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Elevated Brain Cannabinoid CB_1 Receptor Availability in Posttraumatic Stress Disorder: A Positron Emission Tomography Study

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Abstract

Endocannabinoids and their attending cannabinoid type 1 receptor (CB_1) have been implicated in animal models of posttraumatic stress disorder (PTSD). However, their specific role has not been studied in people with PTSD. Herein, we present an *in vivo* imaging study using positron emission tomography (PET) and the CB_1-selective radioligand [^{11}C]OMAR in individuals with PTSD, and healthy controls with lifetime histories of trauma (trauma controls [TC]) and those without such histories (healthy controls [HC]). Untreated individuals with PTSD (N=25) with non-combat trauma histories, and TC (N=12) and HC (N=23) participated in a magnetic resonance (MR) imaging scan and a resting PET scan with the CB_1 receptor antagonist radiotracer [^{11}C]OMAR, which measures volume of distribution (V_T) linearly related to CB_1 receptor availability. Peripheral levels of anandamide, 2-arachidonoylglycerol (2-AG), oleoylethanolamide (OEA),

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palmitoylethanolamide (PEA), and cortisol were also assessed. In the PTSD group, relative to the HC and TC groups, we found elevated brain-wide [^{11}C]OMAR V_T values (F(2,53)=7.96, p=.001; 19.5% and 14.5% higher, respectively) which were most pronounced in women (F(1,53)=5.52, p=.023). Anandamide concentrations were reduced in the PTSD relative to the TC (53.1% lower) and HC (58.2% lower) groups. Cortisol levels were lower in the PTSD and TC groups relative to the HC group. Three biomarkers examined collectively—OMAR V_T, anandamide, and cortisol—correctly classified nearly 85% of PTSD cases. These results suggest that abnormal CB_1 receptor-mediated anandamide signaling is implicated in the etiology of PTSD, and provide a promising neurobiological model to develop novel, evidence-based pharmacotherapies for this disorder.

Keywords

PTSD; Cannabinoid receptors; brain imaging; PET; OMAR

INTRODUCTION

Posttraumatic stress disorder (PTSD) is an anxiety disorder that can develop following exposure to traumatic life events[1]. Central clinical features of PTSD include a persistent, heightened experience of alarm and distress, as well as a failure of extinction processes to diminish the emotional impact of traumatic memories. Investigation of the neural mechanisms that underlie fear acquisition, consolidation, and extinction may thus enhance our understanding of the neurobiological basis of PTSD, and open opportunities for mechanism-based drug discovery and development of the next-generation pharmacotherapies for this disabling disorder.

The process by which emotionally-aversive memories become consolidated is recognized to be an interaction between glucocorticoid hormones and norepinephrine, both of which are released in response to stress[2]. The primary component of this response appears to be a noradrenergic signal that is necessary for encoding emotionally salient information[3]. The hyperconsolidation of traumatic memories in PTSD is driven by a glucocorticoid-hormone-facilitated potentiation of norepinephrine inputs to the basolateral amygdala (BLA)[4, 5]. Recent work has revealed that this glucocorticoid action is mediated by cannabinoid type-1 (CB_1) receptors, a mechanism that is critical for the consolidation of aversive memories[6, 7] and thus implicates CB_1 receptors in the etiology of PTSD. Moreover, there is an emerging body of evidence demonstrating an important role for CB_1 receptor-mediated endocannabinoid signaling in the extinction of aversive memories[8]. Augmenting levels of anandamide in the amygdala modulates short-term fear extinction[9], thereby resulting in long-term reduction in fear[10] and highlighting the endocannabinoid system as a candidate system for developing novel pharmacotherapies for PTSD[11].

CB_1 receptors are the most abundant G-protein-coupled receptors in the central nervous system[12, 13], and are found in high concentrations within an amygdala-hippocampal-cortico-striatal circuit responsible for processing and storing fear-related memories and coordinating fear-related behaviors[14–16]. Animal studies[17] have shown that chronic stress is associated with decreased brain levels of the endocannabinoid anandamide and CB_1 receptor adaptations[17–19], which in turn give rise to an anxious/depressive phenotype[20, 21]. However, it is not clear whether these animal findings apply to PTSD in humans.

The development of a CB_1 receptor selective radiotracer—[^{11}C]OMAR[22]—now makes it possible for the first time to conduct a quantitative assessment of *in vivo* CB_1 receptor availability using positron emission tomography (PET). In the current study, we hypothesized that, relative to healthy non-trauma-exposed (HC) and trauma-exposed

controls (TC), individuals with PTSD would have increased CB_1 receptor availability. In light of data from animal studies[17–19, 23], we further predicted more pronounced CB_1 receptor elevations in women than men with PTSD. A TC group free of lifetime PTSD or other psychiatric illness was recruited in order to assess the relation between trauma exposure alone and CB_1 receptor availability. We also assessed peripheral levels of the endocannabinoids anandamide and 2-arachidonoylglycerol (2-AG); levels of the fatty acid ethanolamides oleoylethanolamide (OEA) and palmitoylethanolamide (PEA); and cortisol. We expected to find lower anandamide and cortisol levels in the PTSD group relative to the HC and TC groups[24]. Finally, psychiatrically relevant biomarkers for PTSD are important yet elusive contributors towards accurate diagnosis and improved clinical care for trauma survivors. We predicted that measures of CB_1 receptor availability, anandamide and cortisol would accurately categorize a majority of participants with regard to PTSD diagnostic status relative to healthy and trauma-exposed controls.

METHODS

Participants

Participants were recruited via public advertisements seeking individuals with non-combat trauma histories and healthy control participants with and without lifetime histories of trauma. None of the participants had ever been treated with psychotropic medications. In addition, none were receiving psychotherapy at the time of scanning. The protocol was approved by the New York University Institutional Review Board, the Yale University School of Medicine Human Investigation Committee, the Yale University Magnetic Resonance Research Center, and the Yale New Haven Hospital Radiation Safety Committee. After providing written informed consent, participants underwent a thorough medical and psychiatric evaluation that included physical examination, electrocardiogram, standard blood chemistry and hematology laboratory tests, urine analysis and toxicology, followed by a magnetic resonance (MR) imaging scan and a resting PET scan with the CB_1 receptor antagonist radiotracer [^{11}C]OMAR. Psychiatric diagnoses were made using Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition – Text Revision (DSM-IV-TR) criteria and the Structured Clinical Interview for DSM-IV (SCID), which was administered by an experienced psychiatric clinician[25, 26]. PTSD symptom severity was assessed using the Clinician-Administered PTSD Scale for DSM-IV (CAPS)[27] and trauma history was assessed using the Traumatic Life Events Questionnaire (TLEQ)[28]. Only traumatic events meeting DSM-IV-TR PTSD criterion A1 for severe trauma exposure, as well as criterion A2, which confirms the emotional response to the trauma (i.e., response involved intense fear, horror, or helplessness), were counted towards participants' trauma history in this study. Additional assessments included the Hamilton Rating Scale for Anxiety (HAM-A)[29], the Montgomery-Åsberg Depression Rating Scale (MADRS)[30], the Alcohol Module of the Addiction Severity Index[31] and the Fagerström Test for Nicotine Dependence (FTND)[32]. To meet TC inclusion criteria, individuals must have been exposed to at least one potentially traumatic event that met DSM-IV-TR PTSD Criteria A1 and A2, but have no lifetime PTSD or other Axis I diagnosis. Participants with significant medical or neurological conditions, substance abuse within 12 months of the PET scan, a lifetime history of substance dependence (including cannabis), or history of head injury with loss of consciousness were excluded from the study. The absence of substance use (including cannabis) was determined by self-report and confirmed by urine toxicology and breathalyzer test at screening, and on the days of MR and PET imaging. Participants were asked to abstain from food, nicotine, and caffeinated beverages after midnight on the day prior to the imaging study until after completion of the scan. Blood samples were collected at the time of tracer injection and processed immediately after collection in the laboratory, which is

adjacent to the scan room and frozen at −80°Celsius until analyzed, as previously described[33].

PET imaging

[^{11}C]OMAR was prepared in high specific activity (109±74 MBq/nmol at end of synthesis). The radiotracer (injected dose: 589±122 MBq, injected mass: 0.05±0.03 μg/kg) was infused over 1 minute through the antecubital vein. The radioactivity concentration in blood from the radial artery was measured continuously using an automated system (PBS101, Veenstra Instruments, Joure, The Netherlands) for the first 7 min after radiotracer administration and manually drawn and counted thereafter. Discrete samples were acquired at selected times and measured on a gamma counter (Wizard 1480, Perkin-Elmer, Waltham, Massachusetts, United States) to determine radioactivity concentration in whole blood and plasma. Five discrete blood samples (5, 15, 30, 60, 90 minutes) were analyzed for the fraction of unchanged [^{11}C]OMAR and its radiometabolites using a column-switching high pressure liquid chromatography method[34]. The fraction of tracer unbound to plasma proteins was determined in triplicate by ultrafiltration[35]. Listmode emission data were collected for 120 minutes after radiotracer administration using the High Resolution Research Tomograph (HRRT; Siemens Medical Systems, Knoxville, Tennessee, United States), a dedicated brain PET scanner with spatial resolution better than 3 mm[36]. Head motion was measured using the Polaris Vicra optical tracking system (Northern Digital Inc., Waterloo, Ontario, Canada) and incorporated into PET image reconstruction with all corrections.[37]. The PET images were registered to subject-specific T1-weighted magnetic resonance images (256 × 256 × 176 grid of 1 mm isotropic voxels) acquired on a 3 Tesla Trio imaging system (Siemens Medical Systems, Erlangen, Germany). Anatomical MR images were in turn nonlinearly registered to an MR template where regions of interest (ROIs) were defined[38]. Regional time activity curves (TACs) were extracted from the dynamic PET data and analyzed using the multilinear analysis method[39] with metabolite-corrected arterial input functions and cutoff time t^*=30 minutes. The kinetic analysis yielded regional estimates of total volume of distribution (V_T), the equilibrium ratio of radioligand concentration in tissue relative to arterial plasma[40], which is directly proportional to CB_1 receptor availability.

Data Analysis

Shapiro-Wilk tests were conducted to assess data distributions of all study variables for normality. Non-normally distributed variables (e.g., [^{11}C]OMAR V_T values, cortisol levels) were transformed using logarithmic-base-10 prior to analysis. Analyses of variance (ANOVA) were then used to compare continuously-distributed demographic and clinical variables of the HC, TC, and PTSD groups; χ^2 tests were used to compare categorical variables. Because [^{11}C]OMAR V_T values across brain regions were highly correlated (r values=.73 to .96), mean composite [^{11}C]OMAR V_T values were computed by averaging [^{11}C]OMAR V_T values across all brain regions for each individual. A series of analyses of covariance (ANCOVA) were then conducted to test for group differences in mean composite [^{11}C]OMAR V_T values, as well as in regions that comprise the amygdala-hippocampal-cortico-striatal circuit implicated in PTSD[41]. In these analyses, group (HC, TC, and PTSD) and sex were entered as independent variables, age as a covariate, and [^{11}C]OMAR V_T values as the dependent variable. Pairwise comparisons—least-squares difference tests—were computed to compare [^{11}C]OMAR V_T values in each of the three groups, with $p<.01$ used to indicate significant group differences. Effect sizes of differences in [^{11}C]OMAR V_T values in the TC and PTSD groups relative to the HC group were expressed using percent difference and Cohen's d ($(M_{group1}-M_{group2})/SD_{pooled}$). Similar ANCOVAs were conducted for anandamide, 2-AG, OEA, and PEA and cortisol values. To examine the relation between [^{11}C]OMAR V_T values, anandamide, and cortisol biomarkers, and PTSD group membership, a series of binary logistic regression analyses were

conducted, with main effects and all combinations of these variables entered as explanatory variables in separate analyses, and PTSD (coded "1") vs. TC+HC group (coded "0") entered as the dependent variable.

RESULTS

Seventy-two participants were recruited into the study and 60 completed the protocol. Reasons for exclusion were previous medication exposure (n=9) and medical reasons that would interfere with correct interpretation of the collected data (n=4). Table 1 shows demographic, trauma, and clinical characteristics of the HC, TC, and PTSD groups whose data were used for analyses. [^{11}C]OMAR injection parameters, age, sex, education, nature of trauma histories, and body mass index did not differ among the groups; there was a greater proportion of white individuals in the HC than TC and PTSD groups. The PTSD group was significantly more likely than the HC and TC groups to currently smoke cigarettes, and to have a lifetime history of mood or anxiety disorder, and alcohol or drug abuse, but the groups did not differ with respect to lifetime and current alcohol use and nicotine dependence. The PTSD group scored higher on the MADRS and HAM-A relative to both control groups, and on the CAPS relative to the TC group.

Bivariate correlations revealed that composite [^{11}C]OMAR V_T values correlated negatively with age (r= −.34, p=.007) and positively with female sex (r= .39, p=.002). Composite [^{11}C]OMAR V_T values also correlated negatively with anandamide levels (r= −.27, p=.038), but not cortisol levels (r= −.06, p=.67); and the correlation between anandamide and cortisol levels was also not significant (r= .02, p=.88). Other demographic variables, BMI, lifetime and current alcohol use, current cigarette smoking status and nicotine dependence, and trauma-related variables and lifetime history of mood or anxiety disorders, and alcohol or drug abuse were not associated with [^{11}C]OMAR V_T values (all r values<|.22|, all p values>.10).

An ANCOVA examining mean composite [^{11}C]OMAR V_T values in the HC, TC, and PTSD groups revealed significant main effects of group (F(2,53)=7.96, p=.001), sex (F(1,53)=5.52, p=.023), and age (F(1,53=11.95, p=.001); there was a trend towards a significant group-by-sex interaction (F(2,53)=2.75, p=.073). Women in the full sample had higher mean composite [^{11}C]OMAR V_T values than men (M=1.233, SE=.040 vs. M=1.369, SE=.042, Cohen's d=.61). As shown in Table 2, mean composite [^{11}C]OMAR V_T values differed by group, such that PTSD group V_T was higher than the TC and HC groups, which did not differ. This same general pattern was also observed in brain regions that comprise the amygdala-hippocampal-cortico-striatal neural circuit implicated in PTSD. As shown in Figure 1, effect sizes for the differences between the PTSD group and HC and TC groups were consistently large in magnitude. Differences between the TC and HC groups were generally small in magnitude. Analyses of [^{11}C]OMAR V_T values in brain regions outside of the amygdala-hippocampal-cortico-striatal neural circuit implicated in PTSD revealed this same pattern of results, with the PTSD group having significantly greater [^{11}C]OMAR V_T values than both the HC and TC groups (all F's for group effect>4.91, all p's<.01; all p's for pairwise comparisons<.01).

Figure 2 shows mean [^{11}C]OMAR V_T values for the PTSD, and HC and TC groups by sex. Pairwise comparisons revealed that mean [^{11}C]OMAR V_T values were significantly higher among women in the HC (p=.009; d=1.26) and PTSD (p=.011; d=1.16) groups, but not in the TC group (p=.65; d=.32).

An ANCOVA examining anandamide levels in the HC, TC, and PTSD groups revealed significant main effects of group (F(2,53)=9.75, p<.001) and sex (F(1,53)=4.23, p=.045), but

age (F(1,53)=1.00, p=.32) and the interaction of group-by-sex (F(2,53)=1.47, p=.24) were not significant. Pairwise comparisons revealed that the PTSD group had lower anandamide levels than both the HC (p=.001; Cohen's d=1.10) and TC (p=.001; Cohen's d=1.36) groups; anandamide levels did not differ between the HC and TC groups (p=.51; Cohen's d=.26). Women had lower levels than men (M=2.44, SE=.24 vs. M=1.76, SE=.23; Cohen's d=.54). OEA levels also differed by group, with the HC group having significantly higher OEA levels than the TC and PTSD groups; age (F(1,45)=2.91, p=.095), sex (F(1,45)=.55, p=.46), and the interaction of group × sex (F(2,45)=.02, p=.98) were not significant. 2-AG and PEA levels did not differ by group.

An ANCOVA examining cortisol levels in the HC, TC, and PTSD groups revealed a significant main effect of group (F(2,52)=12.69, p<.001), but sex (F(1,52)=.05, p=.82), age (F(1,52)=1.84, p=.18), and the interaction of group-by-sex were not significant (F(2,52)=.33, p=.72). Pairwise comparisons revealed that the HC group had higher cortisol levels than both the TC (p<.001; Cohen's d=1.59) and PTSD (p<.001; Cohen's d=1.22) groups; cortisol levels did not differ between the TC and PTSD groups (p=.35; Cohen's d=.34).

Table 3 shows results of binary logistic regression analyses that examined how each of the biomarkers ([^{11}C]OMAR V_T values, anandamide, and cortisol) independently and in various combinations related to PTSD vs. HC/TC group membership. Results revealed that the classification accuracy increased as additional biomarkers were added to the model, with the highest classification accuracy observed when [^{11}C]OMAR V_T values, anandamide, and cortisol were entered simultaneously. None of the interaction terms were significant (all p values>.21).

DISCUSSION

We found that PTSD is associated with a ubiquitously expressed large magnitude elevation (~20%) in [^{11}C]OMAR V_T values, which quantitatively reflects CB_1 receptor availability. Notably, this elevation was found in an amygdala-hippocampal-cortico-striatal neural circuit implicated in PTSD, as well as in brain regions outside this circuit. These results suggest greater brain-wide CB_1 receptor availability in individuals with PTSD relative to control participants with and without histories of trauma exposure. Reduced peripheral anandamide levels in PTSD complemented the brain [^{11}C]OMAR V_T results, suggesting that the elevated CB_1 receptor availability in PTSD may result from a combination of both receptor up-regulation and low receptor occupancy by anandamide. The lack of displacement of CB_1 radioligands by agonists[42–44] which has been attributed to a large receptor reserve[45] suggests that increased [^{11}C]OMAR V_T values are explained to the most part by receptor up-regulation in response to low anandamide levels rather than low receptor occupancy by anandamide. This idea is substantiated by data showing that CB_1 receptor up-regulation in response to low stress-induced synaptic anandamide availability was prevented by enhanced anandamide signaling[46]. OEA levels were higher in HC relative to TC and PTSD participants in the current study, but groups did not differ with respect to 2-AG and PEA levels. Taken together, these data suggest that abnormal CB_1 receptor-mediated anandamide signaling is implicated in the etiology of PTSD.

The sex-related results of the current study accord with animal data demonstrating sex differences in CB_1 receptor regulation, with stress-related up-regulation of CB_1 receptors observed predominantly in female animals[18]. We also found abnormally low cortisol levels in trauma survivors, corroborating prior work[47]. Another key contribution of the current study is the finding that collective consideration of all three of the biomarkers examined—OMAR V_T, anandamide, and cortisol—was highly accurate in classifying PTSD, with nearly 85% of PTSD cases correctly classified and overall classification accuracy

approaching 90%. Results of this study advance the extant literature in three important ways: (1) they contribute to extant knowledge regarding the etiology of PTSD; (2) they identify candidate biomarkers that may be used to support clinical decision-making regarding diagnostic classification of PTSD; and (3) they provide a promising neurobiological rationale to develop novel, evidence-based pharmacotherapies for PTSD.

Our results of reduced peripheral anandamide levels together with a compensatory up-regulation of CB_1 receptors in PTSD suggest lower anandamide tone in PTSD. Notably, elevated rates of cannabis abuse/dependence among individuals with PTSD have been reported[48, 49]. Such findings substantiate, at least in part, emerging evidence that synthetic cannabinoid receptor agonists[50] or plant-derived cannabinoids such as marijuana[51] may possess some benefits in individuals with PTSD by helping relieve haunting nightmares and other symptoms of PTSD. However, such data do not allow the conclusion that self-medication with cannabis with its primary psychoactive constituent tetrahydrocannabinol should be recommended for the treatment of PTSD, as direct activation of CB_1 receptors with plant-derived cannabinoids over an extended period of time leads to down-regulation of CB_1 receptors[52, 53], which may in turn result in a depression-like phenotype in certain individuals[54] and increase risk of addiction[55].

Another important finding in this study is the sex differences in anandamide levels and [^{11}C]OMAR V_T values in both the HC and PTSD groups. Animal data showing higher CB_1 receptor levels in male relative to female animals[18, 56, 57] and receptor fluctuations during the estrous cycle together with changes in affinity of agonist binding[58] highlight the importance of careful considerations of gender and menstrual cycle phase in assessments of CB_1 receptor availability in imaging studies. In addition, we believe, that a conclusive interpretation of the CB_1 receptor profile in males and females requires a broad and dynamic perspective rather than a single observation in a cross-sectional study with a single time point. Our results are largely in agreement with a previous study that used the CB_1 PET tracer [^{18}F]MK-9470 to investigate the effects of age and gender[59]. That report found greater plasma parent fraction and higher normalized brain uptake (SUV) in men, which is consistent with our findings. However, because of the nearly irreversible uptake kinetics of the radiotracer and the lack of significant gender differences in the metabolite-corrected input function in the initial cohort that underwent arterial blood sampling, the [^{18}F]MK-9470 study used brain SUV as the final outcome metric of tracer binding. We performed kinetic analysis of [^{11}C]OMAR data using metabolite-corrected arterial input functions in all participants. This methodology provided estimates of V_T, which – in contrast to SUV, which was greater in men than women – was reduced in men compared to women[60]. Thus, our measurements are compatible with those of the previously reported [^{18}F]MK-9470 data and the discrepant interpretations appear to be accounted for by different endpoints centered on our use of arterial input functions in kinetic analyses rather than the simplified outcome of normalized brain concentration. If, as our results suggest, women show higher CB_1 receptor availability than men already under basal, non-stress conditions, then they may be at increased risk for PTSD when exposed to trauma. This finding may thus provide a neurobiological explanation for why women are at greater risk for developing PTSD following exposure to various types of trauma than men even when sexual trauma—which is more common in women—is excluded[61].

To date, drug development in PTSD has been opportunistic, building almost entirely on empirical observations with drugs approved for other indications. The data reported herein are the first of which we are aware of to demonstrate the critical role of CB_1 receptors and endocannabinoids in the etiology of PTSD in humans. As such, they provide a foundation upon which to develop and validate informative biomarkers of PTSD vulnerability, as well as to guide the rational development of the next generation of evidence-based treatments for

PTSD. Blocking anandamide deactivation or re-uptake, both of which will increase synaptic anandamide availability, may lead to a more circumscribed and beneficial spectrum of biological responses than those produced by direct CB_1 receptor activation[62, 63]. This is of particular interest for the development of mechanism-based novel pharmacotherapies for PTSD, as emerging data have revealed that enhanced anandamide signaling can curb the effects of chronic stress, possibly by maintaining normal amygdala function[64] via extinction-driven reductions in fear resulting in improved stress-reactivity in humans[10].

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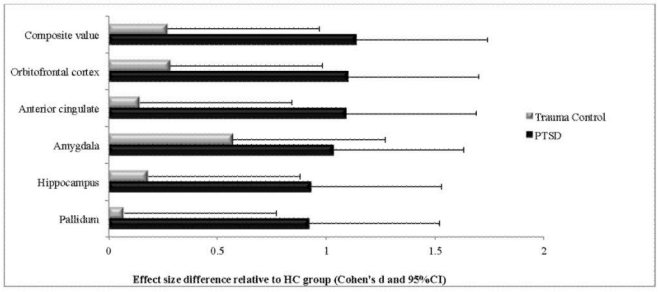

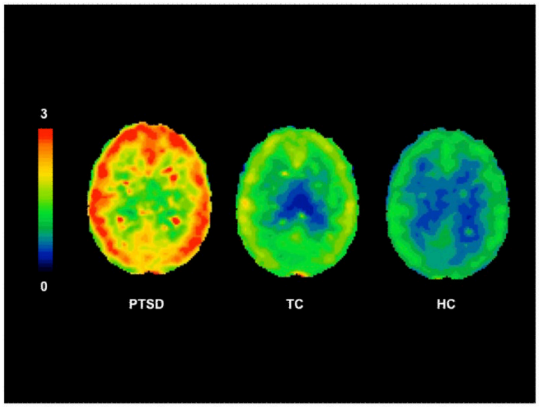

Figure 1.
Cohen's d and 95% confidence intervals of effect size differences in [^{11}C]OMAR volume of distribution (V_T) values in PTSD and TC groups relative to HC group

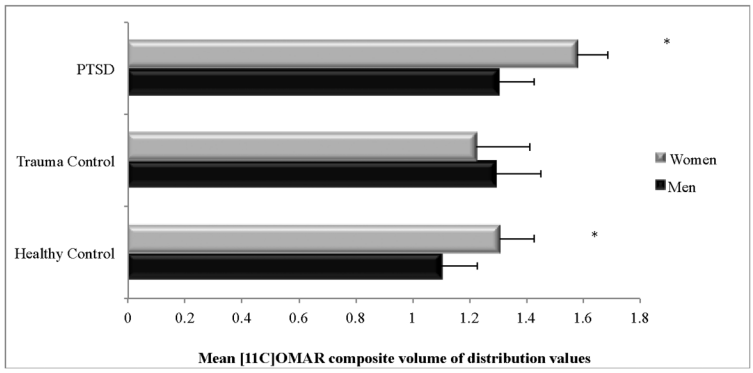

Figure 2.
Cohen's d and 95% confidence intervals of effect size differences in [^{11}C]OMAR volume of distribution (V_T) values in PTSD and TC groups relative to HC group by sex

Table 1

Demographic and clinical characteristics of study groups

	Healthy controls	Trauma controls	PTSD	Test of difference	Pairwise comparisons
N	23	12	25		
	M (SD) or n (%)	M (SD) or n (%)	M (SD) or n (%)		
Age	32.1 (8.5)	29.7 (7.9)	32.2 (9.9)	F(2,57)=.36, p=.70	-
Male sex	11 (47.8%)	7 (58.3%)	11 (44.0%)	$\chi^2(2)$=.67, p=.71	-
White race/ethnicity	14 (60.9%)	2 (16.7%)	8 (32.0%)	$\chi^2(2)$=7.56, p=.023	HC>TC,PTSD
Education (years)	16.0 (2.1)	14.1 (1.8)	14.6 (3.1)	F(2,57)=2.86, p=.066	-
Body mass index	25.0 (3.4)	26.6 (4.5)	25.3 (4.7)	F(2,57)=.56, p=.57	-
Ever drank alcohol in lifetime	11 (73.3%)	3 (42.9%)	12 (57.1%)	$\chi^2(2)$=2.04, p=.36	-
Number of years used alcohol	5.7 (6.3)	8.0 (11.5)	5.0 (6.0)	F(2,38)=.44, p=.65	-
Drank alcohol in past 30 days	9 (56.3%)	6 (54.5%)	10 (47.6%)	$\chi^2(2)$=.31, p=.86	-
Number of days drank alcohol in past 30 days	2.4 (3.3)	3.7 (5.0)	2.5 (3.4)	F(2,45)=.48, p=.62	-
Current smoker	0 (0%)	0 (0%)	9 (36.0%)	$\chi^2(2)$=14.82, p=.001	PTSD>HC,TC
Nicotine dependence	0 (0%)	0 (0%)	3 (12.0%)	$\chi^2(2)$=4.42, p=.11	-
Indices of lifetime trauma					
Age at first trauma	-	13.0 (4.8)	13.9 (10.3)	F(1,35)=.09, p=.77	-
Age at presenting trauma	-	16.5 (8.7)	18.2 (11.1)	F(1,35)=.22, p=.64	-
Number of traumas	-	3.0 (2.0)	3.5 (3.7)	F(1,35)=.18, p=.68	-
Index traumatic event				Fisher's exact test=6.38, p<.001	
Physical assault	-	9 (75.0%)	22 (88.0%)		
Motor vehicle accident	-	3 (25.0%)	0 (0%)		
Witnessed suicide	-	0 (0%)	3 (12.0%)		
Lifetime mood or anxiety disorder	0 (0%)	0 (0%)	13 (52.0%)	$\chi^2(2)$=23.23, p<.001	PTSD>HC, TC
Lifetime alcohol or drug abuse	0 (0%)	0 (0%)	9 (36.0%)	$\chi^2(2)$=14.82, p=.001	PTSD>HC, TC
CAPS score	-	5.6 (7.6)	75.5 (17.4)	F(1,35)=175.99, p<.001	PTSD>TC
MADRS score	2.2 (3.0)	3.5 (6.5)	22.7 (10.0)	F(2,57)=54.89, p<.001	PTSD>HC, TC
HAM-A score	1.6 (2.5)	2.3 (3.3)	21.4 (10.4)	F(2,57)=55.77, p<.001	PTSD>HC, TC

Note. HC=Healthy controls; TC=Trauma Controls; SD=standard deviation; PTSD=Posttraumatic stress disorder; SD=standard deviation; CAPS=Clinician-Administered PTSD Scale; MADRS= Montgomery-Åsberg Depression Rating Scale; HAM-A=Hamilton Anxiety Rating Scale. Physical assault includes sexual abuse, domestic violence, and other non-combat related physical violence. Some frequencies and denominator degrees of freedom do not sum to total n due to missing data.

Table 2

[^{11}C]OMAR volume of distribution (V_T) values, anandamide, 2-AG, OEA,PEA, and cortisol levels by group

	Healthy controls	Trauma controls	PTSD	Test of difference	Pairwise comparisons	Mean % difference PTSD vs. HC	Mean % difference PTSD vs. TC	Mean % difference TC vs. HC
N	23	12	25					
	M (SE)	M (SE)	M (SE)					
[^{11}C]OMAR V_T values								
Mean composite	1.205 (.044)	1.258 (.062)	1.440 (.042)	F(2,53)=7.96, p=.001	PTSD>HC,TC	+19.5%	+14.5%	+4.4%
Anterior cingulate	1.400 (.049)	1.432 (.069)	1.648 (.047)	F(2,53)=7.54, p=.001	PTSD>HC,TC	+17.7%	+15.1%	+2.3%
Amygdala	1.322 (.056)	1.444 (.079)	1.594 (.054)	F(2,53)=6.13, p=.004	PTSD>HC	+20.6%	+10.4%	+9.2%
Caudate	1.080 (.047)	1.104 (.067)	1.287 (.046)	F(2,53)=5.62, p=.006	PTSD>HC,TC	+19.2%	+16.6%	+2.2%
Hippocampus	1.214 (.052)	1.257 (.073)	1.440 (.050)	F(2,53)=5.36, p=.008	PTSD>HC,TC	+18.6%	+14.6%	+3.5%
Pallidum	1.638 (.085)	1.666 (.121)	2.008 (.082)	F(2,53)=5.60, p=.006	PTSD>HC,TC	+22.6%	+20.5%	+1.7%
Orbitofrontal cortex	1.265 (.043)	1.321 (.061)	1.490 (.042)	F(2,53)=7.31, p=.002	PTSD>HC,TC	+17.8%	+12.8%	+4.4%
Anandamide	2.43 (.25)	2.73 (.35)	1.14 (.24)	F(2,53)=9.75, p<.001	HC,TC>PTSD	−53.1%	−58.2%	+12.3%
2-AG	7.16 (2.41)	10.01 (3.71)	13.31 (2.16)	F(2,41)=1.81, p=.18	-	-	-	-
OEA	156.41 (23.20)	25.01 (38.78)	35.12 (22.16)	F(2,45)=8.45, p=.001	HC>TC,PTSD	−77.5%	+40.4%	−84.0%
PEA	8.87 (1.54)	10.22 (2.58)	9.68 (1.48)	F(2,45)=13, p=.88	-	-	-	-
Cortisol	12.47 (.71)	7.18 (1.00)	8.33 (.70)	F(2,52)=12.69, p<.001	HC>TC,PTSD	−33.2%	+16.0%	−42.4%

Note. SE=standard error of the mean. V_T=volume of distribution. 2-AG=2-Arachidonoylglycerol; OEA=Oleoylethanolamine; PEA=Palmitoylethanolamide. All models are adjusted for age and sex. Denominator degrees of freedom are lower for F tests examining group differences in 2-AG, PEA, OEA, and cortisol due to missing data.

Table 3

Classification accuracy statistics for logistic regression model examining relation between [^{11}C]OMAR V_T, anandamide, and cortisol bio markers and PTSD

Biomarker	**Overall classification accuracy**	**% PTSD cases correctly classified**	**Nagelkerke's R^2**
Cortisol	61.0%	33.3%	.134
Composite [^{11}C]OMAR V_T	70.0%	52.0%	.217
Anandamide	73.3%	76.0%	.348
Cortisol + AEA	72.9%	70.8%	.482
Composite [^{11}C]OMAR + Anandamide	75.0%	68.0%	.472
Composite [^{11}C]OMAR + Cortisol	76.3%	66.7%	.357
Composite [^{11}C]OMAR + Cortisol + Anandamide	88.1%	83.3%	.661
Final logistic regression model Hosmer and Lemeshow test=9.17, p=.33			
	Wald χ^2, p	**OR (95%CI)**	
Composite [^{11}C]OMAR V_T	6.96, .008	3.09 (1.34–7.16)	
Cortisol	7.40, .007	.24 (.08–.67)	
Anandamide	9.88, .002	.13 (.03–.46)	

Note. V_T=volume of distribution; OR=odds ratio; 95%CI=95% confidence interval.