). Figure 1 shows BP_F estimates for the PTSD and healthy volunteer groups in the 13 ROIs, and Figure 2 presents voxel maps of mean BPF levels for each of the two groups.

Previously published PET studies in PTSD reported 5-HT_{1A} radioligand binding with an alternate outcome measure, BP_{ND} (= (V_T–V_{ND}) / V_{ND}; the ratio at equilibrium of specifically bound radioligand to that of nondisplaceable radioligand in tissue). Therefore, we also compared diagnostic groups using this outcome measure and found the PTSD group did not differ from healthy volunteers on 5-HT_{1A} BP_{ND} ($F_{1,64}$ = 1.9, P = .18), nor was there an effect of sex ($F_{1,64}$ = 0.10, P = .75).

PTSD-ALONE VERSUS PTSD + MDD

In the PTSD group, 13 of 20 had a current comorbid MDE (PTSD + MDD). To rule out an effect of depression comorbidity on binding, we compared binding in the seven PTSD patients without current MDD (PTSD –MDD) with healthy volunteers,finding higher 5-HT_{1A} BP_F in the PTSD-MDD group ($F_{1,66}$ = 4.9, P = .03). The two PTSD subgroups (PTSD + MDD; PTSD – MDD) did not differ in 5-HT_{1A} BP_F from each other ($F_{1,66}$ = 0.25, P = .62). See Figure 3.

NOT RECENTLY MEDICATED GROUP

The 13 patients (six PTSD – MDD and seven PTSD + MDD) without recent (within 4 months of PET scan) antidepressant exposure (hereafter designated “not recently medicated,” NRM) also had higher 5-HT_{1A} BP_F compared with healthy volunteers ($F_{1,65}$ = 8.07, P = .0060). Moreover, NRM and more recently medicated PTSD subgroup (median time off antidepressants of 47 days) did not differ from each other ($F_{1,65}$ = 1.38, P = .24).

5-HT_{1A} PROMOTOR POLYMORPHISM

The C(−1019)G genotype showed an association with PTSD (Table 1) whereby the GG genotype was more common in PTSD (40%) compared with healthy volunteers (6.3%: Fisher’s Exact Test, P = .004). Testing for an effect of PTSD diagnosis on raphe nuclei 5-HT_{1A} BP_F by the linear mixed effects model, with sex, age, aggression history, and 5-HT1APR genotype as factors, effects of PTSD diagnosis ($F_{1,66.6}$ = 17.0, P = .00011) and sex ($F_{1,71.8}$ = 18.4, P = .00007) remained. The effect of genotype was not statistically significant, although there was a strong trend ($F_{2,24.0}$ = 3.1, P = .053).

DISCUSSION

We found higher regional brain 5-HT_{1A} binding (BP_F) in PTSD compared to healthy volunteer participants using the 5-HT_{1A} PET radioligand [11C]WAY100635 and a metabolite-corrected, arterial input function. Higher binding (by 26–43%) was present in PTSD in every ROI examined except hippocampus, and it was highest in raphe nuclei. As we have reported previously for healthy volunteers and those with depression, women had higher 5-HT_{1A} BP_F than men. Neither age nor lifetime aggression severity score were related to 5-HT_{1A} BP_F in the linear mixed effects model.

Our previous reports,[16, 38] based on two independent samples of MDD patients imaged during a MDE, showed higher 5-HT_{1A} binding in NRM MDD. We have additionally reported that this effect is present in MDD during remission, indicating a trait abnormality.[40] This raises the question as to whether comorbidity of a current MDE in the PTSD group (13/20 PTSD patients) explains the present findings. Since the PTSD subgroup without current MDD (PTSD-MDD group) also had higher binding compared with healthy volunteers, and there was no difference in 5-HT_{1A} binding between the PTSD + MDD and the PTSD – MDD subgroups, we find that higher 5-HT_{1A} BP_F in PTSD is not explained by MDD comorbidity.

This similar biological abnormality involving greater 5-HT_{1A} binding in both MDD and PTSD is of potential importance, as it may help explain why comorbidity between PTSD and MDD is common; 48% of the general population who report lifetime PTSD also report lifetime MDD diagnosis.[44] Both PTSD and MDD can be reactions to traumatic exposures, as seen after the attack on the World Trade Center on 11 September 2001.[45] There is also substantial symptom overlap between the disorders. Therefore, we can now add higher 5-HT_{1A} binding to the clinical evidence suggesting that PTSD and MDD to some degree are alternative manifestations of the same underlying diathesis. Greater 5-HT_{1A} binding may be a biological manifestation of this common diathesis or vulnerability to stressful experiences that can result in either MDD or PTSD or both. Moreover, hypothalamic–pituitary–adrenal (HPA) axis abnormalities in comorbid PTSD + MDD may also represent a common central abnormality in glucocorticoid regulation[46, 47] that may be related to regional brain 5-HT_{1A} density. However human and nonhuman primate studies have yet to detect cortisol effects on radioligand binding to 5-HT_{1A}.[48, 49]

Our cross-sectional study needs extension to determine whether higher 5-HT_{1A} binding antedates the development of PTSD (or is still present after remission) indicating that it may be a predisposing biological trait. Reported childhood adversity such as exposure to physical and/or sexual abuse during development, which has been associated with HPA axis dysregulation in adulthood,[50] may contribute to diathesis, consonant with animal models showing lasting changes in 5-HT_{1A} binding resulting from developmental adversity;[51,52] but also see refs.[53].

To date, we know of one study of in vivo 5-HT_{1A} binding in PTSD using PET imaging, which used an alternate 5-HT_{1A} ligand [F-18]FC-WAY.[18] The main outcome measure, regional distribution volume (V_T), did not differ between 12 PTSD participants and 11 healthy volunteers, nor did the regional nondisplaceable binding (BP_{ND}). That no difference was detected may be attributable to (1) challenges for quantitative modeling of 5-HT_{1A} brain binding using this ligand due to a radiometabolite ([F-18]fluorocyclohexanecarboxylic acid) that crosses the blood brain barrier, as well as defluorination with F-18 uptake by skull[19] and (2) use of total cerebellum as reference region, which has measurable 5-HT_{1A} binding,[20] for calculation of BP_{ND}, as this runs counter to the assumption for simplified reference tissue modeling (SRTM) of no specific binding.[37] Therefore, methodological limitations may have prevented this prior study from detecting the binding differences we report. We also identified significant differences in free fraction of the tracer (f_P) between PTSD patients and healthy volunteers ($P < .0001$), but our outcome measure, BP_F, takes into account any differences in f_P between diagnostic groups (note: at equilibrium $f_{ND} = f_P / V_{ND}$).

The functional C-1019G promoter polymorphism 5-HT1APR GG genotype in vitro is associated with higher 5-HT_{1A} transcript expression in raphe but not hippocampal neurons.[54] Because genotyping for this polymorphism was available for participants in this study, we explored whether there was a role for this genotype in partially explaining elevated raphe nuclei 5-HT_{1A} BP_F in the PTSD group; yet such results must be considered very preliminary as the study was grossly underpowered for exploring any relationships with genotype. We have previously reported the G-allele is associated with higher brainstem raphe nuclei 5-HT_{1A} binding in both MDD and bipolar depression.[21, 38] In this sample, the GG genotype is overrepresented in the PTSD group; and when presence of PTSD is considered in the linear mixed effects model, the effect of diagnosis on binding is not all explained by genotype as only a strong trend for genotype effect ($P = .053$) was identified. Given the lack of statistical power for exploring genotype effects on raphe nuclei 5-HT_{1A} binding, this trend is of interest and raises the possibility that a larger sample may confirm the finding.

A recent course of antidepressants did not explain our findings, because the PTSD subgroup with no antidepressant exposure within 120 days prior to scanning also had higher 5-HT_{1A} BP_F compared with healthy volunteers and did not differ from the more recently medicated PTSD subgroup.

Brain regions with the largest differences in binding between PTSD and healthy volunteers, namely the autoreceptors on raphe neurons in midbrain and terminal field receptors in amygdala and several prefrontal cortical regions, can be related to the neural circuits implicated in PTSD. In PTSD, amygdala responses subserving acquisition and recall of fearful responding are putatively exaggerated and prefrontal cortical–hippocampal interactions mediating contextual extinction are deficient, resulting in “failure of recovery” from trauma via impaired extinction memory.[55] The 5-HT_{1A} receptor is implicated in extinction learning.[6, 56] More autoreceptors and less serotonin firing and release may result in deficient serotonergic neurotransmission through forebrain 5-HT_{1A}, thereby impairing extinction memory recall[57] as posited in PTSD.

Recent PET imaging studies have reported regional brain binding differences in other key proteins in the serotonin system, namely the serotonin transporter[58] and the serotonin-1B receptor (5-HT_{1B}),[59] in PTSD (versus healthy volunteers) and in a severe trauma exposed group (versus nonexposed), respectively. The groups compared in the serotonin transporter PET study were similar to those compared in the present study, but transporter-binding differences in the PTSD group appeared localized to amygdala, contrasting with the higher 5-HT_{1A} binding identified throughout several forebrain and raphe region ROIs in our report. The 5-HT_{1B} study compared severe trauma exposure (with and without PTSD) to healthy volunteers without trauma exposure, finding less binding in amygdala, anterior cingulate, and caudate. Thus, the 5-HT_{1B} differences appear to be an effect of severe trauma exposure per se, rather than specific to, or a risk factor for, development of PTSD. Our present study and the transporter study both have the limitation of not including a third matched trauma-exposed healthy volunteer group. Thus, identified differences in 5-HT_{1A} and 5-HT_{1B} in the respective studies may represent effects of trauma exposure per se rather than being PTSD specific.

Another limitation in the present study was heterogeneity of the trauma reported by the PTSD group, both in terms of the developmental stage at which traumas occurred and single versus repeated or chronic trauma. Future work should strive for greater homogeneity in trauma typology and include a trauma-exposed “resilient” control group matched for trauma typology, time elapsed since index trauma, and developmental stage of trauma occurrence, as well as other factors relating to 5-HT_{1A} binding such as sex. Using 5-HT_{1A} BP_F as outcome measure, future studies would do well to examine the role of 5-HT_{1A} receptors in other anxiety disorders and the impact of successful treatments.

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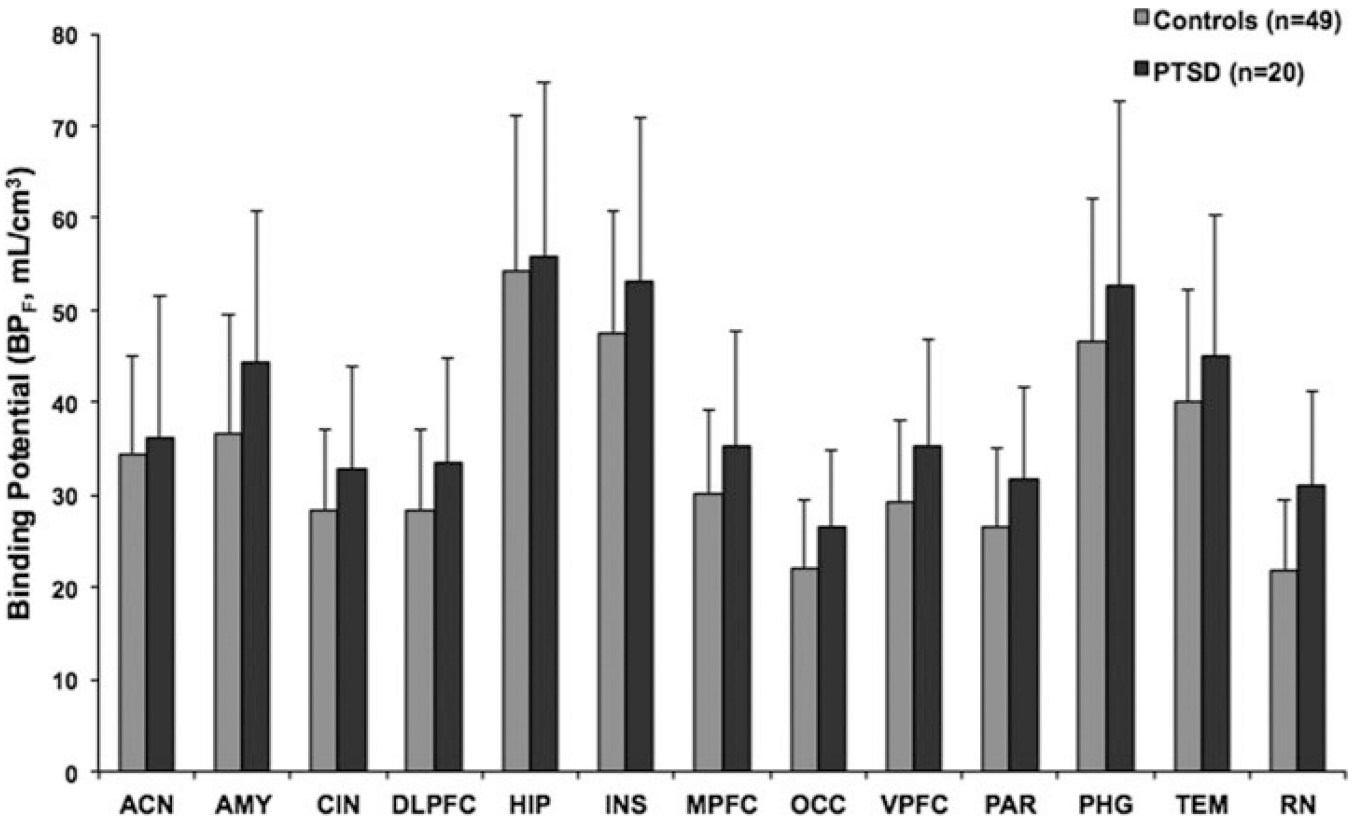

Figure 1.

Radiolabeled [Carbonyl-C-11]WAY-100635 binding potential (BP_F) estimates for the 5-HT_{1A} receptor in PTSD patients and healthy volunteer participants in 13 ROIs. Comparison of 5-HT_{1A} BP_F between PTSD group and healthy volunteer group demonstrates higher 5-HT_{1A} BP_F in PTSD patients ($P = .0006$). Post hoc comparisons demonstrate higher 5-HT_{1A} BP_F in the PTSD group in every ROI examined except hippocampus. The height of each vertical bar represents the weighed mean of 5-HT_{1A} BP_F for the region, and the error bar represents the standard error of the weighted estimate. ACN, anterior cingulate cortex; AMY, amygdala; BP_F, binding potential; [Carbonyl-C-11]WAY-100635, N-(2-(4-(2-methoxyphenyl)-1-piperazinyl)ethyl)-N-(2-pyridinyl)cyclohexanecarboxamide; CIN, posterior cingulate; DLPFC, dorsolateral prefrontal cortex; HIP, hippocampus; 5-HT_{1A}, serotonin-1A receptor; INS, insula; MPFC, medial prefrontal cortex; OCC, occipital cortex; PAR, parietal cortex; PHG, parahippocampal gyrus; TEM, temporal cortex; VPFC, ventral prefrontal cortex; RN, raphe nuclei.

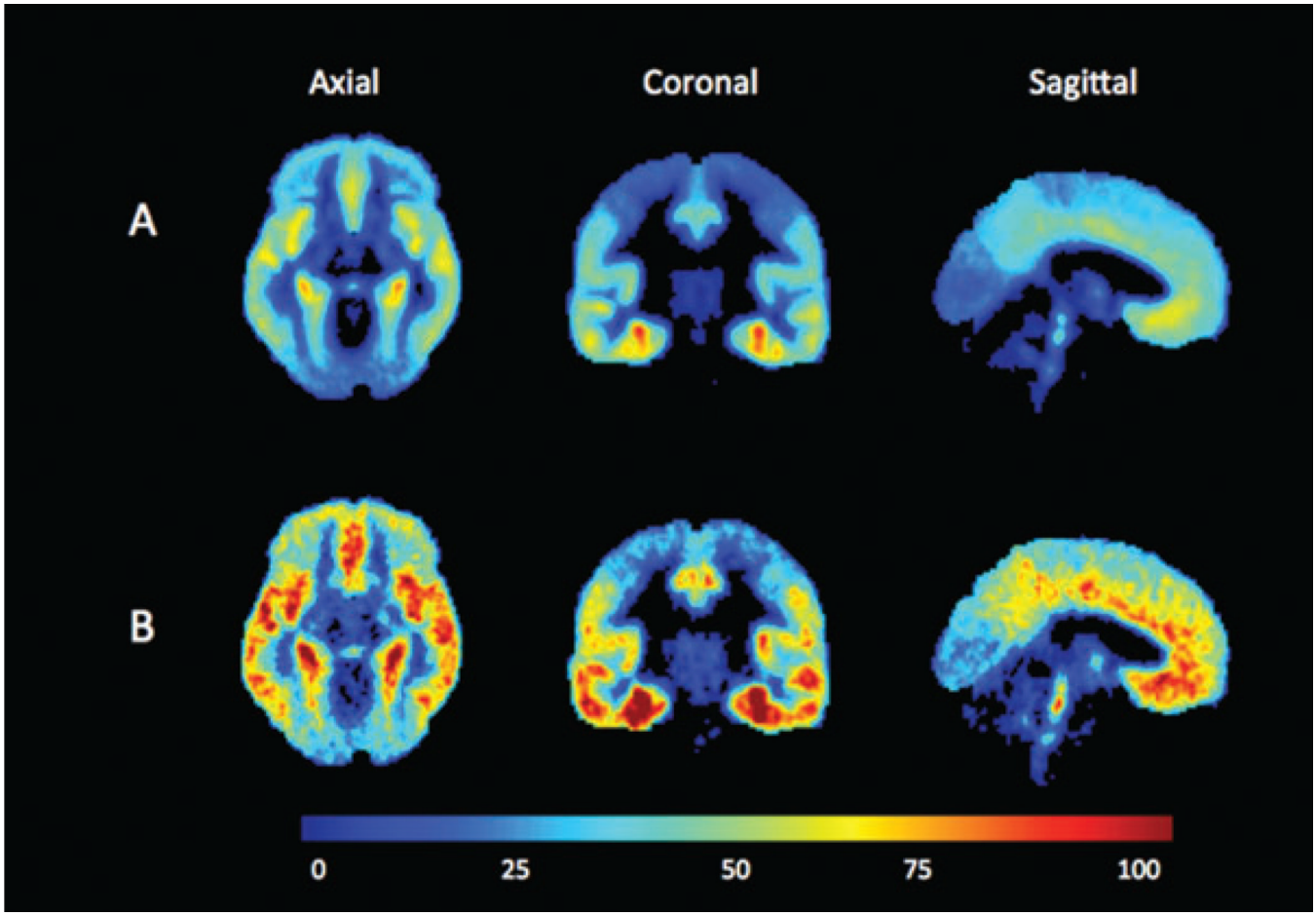

Figure 2.
Voxel-based mean binding potential (BPF) maps were produced as previously described [16] for A) the healthy volunteer group (n = 49) and B) the posttraumatic stress disorder group (n = 20). Each voxel intensity is the mean of the group's single voxel 5-HT1A BPF measurement. The positron-emission tomography data were registered using each individual's magnetic resonance image to the Montreal Neurological Institute (MNI) space. The color bar represents 5-HT1A BPF level in milliliters per gram.

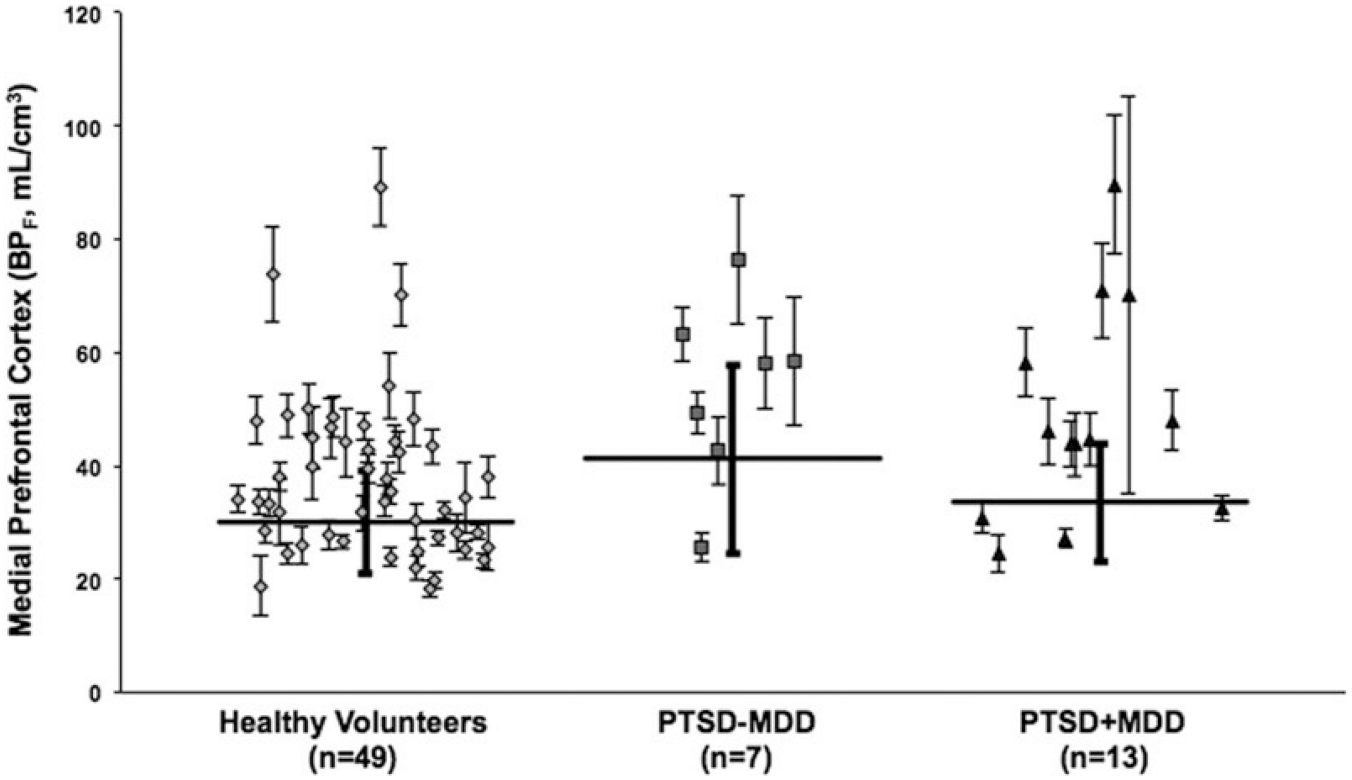

Figure 3.

Radiolabeled [Carbonyl-C-11]WAY-100635 binding potential (BP_F) estimates for the 5-HT_{1A} receptor in medial prefrontal cortex for healthy volunteer, PTSD without current MDD (PTSD – MDD), and comorbid PTSD + MDD participants. Diamonds, squares, and triangles represent single measurements of BP_F in healthy volunteer participants, the PTSD – MDD participants, and the PTSD + MDD participants, respectively. Thin capped vertical error bars represent standard errors computed using a bootstrap algorithm that takes into account errors in metabolite, plasma, and brain data.[42] Weighted group mean and standard error of the weighted mean of BP_F are represented by thick horizontal lines and thick-capped vertical lines, respectively. BP_F, binding potential; [Carbonyl-C-11]WAY-100635, N-(2-(4-(2-methoxyphenyl)-1-piperazinyl)ethyl)-N-(2-pyridinyl)cyclohexanecarboxamide; 5-HT_{1A}, serotonin-1A.

TABLE 1

Demographic and clinical data of the study groups

	Diagnostic groups				Group comparisons		
	HVs (*n* = 49)		PTSD (*n* = 20)		*t*-test		
	Mean	***SD***	**Mean**	***SD***	***t*-value**	***df***	***P*-value**
Age	37.3	14.8	40.7	12.2	−0.91	67	NS (.37)
Years of education	16.7	2.9	14.9	2.9	2.36	67	.024
HDRS-24	0.7	0.9	22.3	9.3	−10.41	19.16	<.001
Beck Depression Inventory[a]	1.6	2.7	22.0	13.1	−6.56	17.48	<.001
Lifetime aggression	15.0	3.7	20.2	5.2	−4.73	67	<.001
Global Assessment Scale[a]	90.2	4.5	57.0	14.8	9.35	18.15	<.001
					χ^2 or FET		
	No. (%)		No. (%)		Value	*df*	*P*-value
Sex (female)	28 (57.1)		14 (70.0)		0.99	1	NS (.32)
Comorbid current MDD	0 (0)		13 (65.0)				
Abuse history—Lifetime	3 (6.1)		13 (65.0)				<.001
Abuse history —at <15yo	3 (6.1)		10 (50.0)				<.001
Prior antidepressant exposure	0 (0)		11 (55.0)				
						FET	
5-HT1APR genotype[b]	No. (%)		No. (%)				*P*-value
CC	16 (33.3)		5 (25)				.004
CG	29 (60.4)		7 (35)				
GG	3 (6.3)		8 (40)				

Abbreviations: FET, Fisher's Exact Test (two-sided); HDRS-24, Hamilton Depression Rating Scale 24-item version; HVs, healthy volunteers; MDD, major depressive disorder; PTSD, posttraumatic stress disorder.

[a]BDI and GAS scores missing for two participants.

[b]Genotype missing for 1 participant.

TABLE 2

Post hoc comparisons of 5-HT_{1A} BP_F in PTSD (n = 20) v. HVs (n = 49) in ROIs

Region of interest	Percent higher 5-HT_{1A} BP_F in PTSD	*t*-test		
		t-value	*df*	*P*-value
Raphe nuclei	43%	2.99	803	.0028
Amygdala	34%	2.87	803	.0042
Medial prefrontal cortex	34%	3.10	803	.0020
Dorsolateral prefrontal cortex	33%	3.02	803	.0026
Ventral prefrontal cortex	32%	2.99	803	.0029
Parietal cortex	30%	2.81	803	.0050
Anterior cingulate cortex	30%	2.78	803	.0055
Posterior cingulate cortex	30%	2.78	803	.0056
Occipital cortex	28%	2.55	803	.0110
Temporal cortex	28%	2.63	803	.0088
Parahippocampal gyrus	27%	2.49	803	.0130
Insular cortex	27%	2.56	803	.0110
Hippocampus	19%	1.75	803	NS (.080)

Abbreviations: BP_F, binding potential; *df*, degrees of freedom; HVs, healthy volunteers; NS, not significant; PTSD, posttraumatic stress disorder; ROIs, regions of interest; 5-HT_{1A}, serotonin-1A receptor.