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Differential Role of mGluR5 in Cognitive Processes in Posttraumatic Stress Disorder and Major Depression

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Abstract

Background: A robust literature supports the role of the metabotropic glutamate receptor type 5 (mGluR5) in cognitive functioning. mGluR5 is also implicated in the pathophysiology of posttraumatic stress disorder (PTSD) and major depressive disorder (MDD), which are characterized by cognitive alterations. However, the relationship between mGluR5 and cognition in MDD and PTSD has not yet been directly investigated. To address this gap, we examined the relationship between *in vivo* mGluR5 availability and cognition in PTSD, MDD, and matched healthy adults (HA).

Methods: Individuals with PTSD ($N = 28$) and MDD ($N = 21$), and HA ($N = 28$) were matched for age, gender, and smoking status. Participants completed ^{18}F-FPEB positron emission tomography (PET) scan, psychiatric and cognitive assessments.

Results: Across models examining the relationship between mGluR5 availability and different domains of cognition across diagnostic groups, only the interaction of diagnosis*attention was significant ($F_{4,64} = 3.011$, $P = .024$). Higher mGluR5 availability was associated with poorer attention in PTSD in 4 frontolimbic regions of interests (ROI's: OFC ($r = -.441$, $P = .016$), vmPFC ($r = -.408$, $P = .028$), dlPFC ($r = -.421$, $P = .023$), hippocampus ($r = -.422$, $P = .025$). By contrast, mGluR5 availability in the MDD group was positively related to Attention (ATTN) in the OFC ($r = .590$, $P = .006$), vmPFC ($r = .653$, $P = .002$), and dlPFC ($r = .620$, $P = .004$). Findings in the hippocampus for MDD followed the same pattern but did not survive correction for multiple comparisons ($r = .480$, $P = .036$). ATTN and mGluR5 availability were not significantly related in the HA group. Of note, in MANOVA analyses group*ATTN interaction results in the OFC did not survive multiple comparisons ($P = .046$). All other findings survived correction for multiple comparisons and remained significant when covarying for potential confounds (eg, depressed mood).

Conclusions: We observed a significant relationship between frontolimbic mGluR5 availability and performance on tests of attention in individuals with MDD and PTSD. This finding aligns with animal work showing dysregulation in mGluR5 in cognitive functioning, and differed as a function of diagnosis. Results suggest interventions targeting mGluR5 may help bolster cognitive difficulties, highlighting the importance of employing different mGluR5 directed treatment strategies in MDD and PTSD.

Keywords
mGluR5, PTSD, MDD, attention, cognition, PET

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Introduction

A growing body of preclinical,[1–5] postmortem, and human[6,7] research has demonstrated the critical role of the metabotropic glutamate receptor subtype 5 (mGluR5) in multiple aspects of cognition.[1] The mostly postsynaptic receptor is concentrated heavily in the frontal cortex and hippocampus,[5] areas crucial to higher cognitive functions, and has been shown to play key roles in processes including attention,[8,9] learning,[10] and memory.[1,11–13] In rodents, knockout or deletion of mGluR5 results in impairment of spatial[4] and inhibitory learning.[14] Similarly, in both rodents and healthy adult

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humans, application of mGluR5 antagonist MPEP impairs working and spatial memory.[5,10,15,16] By contrast, application of positive allosteric modulators (PAMs) of mGluR5 can induce pro-cognitive effects,[17] including improved object recognition[18] and reaction time.[8,9] Moreover, the modulation of glutamate neurotransmission by mGluR5 has been observed in preclinical models of neuropsychiatric disorders characterized by specific impairments in cognition, including Fragile X syndrome,[19] schizophrenia,[20] Parkinson's disease,[21] and Alzheimer's disease.[22–24] Consistent with preclinical findings, recent studies using positron emission tomography (PET) have observed relationships between worse performance on tests of cognition and lower mGluR5 availability in schizophrenia[7] and Alzheimer's disease.[6] Together, these findings have motivated development of pharmacotherapies targeting mGluR5 to ameliorate cognitive impairment in a variety of neuropsychiatric diseases or disorders.[25]

In addition to cognition, the role of mGluR5 has been evaluated in mood and anxiety disorders, including major depressive disorder (MDD) and posttraumatic stress disorder (PTSD). Converging evidence suggests mGluR5 plays significant but distinct roles in the neurobiology of MDD and PTSD, respectively. In the case of MDD, preclinical studies in rodents consistently show knockout or blockade of mGluR5 results in antidepressant effects.[26,27] However, in humans, results concerning mGluR5 and depressive symptoms are less consistent. For example, one group has reported no differences in mGluR5 availability *in vivo* (using PET) between individuals with MDD and matched healthy adults,[28] while another group observed lower mGluR5 availability in MDD both *in vivo* and postmortem.[29] In PTSD, a robust body of preclinical research has demonstrated that mGluR5 is necessary for fear conditioning. Antagonism of mGluR5 can block both acquisition[30] and consolidation[12] of fear memories, while knockout[31] and antagonism[12] of mGluR5 disrupts fear extinction. Further, recent *in vivo* PET studies provide direct support for the role of mGluR5 in PTSD, showing relationships between higher mGluR5 availability and PTSD diagnosis, symptom severity,[32] and suicidal ideation in PTSD.[33] Notably, in the same paper the opposite pattern was observed in MDD; lower mGluR5 was associated with greater clinical symptom severity.[33] Thus, data supports a role for mGluR5 as a potential treatment target for new therapies in PTSD and possibly MDD. However, very different mGluR5 directed interventions may be beneficial in each case.

Notably, both PTSD and MDD are also characterized by substantial alterations in cognition, including marked impairment in memory,[34–36] attention and concentration,[37–39] and executive function.[39–43] In fact, loss of concentration is considered so central to the clinical presentation of both disorders that it is included in the DSM-5 diagnostic criteria for each.[44] Despite this, no currently published study has investigated the relationship between cognition and mGluR5 availability in MDD or PTSD. This is an oversight, as cognitive impairments predict impaired psychosocial function, lower quality of life, and symptom relapse in both PTSD[45,46] and MDD.[47,48] Moreover, deficits in memory and attention have been linked to risk for suicidal behavior in both disorders.[49–51] Thus, the extent to which mGluR5 availability relates to cognitive functioning in these disorders will both inform its importance as a target for intervention, and provide outcomes by which success of such interventions can be measured. Moreover, examination of the relationship between cognition and mGluR5 in MDD relative to PTSD could meaningfully inform developing understanding of the receptor's role in the neurobiology of both disorders. Observation of differential relationships between mGluR5 and cognition in MDD and PTSD, as seen in clinical variables, would add to mounting evidence suggesting different mGluR5 targeted interventions may be indicated for each disorder, or in the case of specific clinical symptom presentations (eg, primarily anxious vs. anhedonic).

We examined the relationship between cognition and *in vivo* mGluR5 availability in individuals with PTSD (with and without comorbid MDD), MDD only, and matched healthy adults (HA) using PET. More specifically, we sought to determine if the relationship between cognitive performance and mGluR5 availability differed as a function of psychiatric diagnosis. Based on our previous work[28,32] and preclinical evidence, our primary study hypothesis was that greater impairment in cognition (across domains) would be associated with higher prefrontal mGluR5 availability in PTSD, and lower prefrontal mGluR5 in both MDD and HA. Contributions of age and mood to any relationships between mGluR5 availability and cognition were also explored.

Methods and Materials

Participants

Twenty-eight individuals with PTSD (mean ± SD age = 36.72 ± 11.6 years; 14 females, 18 with current comorbid MDD), twenty-one individuals with MDD (mean ± SD age = 38.71 ± 13.90 years; 12 females), and twenty-eight HA participants (mean ± SD age = 39.48 ± 15.09 years; 14 females) completed the study. Groups were matched by age, sex, and smoking status (see Table 1). Of note, data for some participants in this study sample (ie, MDD, $n = 19$;[52] PTSD, $n = 23$,[22] HA, $n = 18$[22,52]) has been reported in previous studies. Eight individuals within the MDD group met criteria for comorbid DSM-5 anxiety disorders excepting current or historical PTSD, which was exclusionary. At the time the study was conducted, 13 PTSD participants and 7 MDD participants reported using one SSRI or SNRI medication (stable use at the same dosage for a minimum of 6 months). Participants were excluded for any other use of psychiatric medication. All participants completed an initial

Table 1. PET Study Participant Characteristics.

Variable	PTSD (n = 28)	MDD (n = 21)	Healthy Adults (n = 28)	*P*-value[a]
Sex (m:f)	14:14	9:12	14:14	.502
Age (yrs)	36.72 (11.69)	38.71 (13.91)	39.48 (15.10)	.786
No. of smokers	7	7	6	.402
Medicated	13	7	-	.103
Weight (scan day;kg)	30.55 (5.57)	27.83 (5.40)	27.72 (3.28)	.343
WTAR (Verbal IQ)	39.93 (8.795)	40.40 (8.348)	35.38 (10.22)	.128
PCL-S	54.1 (12.7)	-	-	-
MADRS	19.07 (7.73)	23.50 (7.42)	.59 (1.30)	<.001**
ATTN Composite	89.32 (15.24)	90.83 (9.72)	95.59 (11.01)	.779
WM Composite	95.12 (11.53)	96.98 (13.84)	99.35 (7.95)	.339
EF (GML)	93.77 (14.28)	92.63 (11.71)	100.99 (9.02)	.001*
VL (ISL)	99.84 (8.21)	93.80 (14.13)	102.97 (8.79)	.011*
OFC mGluR5	35.74 (6.56)	29.77 (5.41)	30.06 (5.70)	.038*
vmPFC mGluR5	36.33 (8.27)	32.50 (7.83)	33.38 (6.59)	.170
dlPFC mGluR5	38.54 (8.74)	32.81 (6.37)	33.14 (6.20)	.027*
hippocampus mGluR5	28.73 (5.76)	23.84 (4.38)	24.60 (4.00)	.134
Injected mass of FPEB (μg)	0.005 (0.003)	0.004 (0.003)	0.0039 (0.003)	.609
Injected dose (MBq)	4.45 (0.82)	4.20 (1.20)	4.48 (0.61)	.460

BMI: Body Mass Index; PCL: PTSD Checklist; MADRS: Montgomery-Asberg Depression Rating Scale; HAM-D: Hamilton depression rating scale; WTAR: Weschler Test of Adult Reading; ATTN: Attention; WM: working memory; EF: executive functioning; VL: verbal learning; OFC: orbitofrontal cortex; vmPFC: ventromedial prefrontal cortex; dlPFC: dorsolateral prefrontal cortex.

[a]*P*-values obtained from ANOVA and chi-squared analyses comparing PTSD, MDD, and HA (where applicable).

*$P > .05$,**$P > .001$.

screening visit, including physical, psychiatric, and neurological examinations to establish diagnosis and rule out major medical or neurological illness. Screening included electrocardiography, complete blood counts, serum chemistries, thyroid function test, liver function test, urinalysis, and urine toxicology screening. Additionally, female participants completed a urine pregnancy screen on scan-day. Psychiatric assessments administered at the screening visit included the Structured Clinical Interview for DSM-5,[53] Montgomery-Asberg Depression Scale (MADRS),[54] PTSD Checklist for DSM-5 (PCL-5),[55] and Weschler Test of Adult Reading (WTAR). Assessments administered on scan-day included the MADRS and Profile of Mood States (POMS), a measure of mood disturbance and lability. Scan-day scores on psychiatric assessments were used in the analyses reported below. Reported criterion A traumatic events in the PTSD group included sexual assault or abuse ($n = 9$), witnessing violence ($n = 6$), sexual/physical abuse ($n = 7$), combat exposure (n = 2), exposure to human trafficking (n = 1), and sudden and unexpected death of a loved one (n = 1). Twelve MDD participants reported trauma exposure including physical abuse ($n = 4$), car accident ($n = 6$), sexual assault (n = 1), and sudden and unexpected death of a loved one (n = 1). Information concerning trauma was not collected from HA participants. Participants were excluded from MDD and PTSD groups if they met criteria for: substance use disorder (mild past 6 months, moderate/severe past 12) except nicotine, positive urine toxicology or pregnancy tests, history of loss of consciousness over 5 min, and/or contraindications to magnetic resonance imaging (MRI). HA participants could not meet current or lifetime criteria for any DSM-5 psychiatric diagnosis (excepting nicotine use disorder) or have a first-degree relative who met such criteria. The study was approved by the Yale University HIC and RDRC. All participants provided written informed consent.

Assessment of Cognition

Seven tests were selected from the Cogstate computerized battery to measure four cognitive domains for analysis relevant to MDD and PTSD.[37,56,57] Attention [ATTN] was measured with the Identification (IDN) and Detection (DET) tests, based on reaction time paradigms. Working memory [WM] was measured with the One Back (ONB) and One Card Learning (OCL) tests, based on N-Back and pattern separation paradigms. Executive function [EF] was measured with the Groton Maze Learning Test (GMLT), based on the hidden pathway maze learning paradigm, and verbal learning and memory [verbal learning (VL)] was measured using the International Shopping List test (ISLT), a word list learning paradigm. These tests have been described in detail previously[58–61] and were administered according to standard instructions with the presentation of stimuli and recording of responses controlled by a laptop computer under supervision of a trained rater. Completion of the test battery required less than 30 min.

Prior to analyses, the main performance measure for each cognitive outcome measure was standardized using the mean and standard deviation of age stratified normative data.[62,63] Because the direction indicating abnormal scores differed for tests using accuracy and speed, the signs of standardized scores were adjusted such that negative scores indicate performance worse than the relevant age-matched mean and vice versa for all tests. To reduce Type I error, four of the seven original cognitive tests were used to compile two previously validated composite scores.[61] Specifically, an ATTN composite was computed by averaging the age-standardized scores from the DET and IDN test, and a WM composite was computed by averaging the age standardized scores on the OCL and ONB tests. Thus, four age-standardized outcome measures (hereafter referred to as cognitive domain scores) were used in final study analyses: ATTN, WM, EF, and VL.

MRI and PET Procedures

T1-weighted MRI scans were acquired for all participants on a 3T scanner (Trio, Siemens Medical Systems, Erlangen, Germany). This was done both to evaluate potential structural abnormalities and to facilitate co-registration with PET data. The radiotracer, [^{18}F]FPEB, was synthesized onsite at the Yale PET Center as described previously.[64] [^{18}F]FPEB was injected intravenously using a bolus plus infusion (B/I) paradigm over 120 min as described previously.[65,66] There were no significant differences in the injected dose or mass between HA, MDD, or PTSD groups ($t = .531$, $P = .590$; see Table 1 for average values). Dynamic scan data were reconstructed with corrections for attenuation, normalization, randoms, scatter, deadtime, and motion using the ordered-subset expectation maximization (OSEM)-based MOLAR algorithm.[67] All imaging data (both PET and MR) was evaluated to ensure quality (eg potential motion effects, image distortion, abnormalities in time activity curves, etc). No subjects were excluded from analyses due to imaging issues.

PET Imaging Analysis

All PET images were first co-registered to participant's T1-weighted MRI images using a six-parameter mutual information algorithm (FLIRT, FSL 3.2, Analysis Group, FMRIB, Oxford, UK). Images were then co-registered to the MR template via nonlinear transformation using the Bioimagesuite software (version 2.5). Regions of interest (ROIs) were identified using AAL (Anatomical Automatic Labeling for SPM2) template. Primary analyses focused on 4 brain regions, selected based on the strength of empirical evidence supporting their relevance to cognitive functioning both overall and in MDD and PTSD specifically. This included 3 frontal cortical regions (dlPFC, OFC, vmPFC), and one subcortical region (hippocampus). Gray matter segmentation was conducted using the computational anatomy toolbox for SPM2 (CAT). No appropriate reference region completely devoid of mGluR5 is available in the human brain.[68] As such, our outcome measure was calculated as volume of distribution (V_T: ratio of metabolite corrected radioligand concentration in region of interest to radioligand concentration in plasma, calculated at equilibrium). V_T was estimated using the equilibrium analysis method with venous input function;[32,52,64] this method of analysis was judged appropriate as clearance rates of the radiotracer did not differ significantly across participants. No differences were observed in plasma free fraction (f_p). Therefore, as described previously,[33] [^{18}F]FPEB V_T was used to quantify mGluR5 availability.

Statistical Analysis

Statistical analyses were completed using SPSS Statistics v26 (Armonk, NY: IBM Corp). Independent-samples *t*-tests and one-way analysis of variance (ANOVAs) were used to assess demographic and clinical differences across groups. Cohen's *d* was computed to estimate effect sizes of group differences in cognitive domain scores; percent differences were computed to express the magnitude differences in mGluR5 availability across groups. Group differences in the relationship between cognitive domain score outcomes and mGluR5 availability were assessed using four multivariate ANOVAs. In each case, diagnostic group, cognitive domain score outcome, and the interaction of group*domain score were entered as the independent variables, with mGluR5 V_T in study ROIs as dependent variables. Tukey's HSD post-hoc comparisons were performed to evaluate region-specific differences. Statistical significance for all tests was determined using the Benjamini-Hochberg procedure.[69] *A priori* power analyses confirmed a minimum of 80% power to conduct planned analyses.

Results

Preliminary Analyses: Demographic and Clinical Characteristics

Preliminary analyses were conducted to provide context for primary analyses involving the relationships between mGluR5, cognition, and psychiatric diagnosis. First, groups were matched by age, sex, and smoking status; analyses confirmed groups did not differ significantly in age, race, gender, weight, depressive symptom severity, [^{18}F]FPEB dose, or other potentially relevant variables (See Table 1). Second, bivariate correlations between the primary dependent variables (mGluR5 availability in the 4 study ROIs) and demographic variables were examined to evaluate their potential to confound analyses. In the full study sample, age was observed to be significantly associated with mGluR5 availability in the dlPFC ($r = -.253$, $P = .026$) and vmPFC ($r =$

−.308, $P = .006$). As such, to be conservative, groups were age-matched and age was controlled for primary analyses.

Univariate analyses confirmed previous findings concerning differences in mGluR5 availability across diagnostic groups: mGluR5 availability was significantly higher in the PTSD group relative to both MDD (P's = .007-.011, 14%-19% difference) and HA (P's = .01-.035, 13-18% difference; See Figure 1) in the OFC and dlPFC, with no significant difference between MDD and HA. Comparison of cognitive domain scores indicated that no other group differences in cognition were observed (See Figure 2).

Primary Analyses: mGluR5 and Cognition

We conducted four multivariate ANOVAs to evaluate differences in the relationship between cognitive domains (ATTN, WM, EF, and VL) and mGluR5 availability across groups. Findings from MANOVAs examining WM, EF, and VL revealed no significant interactions between diagnostic group*cognitive domain score suggesting that the relationship between mGluR5 availability and cognitive domain score results did not differ significantly across PTSD, MDD, and HA groups. In the fourth MANOVA, however, we observed a significant interaction of group*ATTN ($F_{4,64} = 3.011$, $P = .024$), indicating that the relationship between mGluR5 availability and ATTN composite score differed significantly across diagnostic groups (Figure 3). More specifically, post hoc Tukey's HSD tests suggested the interaction effect was significant in the dlPFC ($P = .014$), vmPFC ($P = .015$), and hippocampus ($P = .005$); findings in the OFC were not significant following correction for multiple comparisons ($P = .046$). Bivariate analyses showed a significant negative relationship between ATTN and mGluR5 availability in PTSD: OFC ($r = -.441$, $P = .016$), vmPFC ($r = -.408$, $P = .028$), dlPFC ($r = -.421$, $P = .023$), hippocampus ($r = -.422$, $P = .025$). By contrast, in the MDD group ATTN was positively related to mGluR5 availability across ROIs OFC ($r = .590$, $P = .006$), vmPFC ($r = .653$, $P = .002$), and dlPFC ($r = .620$, $P = .004$). Findings in the hippocampus for MDD followed the same pattern, but did not survive correction for multiple comparisons ($r = .48$, $P = .036$). ATTN and mGluR5 availability were not significantly correlated in the HA group. Although the main effect was not significant, bivariate analyses revealed a significant negative relationship between mGluR5 availability and EF in the vmPFC ($r = .461$, $P = .02$) and dlPFC ($r = .51$, $P = .008$) of the PTSD group (blue).

Secondary Analyses

Secondary analyses were conducted to confirm that the relationships observed could not be explained by the effects of mood symptoms as these have been shown to be related to both cognitive impairment and, in some cases, to mGluR5 availability.[33,70,71] Specifically, we repeated the MANOVAs with MADRS total score (model 1) and POMS total score (model 2) entered as additional independent variables. We did not observe significant effects of mood on above findings. In both models 1 and 2, the interaction between diagnostic group*ATTN remained significant; post hoc Tukey's HSD tests suggested the interaction effect was significant in all ROIs: OFC (model 1 $P = .016$; model 2 $P = .024$), dlPFC (model 1 $P = .007$; model 2 $P = .011$), vmPFC (model 1 $P = .007$; model 2 $P = .007$), and hippocampus (model 1 $P = .003$; model 2 $P = .007$). In both models, the negative relationships between mGluR5 and ATTN remained significant across ROIs in the PTSD group (P's < .01). Similarly, in both cases the positive relationship between mGluR5 and ATTN remained significant in all but the hippocampus in the MDD group.

Exploratory Analyses

In an effort to more comprehensively examine the relationship between mGluR5 availability, cognition, and diagnosis, we performed exploratory analyses. Specifically, we examined five additional ROIs with relevance to the pathophysiology of MDD and PTSD, and demonstrated relevance to cognitive functioning in the research literature: the amygdala, insula, anterior cingulate, caudate, and putamen. No significant relationships were observed between mGluR5 availability and EF, WM, or VL within or across diagnostic groups. However, mGluR5 availability was again observed to be significantly negatively related to ATTN in the PTSD group in four of the exploratory ROIs (r's = −.534 to −.50, P's = .010-.018) excluding the caudate ($r = -.379$, $P = .075$), and significantly positively related to ATTN in MDD in all five exploratory ROIs (r's = .57 to .68, P's = .001-.008).

Discussion

Results of this study provide the first evidence in individuals with MDD and PTSD for the role of mGluR5 in cognitive functioning. Specifically, we observed significant differences in the relationship between ATTN and mGluR5 availability in study ROIs in individuals diagnosed with PTSD relative to those with MDD. In PTSD, worse attention and psychomotor speed were associated with higher availability mGluR5. In contrast, in MDD, worse attention and psychomotor speed were associated with lower mGluR5 availability. Importantly, these relationships remained when variability in mood symptoms was controlled in the analyses. Contrary to hypotheses, associations between EF, WM, VL and mGluR5 availability were not significant in the MDD, PTSD, or healthy adult groups.

Findings concerning attention are particularly meaningful in light of the fact that deficits in this domain have been shown to produce serious and deleterious effects in both PTSD and MDD, including poorer quality of life,[72–74] higher rates of relapse and more difficulty with recovery,[75,76]

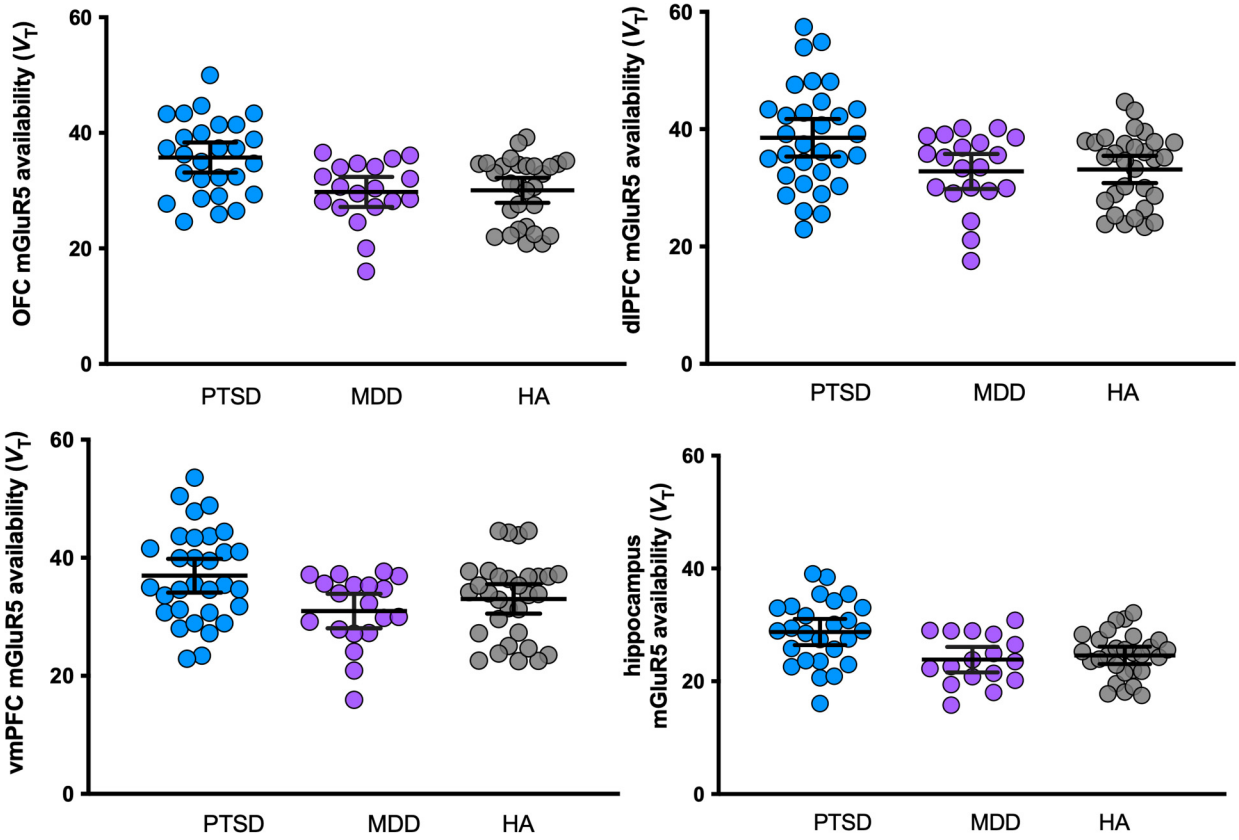

Figure 1. Panels illustrate differences between participants with posttraumatic stress disorder (PTSD, blue), major depressive disorder (MDD, purple), and healthy adults (HA, gray) in *in vivo* mGluR5 availability. Data are displayed for four brain regions (Study ROIs used in primary analyses): orbitofrontal cortex (OFC; top left), ventromedial prefrontal cortex (vmPFC; bottom left), dorsolateral prefrontal cortex (dlPFC; top right), hippocampus (bottom right).

and marked deficits in social and occupational functioning.[73,77] Despite this, currently available pharmaceutical agents largely fail to affect cognitive dysfunction, including attentional deficits.[78–80] Thus, pursuit of mGluR5 as a target capable of improving attention in these population warrants consideration. Significantly, however, our results suggest it may be necessary to pursue different mGluR5 directed treatment strategies in PTSD and MDD respectively. Here we observed differential associations between a clinically significant variable – attention- and mGluR5 availability in PTSD and MDD groups. This pattern of results is similar to our previous observations of a differential role of mGluR5 in mood symptoms in these disorders, and supports and extends a distinct role for mGluR5 in the pathology of PTSD relative to MDD, and thus a potential need to approach mGluR5 targeted treatment differently in each population.

With respect to PTSD, higher mGluR5 in frontal and hippocampal regions was associated with deficits in attention. We have previously observed that higher frontolimbic mGluR5 was associated with more severe PTSD symptom experience, including a relationship between mGluR5 availability and avoidance symptoms replicated in two studies.[32,33] In all cases, associations were moderate to large in magnitude. This pattern of results across studies corresponds to preclinical findings implicating a role for upregulation or activation of mGluR5 in fear conditioning and PTSD. Specifically, preclinical researchers have observed that activation of mGluR5 can enhance contextual fear memory,[13] central to the development of PTSD, while negative allosteric modulation or antagonism of mGluR5 can inhibit acquisition of fear memories, impeding fear conditioning[12,30] and even producing anxiolytic effects.[71,81–85] Further, recent preclinical research suggests that mGluR5 negative allosteric modulators (NAMs) can increase synaptic plasticity (increased dendritic spine density) in both the medial PFC and hippocampus.[86] Taken together, these findings reinforce the value of exploring downregulation of mGluR5 as a potential strategy for symptom reduction in PTSD.

In contrast, in our MDD group higher frontal and hippocampal mGluR5 availability was associated with better attention. In our previous study,[33] we also observed higher frontolimbic mGluR5 to be associated with less severe clinical presentation across a number of symptom domains. In

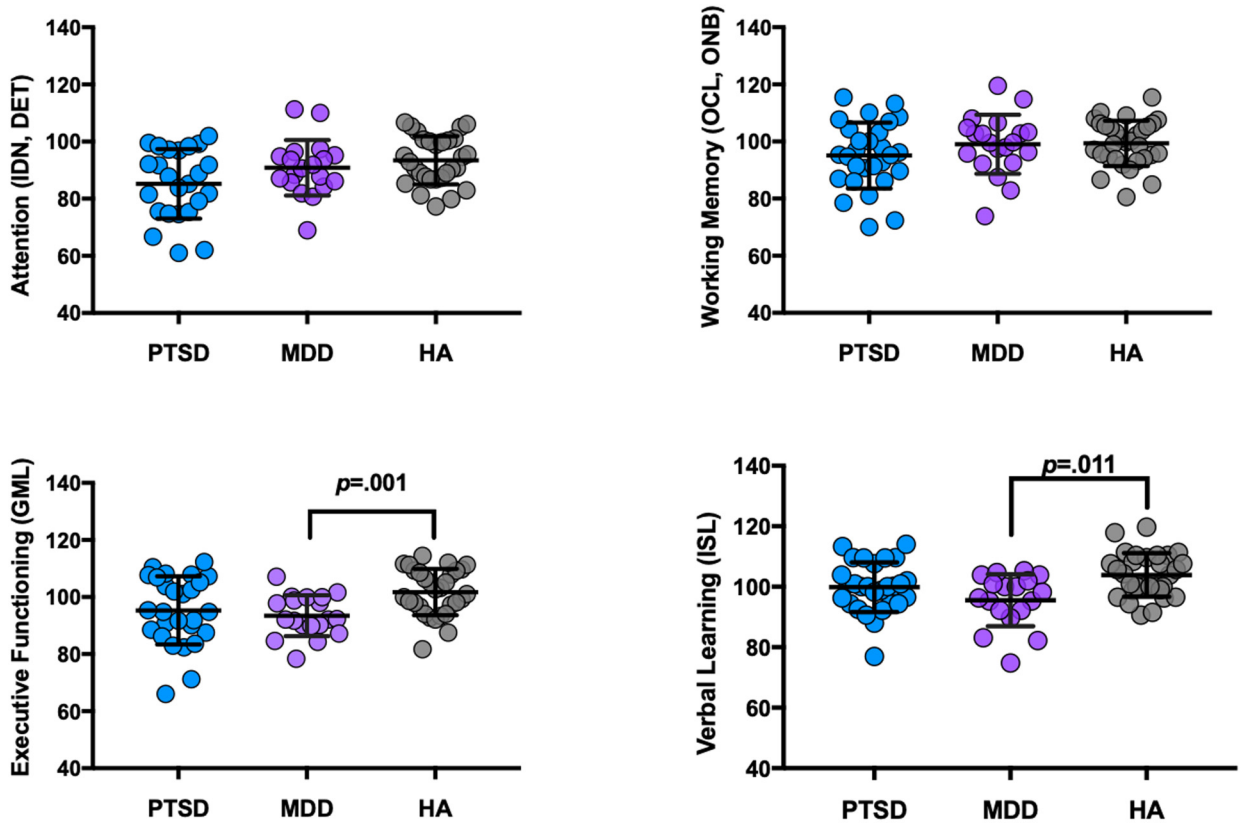

Figure 2. Panels illustrate group differences in cognitive domain score performance between participants with posttraumatic stress disorder (PTSD, blue), major depressive disorder (MDD, purple), and healthy adults (HA, gray). Individuals' data points are illustrated in addition to mean and 95% confidence intervals for each group. Panel A displays results from a composite score derived from two tasks measuring attention and psychomotor speed: Identification (IDN) and Detection (DET) tasks. Panel B displays results from a composite score derived from two tasks measuring working memory: Once Card Learning (OCL), and One Back (ONB) tasks. Panel C displays the results of the Groton Maze Learning (GML) task, a measure of executive functioning. Panel D displays results from the International Shopping List test (ISLT), measuring verbal learning.

both cases, the pattern of findings concerning mGluR5 availability in MDD was opposite in valence to that observed in PTSD, with all associations again of large to moderate magnitude. Key implications of this dissociation are, first, that the relationship between mGluR5 and essential clinical variables differs in MDD and PTSD, and second, that this may mean different treatment strategies are required for each disorder. Specifically, results suggest a strategy targeting upregulation or positive allosteric modulation of mGluR5 is more likely to improve symptoms, including attention, in individuals with MDD without PTSD (as in our sample). Of note, mGluR5 PAMs have demonstrated pro-cognitive effects in preclinical research including enhancing synaptic plasticity[17] and improving performance on tasks involving attention.[18] Significantly, human trials using both mGluR5 NAMs[87] and antagonists[88] have already been undertaken in MDD, and did not result in significant symptom improvement. mGluR5 PAMs are already under consideration as treatment options to address cognitive symptoms in a number of neuropsychiatric conditions (eg Parkinson's, Alzheimer's).

Notably, *in vivo* findings concerning the role mGluR5 in MDD have been mixed,[28,29,89,90] although this may reflect differences in key study characteristics such as demographics, outcome variables, or analytic strategies utilized. Alternatively, such discrepancy may be attributable to the heterogeneity of MDD, and the high rates of comorbidity between MDD and anxiety disorders, including PTSD. Notably, inclusion criteria for this study required exclusion of individuals with comorbid PTSD (currently or historically) from the MDD group. As such, our MDD sample, was necessarily less heterogenous than the typical clinical presentation. Approaching results from a transdiagnostic or RDoCian perspective, it is possible that our results are reflective of underlying differences in negative valence systems (ie, acute and sustained threat) in those classified as PTSD versus MDD in this sample. For individuals in our PTSD group, neurobiological effects of chronic stress may have affected abnormalities in negative valence systems resulting in an upregulation in mGluR5. By contrast in our MDD sample, effects on positive valence systems may be more

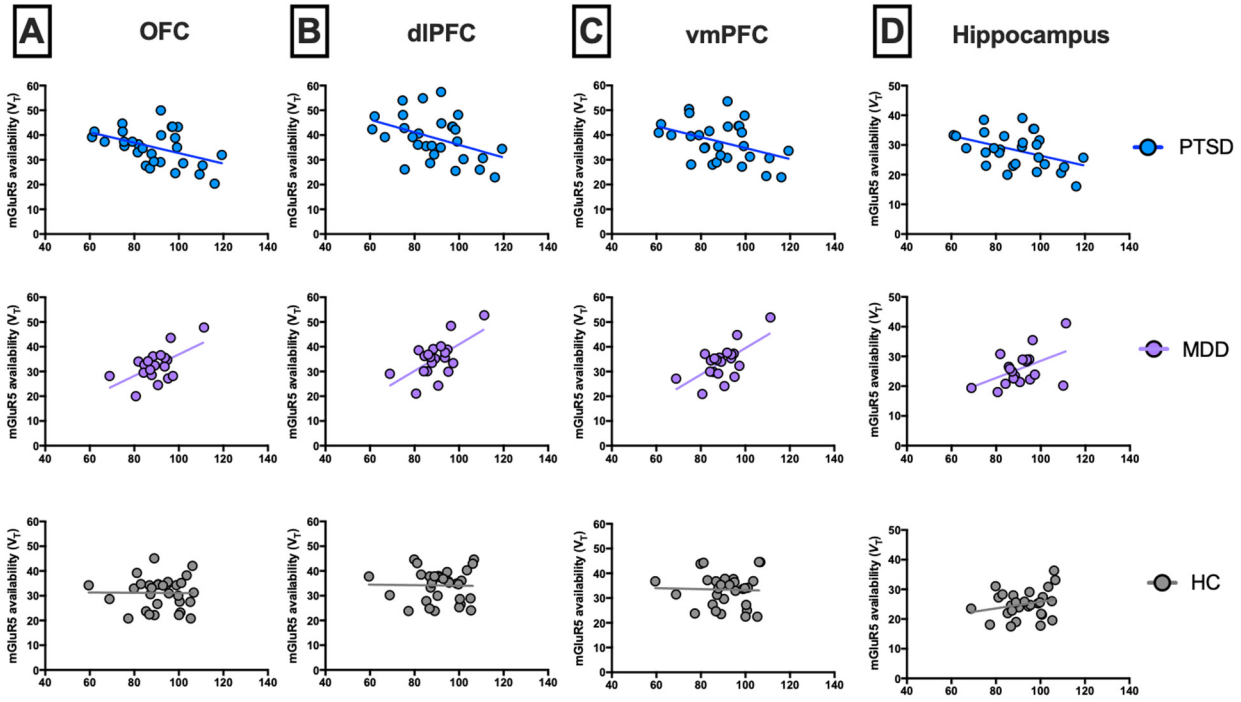

Figure 3. Panels illustrate the relationships between *in vivo* mGluR5 availability in four brain regions orbitofrontal cortex (OFC; A), ventromedial prefrontal cortex (vmPFC; B), dorsolateral prefrontal cortex (dlPFC; C), hippocampus (D) and attention/ psychomotor speed (ATTN) assessed using a composite of the Cogstate identification (IDN) and detection (DET) tasks. mGluR5 availability in the PTSD group (blue, top row) was significantly negatively related to ATTN in all ROIs: OFC ($r = -.441$, $P = .016$), vmPFC ($r = -.408$, $P = .028$), dlPFC($r = -.421$, $P = .023$), and hippocampus ($r = -.422$, $P = .025$). By contrast, mGluR5 availability in the MDD group (purple, middle row) was significantly positively related to ATTN in the OFC ($r = .590$, $P = .006$), vmPFC ($r = .653$, $P = .002$), and dlPFC ($r = .620$, $P = .004$) Findings in the hippocampus for MDD followed the same pattern, but did not survive correction for multiple comparisons ($r = .480$, $P = .036$). ATTN and mGluR5 availability were not significantly related in the HA group (gray, bottom row). Of note, in MANOVA analyses group*ATTN interaction results in the OFC did not survive multiple comparisons ($P = .046$).

profound, differentially affecting the glutamate system and therefore mGluR5. The role and significance of mGluR5 in the pathophysiology of trauma related and depressive disorders will require additional exploration to clarify discrepant findings.

While observed findings concerning group differences in the relationship between ATTN and mGluR5 availability are meaningful and consistent with study hypotheses, we expected to see a similar pattern of findings across the other domains. A number of potential explanations for these negative findings merit consideration. Notably, in both MDD and PTSD, literature concerning the nature and extent of observed cognitive deficits is variable, with some studies observing no differences between clinical groups and HA, and others observing differences of varying magnitudes in some domains, but not others.[39,42,91] Proposed explanations include variability in (a) the nature of the comparison sample (eg, trauma exposed controlled vs. non),[92,93] (b) the nature of the study population (eg, combat veterans vs. civilian, in- vs. outpatient),[94,95] and (c) what variables are controlled for in analyses (eg, comorbid psychiatric conditions).[96,97] For example, a 2004 study examined combat-related PTSD in veterans without comorbid MDD, alcohol, or drug abuse using a veteran comparison group with no reported psychopathology, and observed no differences in performance on attention, learning, or memory.[98] While some researchers speculated that the exclusion of comorbidity accounted for null findings, a subsequent study controlling for the same variables found the opposite: significant deficits in verbal memory and processing speed in the PTSD group.[96] The lack of observed findings in the present study concerning the relationship between mGluR5 availability and cognitive function (beyond ATTN) in PTSD and MDD may generalize. However, the possibility that our findings are related to/ affected by the nature of our sample should be considered. Eighteen participants in the PTSD group were also diagnosed with current comorbid MDD. In each case, the diagnosis of PTSD was primary, and the PTSD/MDD subgroup did not differ significantly from PTSD-only individuals on key study variables, including clinical variables (eg, MADRS, POMS scores), cognitive domain scores, and mGluR5 availability across study regions of interest. However, given our observations concerning the apparent differential presentation of mGluR5 in

PTSD and MDD, the comorbidity could conceivably have affected findings in a number of respects. Similarly, information concerning trauma history was not collected for all healthy adults, and its effect on results could therefore not be systematically assessed. Additional research is required to assess the generalizability of results and the effect of psychiatric comorbidity and demographics on the relationship between cognitive function and *in vivo* mGluR5 availability.

Several study limitations require consideration. First, the participants were matched for age, sex, and smoking status, but not weight, medication status, or trauma history. As detailed in Table 1, groups did not differ on these variables. Nonetheless, future research should consider variables including comorbidity in psychiatric participants and the potential impact of trauma exposure on mGluR5 availability. Second, it is not possible to draw conclusions about the temporal relationships between mGluR5, cognitive functioning, and diagnostic status. It is possible, for example, that upregulated mGluR5 and related attention deficit constituted a preexisting risk factor that contributed to the development of PTSD. Future research should investigate the relationship between mGluR5 availability and clinically relevant variables including attention at multiple time points (eg pre- and post-psychopathology). Third, diurnal variation can affect mGluR5 availability. Participants were scanned at a consistent time of day (13:36 +/− 2.3 h.) to avoid this confound. Fourth, ROIs were selected *a priori* based on strong links in the literature to the pathophysiology of MDD, PTSD, and cognitive functioning. However other regions, including the temporal cortex, are arguably equally relevant and deserving of attention in future work. We selected an ROI based approach in order to explore potentially region dependent and specific differences in findings. In light of the heterogeneity of observed results across ROIs in this study (both those selected *a priori* and for exploratory analyses), future studies should consider circuit based analyses with combined ROI's to conserve statistical power. Fifth, as detailed above separate MANOVA analyses were performed to evaluate the integration between diagnosis and each cognitive domain individually. Corrections for multiple comparisons were conducted within, not across MANOVA analyses. If a more conservative approach involving adjustment for multiple corrections was applied across all tests, the interaction of diagnosis*ATTN would not survive as significant. Sixth, no region in the human brain is entirely devoid of mGluR5.[99,100] As such, it is not possible to measure specific binding; our outcome measure includes specific and nonspecific binding. Finally, the fact that on average participants groups did not differ on measures of ATTN warrants mention. Results warrant replication in a clinical sample showing greater average impairment in ATTN.

This study is the first to investigate the relationship between cognition and mGluR5 availability *in vivo* in both PTSD and MDD. We found a differential relationship between ATTN and mGluR5 availability in PTSD and MDD; poorer performance on measures of attention was associated with higher mGluR5 availability in PTSD, and lower mGluR5 availability in MDD. Controlling for mood symptom severity did not alter results. A number of pharmacological agents designed to affect mGluR5 have been investigated as potential treatments for neuropsychiatric disorders[84,101,102] and are thus readily available for human clinical trials. The next step to this work might be to examine whether such agents are effective in reducing symptoms of PTSD and MDD, including attentional dysfunction. Our evidence suggests downregulating mGluR5 might decrease PTSD symptoms, including disrupted attention. While estimates vary, 20 to 50% of patients do not respond to currently available treatment for PTSD.[103] Thus, continued investigation of mGluR5 as novel treatment target should be prioritized. Evidence concerning differences in *in vivo* mGluR5 availability in MDD is less consistent. However, in light of the acknowledged consequences of cognitive deficit, including attention, in MDD (eg, higher relapse), agents capable of upregulating mGluR5, or mGluR5 PAMs similar to those observed to produce procognitive effects in preclinical research warrant consideration as potential treatment options.

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Author Contributions

MTD contributed to data collection, co-lead study design, led data analysis, drafting, and editing of the manuscript. SD and RC contributed to data collection, and manuscript drafting and editing. SH and SB contributed to study design and manuscript drafting and editing. RP and PM contributed to manuscript drafting and editing. IE led data collection, study design and data collection, and contributed to manuscript drafting and editing.

Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Dr Maruff is a full-time employee of Cogstate Ltd He reports no other potential conflicts of interest. All other authors report no conflicts of interest, and have nothing further to disclose.

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Ethical Approval

Not applicable, because this article does not contain any studies with human or animal subjects.

Informed Consent

Not applicable, because this article does not contain any studies with human or animal subjects.

Trial Registration

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