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ORIGINAL CONTRIBUTION

Interactive effects of BDNF Val66Met genotype and trauma on limbic brain anatomy in childhood

Hilary A. Marusak[1,2] · Nisha Kuruvadi[3] · Angela M. Vila[1] · David W. Shattuck[4] · Shantanu H. Joshi[4] · Anand A. Joshi[5,6] · Pavan K. Jella[7] · Moriah E. Thomason[1,8,9]

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Abstract Childhood trauma is a major precipitating factor in psychiatric disease. Emerging data suggest that stress susceptibility is genetically determined, and that risk is mediated by changes in limbic brain circuitry. There is a need to identify markers of disease vulnerability, and it is critical that these markers be investigated in childhood and adolescence, a time when neural networks are particularly malleable and when psychiatric disorders frequently emerge. In this preliminary study, we evaluated whether a common variant in the brain-derived neurotrophic factor (BDNF) gene (*Val66Met;* rs6265) interacts with childhood trauma to predict limbic gray matter volume in a sample of 55 youth high in sociodemographic risk. We found trauma-by-BDNF interactions in the right subcallosal area and right hippocampus, wherein BDNF-related gray matter changes were evident in youth without histories of trauma. In youth without trauma exposure, lower hippocampal volume was related to higher symptoms of anxiety. These data provide preliminary evidence for a contribution of a common BDNF gene variant to the neural correlates of childhood trauma among high-risk urban youth. Altered limbic structure in early life may lay the foundation for longer term patterns of neural dysfunction, and hold implications for understanding the psychiatric and psychobiological consequences of traumatic stress on the developing brain.

Keywords Brain-derived neurotrophic factor · Early adversity · Mood disorders · Gray matter volume · Medial prefrontal cortex · Adolescence

✉ Moriah E. Thomason
moriah@wayne.edu

1 Merrill Palmer Skillman Institute for Child and Family Development, Wayne State University, 71 E. Ferry Street, Detroit, MI 48202, USA

2 Department of Psychiatry and Behavioral Neurosciences, Wayne State University School of Medicine, Detroit, MI, USA

3 Liberty University College of Osteopathic Medicine, Lynchburg, VA, USA

4 Department of Neurology, David Geffen School of Medicine, University of California, Los Angeles, Los Angeles, CA, USA

5 Brain and Creativity Institute, University of Southern California, Los Angeles, CA, USA

6 Signal and Image Processing Institute, University of Southern California, Los Angeles, CA, USA

7 Department of Radiology, Wayne State University, Detroit, MI, USA

8 Department of Pediatrics, Wayne State University School of Medicine, Detroit, MI, USA

9 Perinatology Research Branch, NICHD/NIH/DHSS, Detroit, MI, USA

Introduction

The human brain retains plasticity throughout life. Consequently, experiences have the potential to shape brain organization. Experiences that occur in early life appear to be especially potent in altering the trajectory of neurodevelopment. In particular, early trauma exposure is linked to changes in brain structure and function that persist decades later into adulthood [15]. Moreover, early trauma predicts nearly 45 % of childhood-onset and 30 % of adult-onset psychiatric disorders [33]. Identifying how trauma and stress are biologically embedded in brain organization during formative years has critical implications for lifelong emotional health and well-being [24].

Neurological consequences of trauma and cumulative stress have been studied most extensively in adults. Neuroimaging studies show gray matter volume (GMV) alterations in a number of regions in individuals with histories of early trauma (for a meta-analysis, see [43]). Notably, volumetric reductions are observed in the hippocampus [15, 41] and medial prefrontal cortex [3, 65], limbic brain regions involved in emotion regulation. It is also these regions that show reduced GMV in mood disorders (see [20] for a review). However, studies in adults are limited given that many years, even decades, have often passed since the trauma. As a result, neuroanatomic differences observed in adults may reflect secondary compensatory effects (e.g., brain reorganization in response to trauma) or new environmental exposures (e.g., substance use, stress in adulthood) rather than being the primary result of early traumatic stress.

Childhood trauma likely becomes biologically embedded in the brain during formative, developmental years. We know that many affective disorders originate in childhood and adolescence [52]. Moreover, limbic brain circuitry continues to develop across late childhood and early adolescence [30, 64] and thus may be especially vulnerable to injurious environmental influences. It is essential that neural correlates of traumatic stress be evaluated in children and adolescents (youth) to identify biological markers associated with early trauma that may underpin vulnerability to emotional psychopathology.

Although childhood trauma strongly predicts the emergence of mood disorders, not all individuals who experience trauma develop clinical conditions. The leading explanation for this disparity is that genetic variability modulates susceptibility to stress. Indeed, prior research provides compelling evidence for gene-by-stress interactions in disease susceptibility [9]. It has been suggested that gene-by-stress interactions explain approximately 60–70 % of variance in vulnerability to affective disorders [35]. Emerging data show that childhood trauma exposure interacts with a common functional variant of the brain-derived neurotrophic factor (BDNF) gene, consisting of a single nucleotide polymorphism (SNP; rs6265) in the 5′ prodomain region. This SNP, leading to a valine-to-methionine substitution at codon 66 (*Val66Met*), is associated with reduced activity-dependent secretion and intracellular trafficking of pro-BDNF, and thus reduced availability of biologically active BDNF. The role of BDNF in the brain is to promote neuronal survival and to aid in neuronal migration, synaptic sprouting, and remodeling [6, 53].

Several lines of research suggest that BDNF genotype interacts with traumatic stress to alter brain anatomy and thereby shift risk for development of emotional psychopathology. The BDNF *Met* allele has been linked to both anxiety and depressive symptomology, particularly in the presence of traumatic events [1, 40, 67]. Additionally, lower levels of BDNF have been reported in depressed individuals, and this effect is diminished with antidepressant medication (see [34] for a review). Animal studies indicate that early life stress reduces BDNF expression, particularly in BDNF-rich limbic brain regions [22, 27], and these effects persist into adulthood [11]. Human research has shown that healthy [28, 29, 36] and depressed adults [7] that carry the BDNF *Met* allele and who have histories of early adversity display reductions in subcallosal medial prefrontal and hippocampal GMV. In contrast, increased GMV in the amygdala has been reported in *Val/Val* homozygotes with histories of early life stress, and for these adults, amygdala GMV additionally predicted higher self-reported anxiety [28]. These observations are consistent with a model in which atypical BDNF function constitutes a risk factor for the development of affective disorders and altered brain limbic structure.

Brain-derived neurotrophic factor operates distinctively at different developmental ages [8, 66]. Consequently, a more complex picture emerges when the function of BDNF is considered across development. A study of 4- to 12-year-olds demonstrated that children institutionalized between 0–5 years with the *Val/Val* genotype had reduced hippocampal GMV, while those with the *Val/Met* genotype had increased GMV of the amygdala, and that BDNF genotype had no impact on amygdala GMV in the absence of stress [8]. Contradiction between adult and pediatric neuroimaging results suggests that interactions in BDNF genotype, brain anatomy, and traumatic stress may vary for different age groups. Given that type [5] and timing [3] of traumatic exposure influence brain and behavioral outcomes, a second possible explanation for these contrary results is that institutionalization constitutes a specific form of trauma (e.g., early relational deprivation), and thus may predict different results than would other forms of early environmental adversity. The goal of this preliminary study is to begin to address these unknowns by evaluating interactions between BDNF genotype and trauma on limbic GMV in a high sociodemographic risk sample of youth, ages 7–15.

Trauma exposure is extreme among African Americans living in impoverished urban areas [2]. Moreover, African American urban residents are nearly two times more likely to develop psychopathology following trauma [32]. Based on these demographic risk factors, i.e., urban, low income, minority, the present study targeted youth residing in high-risk neighborhoods. We hypothesize that BDNF and trauma will interact to predict GMV of limbic brain regions, including the amygdala, hippocampus, and subcallosal area. In particular, we predict that children with the BDNF *Met* allele who are exposed to trauma will show larger amygdala volumes, and smaller hippocampal

and subcallosal volumes. This is consistent with animal research showing that stress increases BDNF expression and produces dendritic growth in the amygdala, whereas it *reduces* BDNF expression and causes dendritic *shortening* in the hippocampus and medial prefrontal cortex (see [47] for a review).

Materials and methods

Participants

55 children and adolescents, ages 7–15, were recruited through classified advertisements placed on Craigslist (Detroit), printed flyers, Wayne State University (WSU) community, and Metro Detroit mental health clinics. Recruitment materials targeted high-risk (urban, minority, low income) neighborhoods and clinics; however, these demographic factors were not considered necessary for study inclusion. Consistent with this, 42 % of study participants were African American and 54 % reported annual incomes <$40,000 (see Table 1). Exclusion criteria included history of neurological injury, significant learning disorder, English as a second language, and presence of MRI contraindications. Prior to the scan session, participants and parents were shown a brief video to prepare them for the MRI scan (http://www.brainnexus.com/links). Symptoms of anxiety and depression were assessed using the Screen for Child Anxiety-Related Emotional Disorders (SCR-C; [4]) and the Children's Depression Inventory (CDI, short version; [42]). Full-Scale IQ was determined using the Kaufman Brief Intelligence Test, Second Edition (KBIT2; [39]) and pubertal development was assessed using the self-reported Tanner stages questionnaire [45]. Written informed consent and child/adolescent assent was obtained for all participants and their parents as approved by the WSU Institutional Review Board.

BDNF polymorphism genotyping

Genetic analyses were carried out at the WSU Applied Genomics Technology Center. DNA was isolated from saliva collected in Oragene DNA collection tubes using EZ1 Advanced (Qiagen) with standard conditions. The BDNF *Val66Met* polymorphism (rs6265) was investigated using a 5′-nuclease assay (Life Technologies TaqMan assay C_11592758_10). Assays were run in a 5 µl reaction under standard TaqMan conditions on a QuantStudio 12K Flex (Life Technologies). Data were analyzed using Taqman Genotyper software (v.1.3; Life Technologies).

Trauma and BDNF groups

Participants were characterized based on trauma exposure and genotype. Participants who experienced at least one trauma indicated on the Children's Trauma Assessment Center Screen Checklist were categorized as 'trauma'. Trauma checklist items are provided in Table 1. In this preliminary study, we were underpowered to dissociate different trauma types. Nonetheless, we excluded three checklist items narrowing trauma to deprivation (e.g., neglect) and victimization or threats to safety (e.g., abuse, violence exposure), distinct [49], but central trauma types. We excluded: exposure to drug activity, parental/caregiver drug use/substance abuse, and frequent and multiple moves or homelessness. Checklist items were reviewed with both parent/caregiver and child in interviews conducted by trained clinical psychology graduate students. 21 of the 55 participants endorsed trauma exposure. BDNF groups consisted of *Val/Val* homozygotes ($n = 46$) and *Val/Met* heterozygotes ('*Met* carriers'; $n = 9$). Consistent with the rarity of the *Met* allele, no participants possessed a *Met/Met* genotype. Importantly, genotypic distribution did not differ between trauma and comparison groups, $\chi^2 = 0.107$, $p = 0.743$ ($n = 6$ comparison *Val/Val*), and genetic distribution across the sample was in Hardy–Weinberg equilibrium, $\chi^2 = 2.475$, $p = 0.116$. African American and Caucasian participants (the largest racial groups) were also in Hardy–Weinberg equilibrium for their expected genotypic frequencies, $\chi^2 = 0.045$, $p = 0.835$ and $\chi^2 = 2.659$, $p = 0.103$, respectively. African American and Caucasian participants did not differ on whole-brain volume or GMV in regions assessed ($ps > 0.3$).

Trauma and comparison groups were matched on sex and race distribution, age, pubertal stage, anxiety and depressive symptoms, and highest level of parent educational attainment (median for both trauma and comparison groups: 4-year degree; $p > 0.1$). Average annual income was lower for trauma participants; however, this effect did not reach significance, $p = 0.06$ (see Table 1). Average IQ was lower for trauma relative to comparison youth (see Table 1), an effect anticipated based on prior work (e.g., [16]). To account for this group difference, we either controlled for IQ in statistical analyses or evaluated effects of BDNF separately within each group, as detailed below. In addition, groups differed on whole-brain volume (mean ± SD; trauma = 1422096.19 ± 1410 21.1 mm^3; comparison = 1343082.65 ± 110538.21 mm^3), $t(53) = 2.316$, $p = 0.02$. All GMV values were adjusted for whole-brain volume (described below). BDNF groups did not differ on sex or race distribution, age, pubertal stage, IQ, annual household income, anxiety or depressive symptoms, highest level of parent educational attainment, or whole-brain volume ($ps > 0.1$).

Table 1 Demographic and clinical characteristics by trauma group

Demographic information	Trauma (*n* = 21)	Comparison (*n* = 34)	*p*
Age, m (SD)	12.2 (2.3)	11.4 (2.6)	ns
Sex (Female), *n* (%)	10 (41.7 %)	24 (70.6 %)	ns
IQ, m (SD)	97 (13.3)	106.1 (13.2)	0.03
Tanner stage, m (SD)	3.19 (1.25)	2.81 (1.47)	*ns*
Ethnicity/race, *n* (%)			
African American	9 (42.9)	14 (41.2)	ns
Caucasian	5 (23.8)	13 (38.2)	
Mixed	4 (19)	3 (8.8)	
Hispanic	1 (4.8)	1 (2.9)	
Not reported	2 (9.5)	3 (8.8)	
Annual Household Income, *n* (%)			
<$40,000	15 (71.4)	15 (44.1)	ns
$40,000–$60,000	2 (9.5)	9 (26.5)	
$60,000–$80,000	0	5 (14.7)	
$80,000–$100,000	1 (4.8)	1 (2.9)	
Over $100,000	2 (9.5)	4 (11.8)	
Not reported	1 (4.8)	0	
Type of trauma endorsed, *n* (%)			
Physical abuse	3 (14.3)	0	
Neglectful home environment	4 (19)	0	
Emotional abuse	3 (14.3)	0	
Exposure to domestic violence	7 (33.3)	0	
Exposure to other violence (e.g., violent crime)	9 (42.8)	0	
Multiple separations from parent or caregiver	10 (47.6)	0	
Sexual abuse or exposure	2 (9.5)	0	
Anxiety symptoms (SCR-C), m (SD)	16.8 (12.6)	15.2 (11.8)	ns
Depressive symptoms (CDI), m (SD)	2.1 (3.1)	2.8 (3.3)	ns

P values derived from *t* tests (age, IQ, Tanner stage, SCR-C), Chi-square tests (sex, race), or Mann–Whitney *U* tests (income, CDI)

m mean, *ns* not significant, *IQ* intelligence quotient, *SCR-C* screen for child anxiety-related emotional disorders, *CDI* children's depression inventory

Magnetic resonance imaging data acquisition

Magnetic resonance imaging scanning was conducted at the WSU School of Medicine with a single Siemens 3.0 Tesla system (MAGNETOM Verio, Siemens Medical Solutions) equipped with a 12-channel head coil. High-resolution T1-weighted anatomical images were acquired for each subject. A three-dimensional T1 magnetization-prepared rapid gradient-echo (MP-RAGE) sequence was used with the following parameters: TR: 1680 ms, TE: 3.51 ms, orientation: axial, matrix: 384 × 384, 176 slices, flip angle: 90°, voxel size: 0.7 × 0.7 × 1.3 mm.

Structural image processing

Before analysis, T1-weighted anatomical images were screened for motion artifacts (ghosting, blurring). Six participants with scans exhibiting severe artifacts were excluded from the study sample. For remaining participants ($N = 55$), individual participant whole-brain intracranial masks were generated and manually edited by one rater

(N.K.) using the interactive editing tools in the BrainSuite software package (v.13a4; [58]; http://brainsuite.org/). Intrarater reliability was tested by generating whole-brain intracranial masks twice for five brains, at least 2 weeks apart. Intraclass correlation coefficient (ICC; [60]) was computed using the total number of voxels in each brain mask; reliability was confirmed by an ICC measure of >0.90. Whole-brain masks and MR image volumes were then processed using BrainSuite to produce participant-specific models of brain structure and derive total GMV of regions of interest (ROIs) in left and right hemispheres. Three ROIs were selected a priori: subcallosal area, hippocampus, and amygdala, as illustrated in Fig. 1.

Computation of ROI GMV was achieved through a semi-automated series of steps implemented within BrainSuite. First, surface mesh models of the inner and outer boundaries of the cerebral cortex were produced using a series of steps, including bias field correction, tissue classification, and topology correction [57, 59]. The surface models, tissue maps, and bias-corrected MR images are then processed with SV_{Reg}, a surface and volume registration and labeling module integrated with BrainSuite, which maps the participant data to a reference atlas. SV_{Reg} first performs surface-based registration on a mid-cortical surface produced by averaging the inner and outer cortical surface meshes. Participant-specific ROIs are delineated by aligning participant-specific surface maps to the volume atlas; fits for each ROI are refined using geodesic curvature flow [37]. Coregistered cortical surfaces are used as a constraint to generate full volumetric registration using p-harmonic mapping and intensity-based refinement [38]. Data from 0–3 cases per ROI were missing due to artifacts that prohibited automatic segmentation of brain substructures, following manual masking procedures. Because these values were missing at random, whole-sample mean replacement was used.

Group analysis

Total GMV of each ROI (Fig. 1; separately for left and right hemispheres) was computed and adjusted for intracranial volume (cf. [26]). Outliers were Winsorized to two standard deviations above or below the mean. Results are reported on Winsorized data, and were further confirmed with analyses that excluded outliers and missing values. Main effect of BDNF genotype on ROI GMV was evaluated separately within trauma and comparison groups using two-sample t tests. Effects were considered significant at $p < 0.0083$, Bonferroni corrected for analysis of six ROIs. Significant effects were followed up with analysis of trauma-by-BDNF interaction for that ROI in the full sample (controlling for IQ). Post hoc power analysis suggested an acceptable power level of 0.89 for detecting a reliable group-by-genotype interaction (GPower; [23]). Trauma-by-sex interactions were evaluated in follow-up analyses. Pearson bivariate correlation was used to test for relationships between GMV and symptoms of anxiety; Spearman correlation was used for depressive symptoms given evidence of slight positive skew in CDI scores. Statistical analyses were performed in SPSS v.22 (IBM Corp., Chicago, IL). Follow-up analyses were considered significant at $p < 0.05$.

As a validation step, we repeated trauma-by-BDNF GMV interaction analyses in a case–comparison matched subsample. This addresses the presence of more *Val/Val* than *Met* participants in the study sample. *Met* allele carriers were compared to an equal number of *Val/Val* participants matched in trauma exposure, age, sex, IQ, and race.

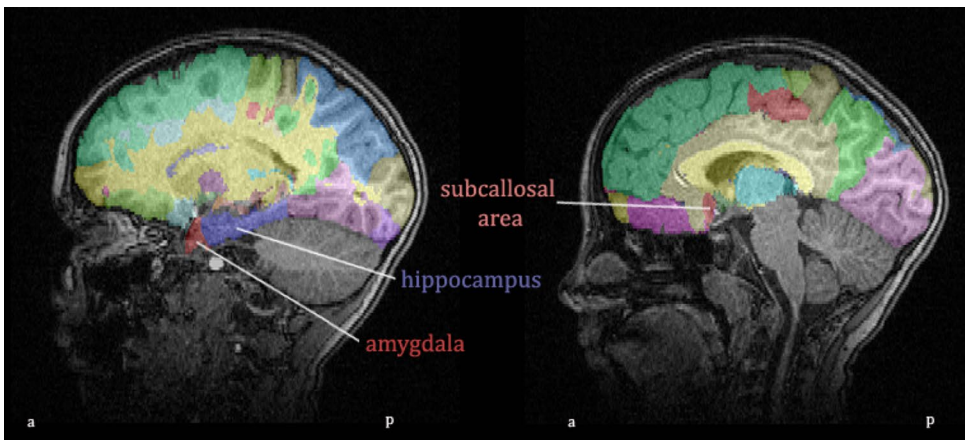

Fig. 1 Limbic regions of interest (ROIs) selected a priori. Gray matter volume (GMV) was calculated using a semi-automated sequence in BrainSuite software. T1-weighted images are overlaid with ROI labels in sagittal section for one representative participant (*a* anterior, *p* posterior)

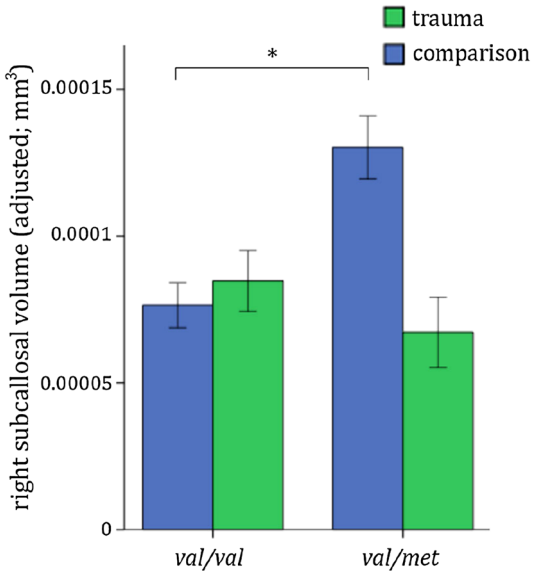

Fig. 2 Effects of BDNF genotype on gray matter volume of the right subcallosal area in comparison, but not trauma-exposed youth. Regional values are adjusted for whole-brain volume. *Error bars* represent standard error. *$p < 0.0083$ (Bonferroni correction for multiple comparisons), within-group *t* tests. Effect of trauma within gene groups was not tested due to the limited number of *Met* allele carriers

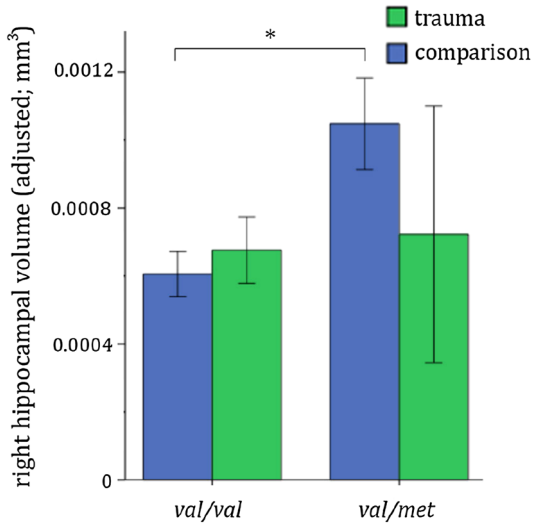

Fig. 3 Effects of BDNF genotype on gray matter volume of the right hippocampus in comparison, but not trauma-exposed youth. Regional values are adjusted for whole-brain volume. *Error bars* represent standard error. *$p < 0.0083$ (Bonferroni correction for multiple comparisons), within-group *t* tests. Effect of trauma within gene groups was not tested due to the limited number of *Met* allele carriers

Results

Interactive effects of trauma and BDNF genotype on subcallosal and hippocampal gray matter volume

Within comparison youth, GMV of the right subcallosal area, $t(32) = 3.08$, $p = 0.004$, and right hippocampus, $t(32) = 2.9$, $p = 0.008$, was higher in *Met* carriers than *Val/Val* homozygotes (see Figs. 2, 3). Effects of BDNF were not observed within trauma-exposed youth ($ts < 0.7$, $ps > 0.5$). Effects of BDNF on amygdala GMV were not significant within trauma-exposed, $p = 0.9$ (left) and $p = 0.97$ (right), or comparison groups, $p = 0.085$ (left) and $p = 0.583$ (right).

Significant within-group findings were further confirmed by trauma-by-BDNF interactions in the full sample (controlling for IQ) for right subcallosal, $F(1,41) = 7.49$, $p = 0.009$, and right hippocampal GMV, $F(1,41) = 4.13$, $p = 0.049$. No main effects of BDNF or trauma on GMV were observed, $ps > 0.09$. Additional supplementary analyses excluding outliers and missing values yielded consistent results: GMV of right hippocampus, $t(30) = 2.59$, $p = 0.015$, and right subcallosal area, $t(32) = 3.08$, $p = 0.004$, was higher in *Met* alleles than in *Val/Met* participants in the comparison group, and BDNF effects were not significant in the trauma group in these areas, $p = 0.87$ and $p = 0.52$, respectively.

To account for racial heterogeneity in the sample, subsequent analyses additionally co-varying for race were conducted, yielding no changes to the results. Specifically, main effects of BDNF genotype were significant for right subcallosal, $F(1, 31) = 8.5$, $p = 0.007$, and right hippocampal GMV, $F(1, 31) = 8.64$, $p = 0.006$, in comparison youth.

Results in the case–comparison matched subsample (equal number of *Val/Val* and *Met* participants) replicated the trauma-by-BDNF interaction on GMV of the right subcallosal area, $F(1,14) = 13.36$, $p = 0.003$. However, the trauma-by-BDNF interaction was not replicated for right hippocampal GMV, $p = 0.32$.

Relation of GMV to age, pubertal stage, sex, and internalizing symptoms

No sex differences in GMV were noted across ROIs, $ps > 0.18$. In addition, no trauma-by-sex interactions were observed for right hippocampal, $F(1,51) = 1.73$, $p = 0.195$, or right subcallosal GMV, $F(1,51) = 2.12$, $p = 0.15$. GMV of right hippocampus and right subcallosal area was not related to age or pubertal (Tanner) stage, $ps > 0.12$. Although anxiety and depressive symptoms did not differ between BDNF and trauma groups, we tested for correlations between ROI GMV and internalizing symptoms. Within the comparison group, right hippocampal GMV was negatively correlated with anxiety symptomology (SCR-C), $r(34) = -0.39$, $p = 0.021$. This relationship was not evident in the trauma group, $r(21) = 0.33$, $p = 0.14$.

Discussion

Emerging research indicates that impairments in neuroplasticity and cellular resilience induced through stress underlie risk for affective disorders (see [21]). As many of these disorders have their roots in childhood and adolescence [52], examining how prominent biological (i.e., altered BDNF function) and environmental (i.e., trauma) risk factors shape the brain in formative years may critically inform pathways responsible for lifelong emotional health. Here, we provide preliminary evidence that childhood trauma and BDNF *Val66Met* genotype interact to predict structural variation in limbic brain regions, known to regulate mood, in a sample of youth at high risk for emotional psychopathology. Altered development of limbic brain circuitry may lead to emotion dysregulation and pathology. Our results suggest that individual variation in BDNF neurobiology plays a central role in modifying vulnerability (or resilience) to traumatic stress.

We demonstrate a trauma-by-BDNF interaction in the subcallosal region, such that BDNF effects on GMV were observed in comparison but not trauma-exposed youth (see Fig. 2). Control participants with a *Met* allele had larger subcallosal GMV. In addition, trauma-exposed *Met* allele carriers appeared to have lower GMV relative to *Met* carriers without histories of trauma, but this difference was not significant possibly due to the modest number of *Met* alleles in the sample. It is nonetheless striking that these observations are consistent with those previously reported in a large ($n = 568$) sample of healthy adults [29]. Gerritsen and colleagues observed lower GMV in the subcallosal region in adults exposed to childhood trauma that also carry the *Met* allele. Volume reduction in this area is a consistent finding in mood disorders (for review, see [20]), and the subcallosal area is a target for deep brain stimulation in the treatment of depression [46]. There is also data to suggest that altered structural integrity of the subcallosal area underlies stress susceptibility [51, 54]. Research in experimental animals implicates the subcallosal region in the regulation of autonomic and neuroendocrine stress responses [61]. Taken together, our results provided preliminary support that subcallosal gray matter alterations could be an early indicator of risk that results from interaction of childhood trauma with genetic susceptibility.

We also found preliminary evidence for differential effects of BDNF genotype on hippocampal GMV in youth that did or did not experience trauma. *Met* allele children without histories of trauma had increased hippocampal GMV relative to *Val/Val* children (see Fig. 3). This effect was not observed in the trauma group. This suggests that BDNF-related hippocampal differences may be evident only in the absence of early traumatic stress. It is likely that certain types of environmental exposures, such as early trauma, can mask or override aspects of genetic disposition, for example through epigenetic mechanisms. As such, experience has the potential to diminish differences between gene groups. Having observed higher hippocampal GMV in children without trauma may reflect differences in plasticity [12], in neurogenesis [55], and/or in learning and memory [18]—all of which have been linked to BDNF profile and hippocampal integrity. It is unknown whether these differences similarly manifest in children that endure difficult early life experiences, but it is possible the gene-related distinctions are reduced.

In contrast to research in previously institutionalized children that was also preliminary [8], we did not observe trauma-by-BDNF effects in the amygdala. In that study, *Met* allele carriers were more likely to show increases in amygdala GMV following early life stress than individuals homozygous for the *Val* allele. Another study found increased GMV of the amygdala in adolescents exposed to maternal depression during infancy [44]. Taken together, amygdala volume changes detected during childhood may relate to trauma experienced during very early postnatal life. This is in line with nonhuman primate research showing that the most rapid rate of amygdala development occurs during infancy [50]. Moreover, given the variable role of BDNF at different developmental ages (see [8]), trauma-by-BDNF effects may differ depending on the age that trauma is experienced. Indeed, BDNF appears to exert either a permissive or obstructive role on activity-dependent synaptic changes, depending on the brain region and developmental stage [56]. This is consistent with the view that stress during different developmental windows may lead to disparate neurobiological and psychiatric consequences [63]. Another possibility for our null finding is that amygdala volume changes may relate to type of trauma (e.g., disrupted early nurturing). If this is the case, variability in types of adversity experienced in our sample (e.g., witnessing domestic violence, physical or sexual abuse) would diminish our ability to detect significant effects at the group level.

It should be noted that GMV changes are difficult to interpret. GMV differences are often interpreted as changes in the number or size of glial cells, neurons, dendrites, or synapses (cf. [20]); however, changes in intracortical myelination may also contribute to GMV alterations (cf. [62]). Moreover, gross volumetric differences might not be as sensitive as effects on subregions. For instance, a recent study in adults reporting histories of childhood trauma found trauma-by-BDNF effects on specific subregions of the hippocampus (i.e., CA2/3; [25]). Continued research will address regional specificity and cellular changes that underlie structural MRI GMV differences, and will

contribute understanding to how BDNF modulates limbic brain structures over the course of development.

Study limitations warrant mention. Due to the limited sample size and the rarity of the *Met* allele, current results are presented as preliminary. These preliminary findings do, however, highlight neurological differences in an understudied population of urban-dwelling, minority youth with a high stress burden. Moreover, our results suggest interacting effects of trauma and BDNF on limbic GMV in ways that differ from an earlier preliminary report in youth [8]. The fact that our findings mirror those reported in a study of adults reporting early stress [29] affords further confidence in the observed pattern. Given the rarity of the *Met* allele, future studies may also consider performing genotyping prior to enrolling participants in the neuroimaging protocol. Next, findings in this report are based on a racially heterogeneous sample. We controlled for possible effects of race (which shows high correspondence with genotyped ancestry markers; [19]) in follow-up analyses; doing so allowed us to increase overall power by including all participants in analyses. While we were underpowered to confirm observed effects within race subgroups, our analyses do support the conclusion that results reported here are not likely attributable to population structure artifact. Similarly, we were underpowered to test for sex-by-BDNF effects on GMV in this sample and we urge future studies to address this important question. In addition, participants spanned a broad age range (7–15 years) and thus impacts of age and pubertal development should be considered. Although this preliminary study was not sufficiently powered to assess the effects of age on study outcomes, we were sensitive to these concerns. We found that age and pubertal stage did not differ between BDNF groups, or between trauma and comparison participants. Additionally, we did not find age- or puberty-related associations with GMV of ROIs showing trauma-by-BDNF effects (i.e., right hippocampus, right subcallosal area). Finally, in an effort to extend prior work in adults [29] and to limit the number of comparisons, we investigated only a subset of ROIs. Future work should evaluate effects of trauma and BDNF on other brain regions.

The present study provides preliminary evidence that, among high-risk urban youth, childhood trauma and BDNF genotype interact to predict variation in limbic brain regions during formative, developmental years. It is notable that BDNF effects were observed only in the absence of traumatic stress, supporting the conclusion that certain environmental contexts may be necessary to mask or unmask gene–brain associations. These data suggest that genetic variability may contribute to variable neurodevelopmental pathways leading to poor outcomes following early life trauma [14]. On the basis of these early results, however, it is unclear whether *Met* allele carriers are more prone to the detrimental effects of trauma on hippocampal and subcallosal gray matter integrity, or instead, trauma leads to decreased GMV, irrespective of genotype, and normalization is impaired in *Met* allele carriers (resulting in no observed effects of BDNF within the trauma group). In addition, trauma-exposed youth did not report higher levels of anxiety or depressive symptomology, suggesting that neurological effects observed in the dynamically developing brain may represent risk or adaptation to adverse early environments. We did, however, observe a negative correlation between hippocampal GMV and anxiety symptomology in youth without histories of trauma. This is consistent with the notion that early experience modulates gene–brain or gene–symptom effects. Future research should examine relationships among trauma, limbic brain circuitry, and psychiatric outcomes over the course of development, considerate of developmental changes in BDNF function.

Conclusions

In summary, this preliminary study demonstrates an interactive effect of BDNF genotype and childhood trauma on limbic GMV in youth. Our results support the notion that the BDNF *Val66Met* polymorphism functions as a stress vulnerability (and/or resiliency) factor in early life. It is critical that these effects were observed in children, whose brains are undergoing substantial maturational changes [17]. Research shows that psychopathology frequently emerges during childhood and adolescence, and once it manifests, it often becomes chronic [13]. It has been demonstrated that about 60 % of youth will experience a traumatic event before adulthood [48] and nearly a third of trauma-exposed youth will go on to develop an affective disorder [31]. These findings are a first step towards understanding the mechanisms through which early adversity forms a prelude to psychopathology, so that predictive biomarkers of risk may be identified. Future research in this area may carry implications for preventive interventions, including those that operate through BDNF pathways to reopen or extend developmental windows of plasticity [10].

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Compliance with ethical standards

Conflict of interest The authors declare no conflicts of interest.

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