COMT Val158Met polymorphism moderates the association between PTSD symptom severity and hippocampal volume

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Background: Memory-based alterations are among the hallmark symptoms of posttraumatic stress disorder (PTSD) and may be associated with the integrity of the hippocampus. However, neuroimaging studies of hippocampal volume in individuals with PTSD have yielded inconsistent results, raising the possibility that various moderators, such as genetic factors, may influence this association. We examined whether the catechol-*O*-methyltransferase (COMT) Val158Met polymorphism, which has previously been shown to be associated with hippocampal volume in healthy individuals, moderates the association between PTSD and hippocampal volume. **Methods:** Recent war veterans underwent structural MRI on a 3 T scanner. We extracted volumes of the right and left hippocampus using FreeSurfer and adjusted them for individual differences in intracranial volume. We assessed PTSD severity using the Clinician-Administered PTSD Scale. Hierarchical linear regression was used to model the genotype (Val158Met polymorphism) × PTSD severity interaction and its association with hippocampal volume. **Results:** We included 146 white, non-Hispanic recent war veterans (90% male, 53% with diagnosed PTSD) in our analyses. A significant genotype × PTSD symptom severity interaction emerged such that individuals with greater current PTSD symptom severity who were homozygous for the Val allele showed significant reductions in left hippocampal volume. **Limitations:** The direction of proposed effects is unknown, thus precluding definitive assessment of whether differences in hippocampal volume reflect a consequence of PTSD, a pre-existing characteristic, or both. **Conclusion:** Our findings suggest that the COMT polymorphism moderates the association between PTSD and hippocampal volume. These results highlight the role that the dopaminergic system has in brain structure and suggest a possible mechanism for memory disturbance in individuals with PTSD.

Introduction

Memory disturbances manifested in the form of intrusive trauma memories, flashbacks and deficits in episodic memory are among the hallmark symptoms of posttraumatic stress disorder (PTSD).[1] These memory alterations have often been described as devoid of spatiotemporal context and other properties that are the defining features of episodic memory.[2] Accordingly, given its role in memory encoding and consolidation and its modulatory influence on hypothalamic–pituitary–adrenal (HPA) axis function, the hippocampus has long been a focus of research on the etiology and maintenance of PTSD.[3] Recent meta-analyses have found evidence for PTSD-associated reductions in hippocampal volume,[4–7]

though results across studies have not been uniform,[8–18] suggesting that various moderating variables, including genetic factors, may influence the association between PTSD and hippocampal volume.

The rs4680 functional variant (Val158Met polymorphism) of the catechol-*O*-methyltransferase (*COMT*) gene is the most widely studied *COMT* single nucleotide polymorphism (SNP), and because of its role in catecholamine regulation, it has garnered substantial interest from investigators studying psychiatric conditions ranging from PTSD[19–21] to obsessive–compulsive disorder[22] and schizophrenia.[23] The rs4680 variant generates an amino acid change from a valine (val) to a methionine (met) at codon 158 (Val158Met), leading to a 4-fold reduction in enzyme activity in Met carriers. Higher

enzyme activity in Val carriers is putatively associated with lower dopamine availability.[24] Importantly, COMT is highly expressed in the hippocampus.[25,26] Recent studies of healthy individuals suggest that Val carriers have smaller hippocampal volumes than Met carriers,[27,28] possibly owing to alterations in the neural correlates of memory function.

Although the role of *COMT* in the hippocampus has to date been largely underexplored, recent evidence suggests that the Val158Met polymorphism modulates dopamine metabolism in the hippocampus.[29] Furthermore, this modulation of dopamine has downstream effects on hippocampally dependent tasks, such as delayed reward alternation and spatial novelty preference, with a positive association between putative levels of dopamine availability and memory performance.[29] More broadly, dopamine availability is known to be involved in facilitating long-term potentiation (LTP) in the hippocampus, which is an important mechanism underlying memory encoding.[30] In humans, COMT enzyme inhibition by the drug tolcapone produces episodic memory enhancement,[31] as does administration of the dopamine agonist L-DOPA.[32] In addition, the Met allele, which is presumed to be associated with higher levels of dopamine, is associated with better episodic memory than the Val allele.[33] Given the central role that memory alterations play in PTSD[34,35] and the evidence that the Val158Met polymorphism is associated with PTSD symptoms,[19,20,36] we examined whether the Val158Met polymorphism moderated the association between PTSD symptom severity and hippocampal volume.

Methods

Participants

We recruited veterans of Operations Enduring Freedom, Iraqi Freedom and New Dawn for participation in this study as part of the Translational Research Center for Traumatic Brain Injury and Stress Disorders (TRACTS) at the Jamaica Plain Division of the VA Boston Healthcare System. Individuals were excluded if their medical history included vascular disease, cardiac conditions, seizures, cognitive disorders not due to traumatic brain injury (TBI), moderate or severe TBI, homicidal or suicidal ideation requiring intervention, or a current psychotic disorder (e.g., schizophrenia, bipolar disorder) based on a DSM-IV diagnosis.[37] For MRI acquisition, individuals were excluded if they had any metal implant, shrapnel, aneurysm clip, or pacemaker, or if they were pregnant. We obtained approval for the study from all institutional review boards and regulatory committees, and informed consent was obtained from all participants before the procedure.

MRI acquisition and processing

Participants were scanned on a Siemens 3 T TIM Trio located at the Jamaica Plain Division of VA Boston Healthcare System. Two 3-dimensional (3D) magnetization-prepared rapid gradient-echo (MP-RAGE) scans were acquired in the sagittal plane and averaged to create a single high contrast-to-noise image (voxel size 1 mm^3, inversion time [TI] 1000 ms, repetition time [TR] 2530 ms, echo time [TE] 3.32 ms). Automated cortical reconstruction and volumetric segmentation were performed with the FreeSurfer image analysis suite (version 5.0), which is available for download online (http://surfer.nmr.mgh.harvard.edu/). The technical details of these procedures are described in prior publications.[38–49] This processing includes motion correction and averaging[50] of multiple volumetric T_1-weighted images, removal of nonbrain tissue using a hybrid watershed/surface deformation procedure,[51] automated Talairach transformation, segmentation of the subcortical white matter and deep grey matter volumetric structures (including the hippocampus).[42,46] We used the ENIGMA pipeline to generate and inspect hippocampal volumes. This pipeline mandates careful inspection of each participant's data to ensure segmentation accuracy (for examples using this pipeline, see van Erp and colleagues[52] and Hibar and colleagues[53]). Automated FreeSurfer hippocampal volumes have been shown to have high overlap and correlation with expert hand-drawn volumes of the hippocampus.[42,54,55] For illustration purposes, Figure 1 shows an example of the automated hippocampal volumes, as defined by FreeSurfer.

DNA genotyping

A trained phlebotomist collected peripheral blood samples from each participant. We isolated DNA from peripheral blood samples on a Qiagen AutoPure instrument with Qiagen reagents and samples normalized using PicoGreen assays (Invitrogen). Samples were run on Illumina HumanOmni2.5–8 BeadChips, which analyze approximately 2.5 million SNPs per sample, including rs4680 (Val158Met). Arrays were scanned using an Illumina iScan System according to the manufacturer's protocol. All participants had genome-wide call rates > 98%, indicating generally good-quality DNA and results. The call rate for rs4680 was 100%. Details regarding the elimination of participants and genotype-based confirmation of ancestry and sex are presented in Appendix 1, available at jpn.ca.

Clinical and cognitive assessment

We assessed PTSD using the Clinician-Administered PTSD Scale (CAPS),[56] which is the gold-standard structured diagnostic interview for the assessment of the disorder. The CAPS assessment was performed by doctoral-level psychologists with advanced training in psychological assessment. On this interview, each DSM-IV PTSD criterion is assessed with 2 CAPS subitems: 1 that reflects the frequency of the symptom on a 0–4 scale and 1 that reflects the intensity of the symptom on a 0–4 scale. The 2 subitems can be combined to reflect symptom severity. We derived a score for each individual using the total score for current PTSD symptoms. The presence of current and past mood and substance use disorders were assessed using the Structured Clinical Interview Scale for DSM-IV disorders (SCID).

Premorbid IQ was estimated using the Wechsler Test of Adult Reading (WTAR).[57] This measure contains

50 irregularly spelled words of increasing difficulty to pronounce. The ability to perform this test remains unchanged following disease and injury.

Statistical analysis

Statistical analyses were performed using SPSS software version 22 (IBM Corp.). Hippocampal volumes were adjusted based on participants' FreeSurfer-derived intracranial volume (ICV) to control for variation in head size using the following formula: adjusted volume = raw volume – (βICV – mean ICV), where β is the regression coefficient when the raw volume is regressed against ICV and mean ICV is the group mean.

Demographic differences among genotype groups were examined using 1-way analysis of variance (ANOVA) or χ^2 tests where appropriate. We examined the association between PTSD severity, genotype and hippocampal volume using hierarchical linear regression. Covariates, including age (mean-centred to improve interpretability), major depression diagnosis, lifetime substance use disorder, handedness and probable mild TBI (assessed by the VA TBI screen), were entered in step 1. To further examine the potential impact of mild TBI, we repeated the regression model removing 69 individuals with mild TBI. The Val158Met genotype (coded ad-

ditively; there was no evidence of a nonlinear trend using a polynomial regression approach: Val/Val = 0, Val/Met = 1, and Met/Met = 2) and current PTSD symptom severity (CAPS score) were entered in step 2. The genotype × PTSD symptom severity interaction was entered in step 3. These models were run separately for the adjusted volumes of the left and right hippocampus. The α for significance was adjusted using Bonferroni correction for the 2 hemispheres ($p = 0.05 \div 2 = 0.025$).

To evaluate the role of additional potential confounders, including education (highest grade completed) and population stratification (see Appendix 1 for a detailed description), we ran post hoc analyses with the potential confounder added to step 1 of the 3-stage models as previously described. To examine whether sex influenced the results, we repeated the analyses after removing the women from the data set.

Results

Sample characteristics

We included 146 (90% male) white, non-Hispanic veterans in our analyses. Group demographic characteristics by Val-158Met genotype are shown in Table 1. The groups did not
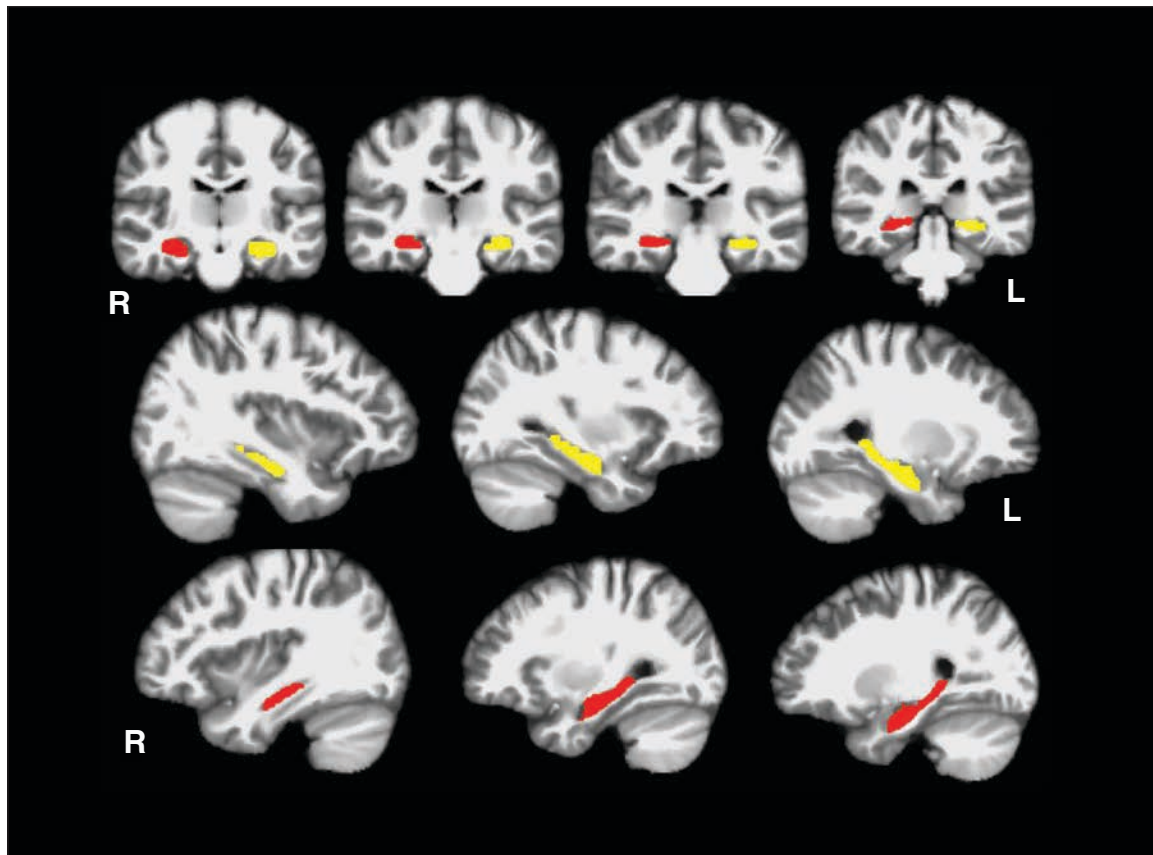
Fig. 1: Automated segmentation of the hippocampus. Coronal and sagittal views showing the right (red) and left (yellow) hippocampal regions of interest as defined by FreeSurfer.

differ significantly in age, sex, WTAR-estimated IQ, number of lifetime mood disorders or substance use diagnoses, CAPS score, duration of symptoms, or probable mild TBI. However, the groups differed in education, with the Met homozygote group having more education than the Val/Met group ($p = 0.032$).

Moderating effect of COMT Val158Met

Hierarchical linear regression showed no significant overall model effect in steps 1 and 2 for the left hippocampus (Table 2). After entering the genotype × PTSD symptom severity interaction in the third step, the overall model was significant ($F_{8,137} = 2.69$, $p = 0.009$, $R^2 = 0.14$), with a significant F change ($F_{1,137} = 5.43$, $p = 0.022$, $\Delta R^2 = 0.03$). Further examination of the interaction term revealed that individuals homozygous for the Val allele showed reduced left hippocampal volume with increasing PTSD symptom severity ($\beta = -0.49$, $p = 0.007$; Fig. 2A). There was no association between left

hippocampal volume and PTSD symptom severity for either the Val/Met group ($\beta = -0.03$, $p = 0.80$; Fig. 2B) or the Met/Met homozygous group ($\beta = -0.01$, $p = 0.90$; Fig. 2C). Using a categorical PTSD variable did not change the pattern of results; the moderating effect of COMT Val158Met on the association between PTSD and left hippocampal volume remained significant.

For the right hippocampus, there were no significant main effects or an interaction effect. For Val/Val homozygotes, there was no association between PTSD symptom severity and right hippocampal volume ($\beta = -0.20$, $p = 0.27$). This was also true for the Val/Met group ($\beta = -0.09$, $p = 0.52$) and Met/Met homozygotes ($\beta = -0.26$, $p = 0.16$).

Post hoc models for potential confounding variables

None of the post hoc models that included additional covariates modified the estimates of the main effects in step 2 or the genotype × PTSD symptom severity interaction in step 3.

Table 1: Sample characteristics

	Group; mean ± SD or no. (%)					
Characterisitc	Total ($n = 146$)	Val/Val ($n = 45$)	Val/Met ($n = 64$)	Met/Met ($n = 37$)	Comparison statistic	p value
Age, yr	31 ± 8	32 ± 8.1	31 ± 8.4	32 ± 8.9	$F_{2,143} = 0.26$	0.77
Male sex	135 (92.5)	43 (95.6)	58 (90.6)	34 (91.9)	$\chi^2_2 = 0.95$	0.62
Education, yr	14 ± 2	14 ± 2.3	14 ± 1.8	15 ± 1.8	$F_{2,143} = 3.51$	0.032§
WTAR estimated IQ*	103 ± 11.5	104 ± 10.9	102 ± 11.4	104 ± 12.4	$F_{2,141} = 0.33$,	0.72
CAPS total score	44 ± 28.6	47 ± 27.7	45 ± 29.2	38 ± 28.6	$F_{2,143} = 1.05$	0.35
Symptom duration, mo†	58 ± 60.5	63 ± 62.8	56 ± 68.6	54 ± 38.8	$F_{2,82} = 0.15$	0.87
Lifetime mood disorder diagnosis	48 (32.9)	16 (35.6)	21 (32.8)	11 (29.7)	$\chi^2_2 = 0.31$	0.86
Lifetime substance use diagnosis	93 (63.7)	32 (71.1)	41 (70.7)	20 (58.8)	$\chi^2_2 = 2.56$	0.28
Probable TBI	69 (47)	23 (51)	28 (44)	18 (49)	$\chi^2_2 = 0.61$	0.74
L hippocampal vol, mm³‡	4355 ± 365	4378 ± 386	4410 ± 330	4232 ± 380	$F_{2,143} = 3.0$	0.05
R hippocampal vol, mm³‡	4456 ± 389	4413 ± 416	4524 ± 354	4391 ± 404	$F_{2,143} = 1.78$	0.17

CAPS = Clinician-Administered PTSD Scale; L = left; PTSD = posttraumatic stress disorder; R = right; SD = standard deviation; TBI = traumatic brain injury; WTAR = Wechsler Test of Adult Reading.
*Information missing for 2 participants.
†Symptom duration available only for individuals with PTSD.
‡Adjusted for intracranial volume.
§The Met/Met group had higher education than the Val/Met group.

Table 2: Summary of hierarchical regression analysis for variables predicting left hippocampal volume

	Model 1				Model 2				Model 3			
Variable	B	SE(B)	β	p value	B	SE(B)	β	p value	B	SE(B)	β	p value
Age	−5.14	3.62	−0.12	0.16	−5.74	3.59	−0.13	0.11	−6.17	3.54	−0.14	0.09
Handedness	211.6	82	0.22	0.011	241.8	82.63	0.25	0.004	238.9	81.34	0.24	0.004
Depression	−74.13	46.96	−0.13	0.12	−57.71	47.54	−0.10	0.23	−74.98	47.38	−0.13	0.12
Substance use	56.22	64.51	0.08	0.39	59.4	65.33	0.08	0.37	83.17	65.12	0.11	0.20
Possible TBI	10.43	61.5	0.01	0.87	33.89	63.16	0.05	0.59	45.50	62.37	0.06	0.47
PTSD symptoms	—	—	—	—	−1.68	1.17	−0.13	0.15	−4.93	1.81	−0.39	0.007
Val/Met	—	—	—	—	−74.34	39.87	−0.15	0.06	−213.6	71.51	−0.44	0.003
PTSD × Val/Met	—	—	—	—	—	—	—	—	3.31	1.42	0.41	0.021
R^2	—	0.07	—	—	—	0.10	—	—	—	0.14	—	—
F for ΔR^2	—	2.08	—	—	—	2.49	—	—	—	5.43	—	—

PTSD = posttraumatic stress disorder; SE = standard error; TBI = traumatic brain injury.

After removing women from the analysis, the F change for the genotype × PTSD symptom severity interaction in step 3 remained significant ($\Delta F_{1,126} = 5.49$, $p = 0.025$, $\Delta R^2 = 0.04$). The results also remained significant after removing all individuals with probable mild TBI ($\Delta F_{1,69} = 6.41$, $p = 0.014$, $\Delta R^2 = 0.07$), despite the reduced sample size ($n = 77$). Taken together, these results suggest that the primary genotype × PTSD symptom severity interaction finding was not explained by several other variables, including mild TBI or the small number of women included in the study.

Discussion

The primary finding from our study was that Val homozygotes with severe PTSD symptomatology exhibited reduced left hippocampal volume in comparison to carriers of the Met allele, suggesting that putatively lower dopamine availability in Val carriers may interact with traumatic stress to negatively affect hippocampal structure. This effect was observed after adjusting for a number of potentially confounding variables, including mood and substance use disorders, suggesting a unique imaging genetic association with hippocampal atrophy in individuals with PTSD. These re-

sults are notable given that prior studies of the association between PTSD and hippocampal volume have yielded inconsistent findings and suggest that examination of genetic variation could improve specificity of the association between traumatic stress and the structure of the hippocampus.

Leading views of hippocampal alterations in individuals with PTSD have often emphasized the effect of glucocorticoids[58] and glutamate[59] in mediating the association between psychological stress and hippocampal structure. However, recent studies have shown that both dopamine and glutamate are required for hippocampally mediated processes, such as long-term potentiation (LTP),[30,60,61] which is associated with neurogenesis in the hippocampus, both in terms of proliferation of progenitor cells and the survival of new cells.[62] This, combined with the evidence that stress inhibits dopamine-modulated LTP[63,64] and that dopamine dysregulation is associated with neurodegeneration[65] points to the possible involvement of dopamine-mediated processes in the association between PTSD and hippocampal structure.

The findings raise plausible implications for understanding memory disturbance in individuals with PTSD. One implication of smaller *COMT*-associated hippocampal volume may be dysfunction in hippocampal–prefrontal cortex connections
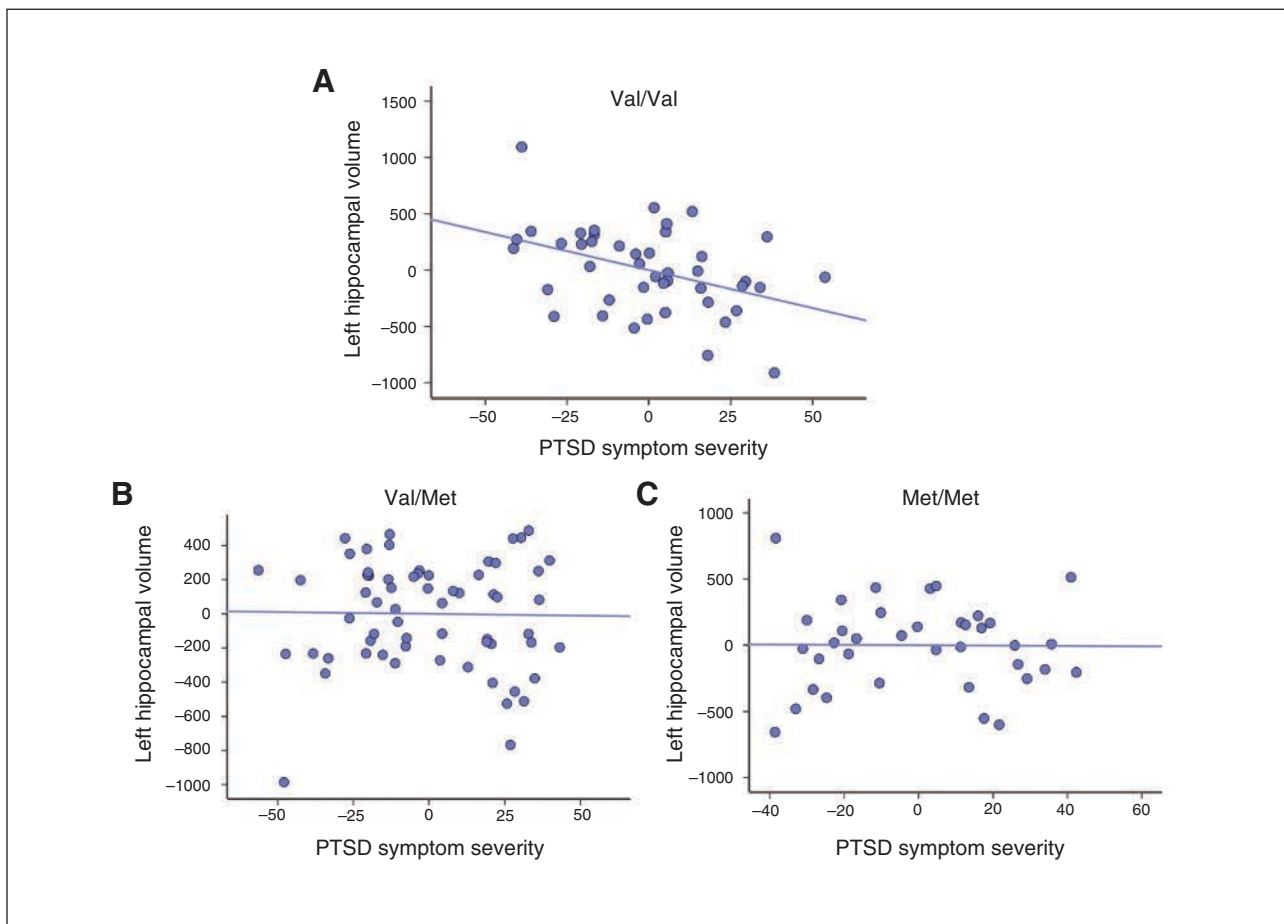
Fig. 2: Partial regression plots accounting for covariates. (**A**) Val/Val homozygotes showed reduced hippocampal volume with increasing traumatic stress. (**B**, **C**) This pattern was not observed in Met carriers. PTSD = posttraumatic stress disorder.

that support episodic memory. Consistent with this, Bertolino and colleagues[66] found that reduced hippocampal–prefrontal cortex coupling was associated with poorer memory retrieval in Val carriers. Further, Schott and colleagues[67] found that Val carriers had less functional connectivity between the hippocampus and prefrontal cortex during memory encoding. Recent evidence suggests that *COMT* Val carriers with PTSD show reduced volume in the anterior cingulate cortex.[68] Thus, Val allele–associated reductions in volume in this region and the hippocampus may lead to dysfunctional connectivity among regions that support episodic memory. Though speculative, it is conceivable that under conditions of traumatic stress, lower dopamine availability creates vulnerability for memory impairments in individuals with PTSD.

The present findings may also have bearing on the function of the hippocampal–ventral tegmental area (VTA) loop, which has been identified as a pathway that subserves memory under conditions of novelty.[69] The VTA, which is the seat of dopaminergic cell bodies of the mesocorticolimbic dopamine system, has connections to and from the hippocampus and has been associated with facilitation of fear extinction.[70] Disturbances in this pathway have been linked to enhanced fear generalization in clinical samples.[71] One implication from these studies is that dopamine-associated hippocampal function is critical for the encoding of distinct memory representations. It is possible that higher dopamine degradation — putatively associated with Val homozygosity — is a catalyst in dopaminergic pathway dysfunction that leads to difficulty in distinguishing related yet novel cues from the previously encoded trauma episode. A potential consequence of such pattern separation failures may be reactivation of trauma memories in individuals with PTSD. Additional research is necessary to examine how Val158Met may regulate dopamine in the hippocampal–VTA loop and whether alterations in this circuit have implications for brain structure in individuals with PTSD.

In the present study, the Val158Met × PTSD effect was observed unilaterally in the left hippocampus. Although 2 prior meta-analytic studies of hippocampal volume in individuals with PTSD reported greater reduction in left hippocampal volume,[5,6,2] other meta-analyses did not find such effects.[4,7] The present results contribute to this body of literature by suggesting that the left-lateralized effects may be influenced by Val homozygosity. Left-lateralized medial temporal lobe dysfunction has been consistently associated with verbal memory deficits.[72] Moreover, poor verbal memory performance has consistently been associated with PTSD.[73] Thus, it is possible that the left-lateralized reductions in volume are related to the verbal memory dysfunction observed in individuals with PTSD.

Limitations

Our study findings and conclusions should be considered in the context of its limitations. First, the cross-sectional nature of these data precludes strong conclusions regarding the direction of the proposed effects. Thus, we are unable to determine whether observed differences in hippocampal volume reflect a consequence of PTSD, a pre-existing characteristic, or both, or the impact of PTSD chronicity. Furthermore, our hypotheses about the downstream functional consequences of hippocampal volume differences and the influence of dopamine on these processes should be considered preliminary, and would benefit from future studies that directly examine hippocampal function and neurocognition. Finally, we note that the findings from this study should be considered provisional until they can be replicated in additional samples. These limitations notwithstanding, the present study should provide impetus for future research investigating the association between PTSD, dopamine and hippocampally based memory systems.

Conclusion

The results of our study suggest that individuals with severe PTSD symptoms who are carriers of the Val/Val genotype are more likely to show reductions in hippocampal volume than Met carriers. These findings advance our understanding of structural hippocampal alterations in individuals with PTSD by identifying a novel molecular mechanism by which exposure to environmental stress is associated with atrophy in a brain region that is thought to be critical in the etiology and maintenance of PTSD. The integration of neuroimaging and genetic approaches as reported in this study can be used to direct future refinement of theories of memory-based alterations in individuals with PTSD.

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Correction: Ventral striatal hypoactivation is associated with apathy but not diminished expression in patients with schizophrenia

In the article "Ventral striatal hypoactivation is associated with apathy but not diminished expression in patients with schizophrenia" by Kirschner and colleagues[1] published in the May 2016 issue of the journal, the paragraph on "experimental design and task" in the Methods section should have mentioned that the task variant used was originally developed by Simon and colleagues.[2] The text and the reference list have been updated in the online version of the article, which is available at jpn.ca We apologize for the error.

Reference

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