Behavioural Brain Research 328 (2017) 48–56

Contents lists available at ScienceDirect

Behavioural Brain Research

journal homepage: www.elsevier.com/locate/bbr

Research report

1826

The BDNF Val^{66}Met polymorphism is associated with structural neuroanatomical differences in young children

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ARTICLE INFO

Article history:
Received 18 September 2016
Received in revised form 5 February 2017
Accepted 7 March 2017
Available online 27 March 2017

Keywords:
BDNF
rs6265
Neurogenetics
sMRI neuroimaging
Gray matter volume
Cortical thickness
Surface area
Development

ABSTRACT

The brain-derived neurotrophic factor (*BDNF*) Val^{66}Met single nucleotide polymorphism (SNP) has been associated with individual differences in brain structure and function, and cognition. Research on BDNF's influence on brain and cognition has largely been limited to adults, and little is known about the association of this gene, and specifically the Val^{66}Met polymorphism, with developing brain structure and emerging cognitive functions in children.

We performed a targeted genetic association analysis on cortical thickness, surface area, and subcortical volume in 78 children (ages 6–10) who were Val homozygotes (homozygous Val/Val carriers) or Met carriers (Val/Met, Met/Met) for the Val^{66}Met locus using Atlas-based brain segmentation. We observed greater cortical thickness for Val homozygotes in regions supporting declarative memory systems (anterior temporal pole/entorhinal cortex), consistent with adult findings. Met carriers had greater surface area in the prefrontal and parietal cortices and greater cortical thickness in lateral occipital/parietal cortex in contrast to prior adult findings that may relate to performance on cognitive tasks supported by these regions in Met carriers. Finally, we found larger right hippocampal volume in Met carriers, although inconsistent with adult findings (generally reports larger volumes for Val homozygotes), is consistent with a recent finding in children.

Gene expression levels vary across different brain regions and across development and our findings highlight the need to consider this developmental change in explorations of *BDNF*-brain relationships. The impact of the *BDNF* Val^{66}Met polymorphism on the structure of the developing brain therefore reflects regionally-specific developmental changes in *BDNF* expression and cortical maturation trajectories.

1. Introduction

Multiple genes and gene by environment interactions regulate the emerging cognitive abilities in the child's developing brain. The *BDNF* gene (located on chromosome 11p14.1) encodes for the brain-derived neurotrophic factor, a member of the nerve growth family of proteins, and has been implicated in brain development, maturation and cognition [1,5,17,19,32,33,47,82]. More specifically, BDNF influences the proliferation, differentiation and survival of neurons, neural morphology and function, synaptic changes (i.e. long-term potentiation [LTP] in the hippocampus), and, correspondingly, neuroplasticity [23]. The listed pathways and processes depend on the amount of neurotrophin present, its appropriate

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http://dx.doi.org/10.1016/j.bbr.2017.03.014
0166-4328/

release, and its binding affinity to target cell membranes [5]. Both animal and human studies suggested that common genetic polymorphisms in *bdnf*/*BDNF* are related to the structure and function of the developing brain; see Bath and Lee [5] for a review of human and animal findings and see Hanover et al. [30], Huang et al. [35] for studies of mouse visual cortex. Despite these studies having established a link between *BDNF* and synaptic changes over development, few studies have examined the relationship between *BDNF* and brain function or structure in young children [34,45,71]. Here, we examine the association between the *BDNF* Val^{66}Met polymorphism (dbSNP rs6265) and individual differences in brain structure in a sample of neurotypical children.

A common missense (i.e., leading to the alteration of the amino acid composition of the protein) single nucleotide polymorphism (SNP) in the *BDNF* gene, rs6265 or Val^{66}Met, affects production of the BDNF protein [19]. Specifically, this polymorphism results in a single amino acid substitution (valine to methionine) in the proBDNF peptide [a precursor peptide to BDNF [32,49]], at codon 66. Two alternative alleles (G/A) are possible at this locus, with G being the ancestral allele, and A – the derived one. Thus, three genotypes are possible: GG, AG, and AA, corresponding to Val/Val, Val/Met or Met/Met, respectively. Activity-dependent BDNF release is highest in Val/Val individuals relative to Val/Met and Met/Met individuals (however as discussed below this may vary with development). Moreover, differences in the activity-dependent BDNF release between Val/Val, Val/Met and Met/Met carriers have been observed to be associated with behavioral differences as well as differences in brain structure (e.g., white matter architecture; [85]) and function, in animals [5,30,35] and human adults [19,32].

Behaviorally, the *BDNF* Val^{66}Met polymorphism has been associated with multiple aspects of cognition and, most notably, memory function. In studies with adult samples, Val homozygotes generally perform better than Met carriers on measures of declarative and working memory [9,24,31], as well as other aspects of cognition, including attention [61,64,84], and executive function [1,65]. Working memory (WM) capacity involves a system for combining information storage and manipulation to involved in cognitive activities. This is often measured using an n-back task, where the participant is asked to monitor a series of stimuli (e.g., numbers, letters) and make a response when a stimulus presented is same as that presented *n* trials previously. During such an n-back working memory task, Met carriers were found to show reduced brain activation, compared to Val homozygotes, in brain regions including the frontal lobe [11]. Compared to Val homozygotes, Met carriers also demonstrate reduced declarative memory, which includes long term storage of episodic and semantic knowledge [38]. However, Dodds et al. [18] suggests that the Val^{66}Met polymorphisms may have an effect on memory retrieval, and not on memory encoding.

However, the relationships between the *BDNF* gene and cognition have been almost exclusively documented in samples of healthy adults ([34], see [71]) and psychiatric patient populations [16,25,43,61,64–66,84], but see Hashimoto et al. [34] for relevant research on the Val66Met polymorphism in child and adolescent brain structure. The impact of this polymorphism on the healthy development of the brain and cognition in children is not fully understood.

At the neural level, studies with adults have revealed that the Val^{66}Met polymorphism is associated with structural variation in both cortical and subcortical gray and white matter structure, including volume, cortical thickness, and white matter integrity [12,19,32,56,69], and brain function [18,19,32,39,43]. Most prominently, this polymorphism has a well-documented effect on hippocampal structure and function, with most studies finding that the Val^{66}Met polymorphism has an atrophic effect on the hippocampus. Indeed, murine studies have found that homozygous carriers of the Met allele have reduced hippocampal volumes, less dendritic arbors, and a 30% reduction in activity-dependent release of bdnf protein (c.f. [12]). In human neuroimaging studies, reduced hippocampal volume has also been observed in Met carriers, compared to Val homozygotes [19,32,38,56,69].

BDNF is also abundantly expressed in the frontal lobes, the occipital lobe and in the temporal lobe, which connect with the hippocampus through its afferent connections [3,4]. Correspondingly, the Val^{66}Met polymorphism has also been associated with cortical structure in these regions, specifically, Met carriers have generally demonstrated reduced gray matter volume in the superior and middle frontal gyri, including the dorsolateral prefrontal cortex [22,46,56] anterior cingulate cortex [26,46,50], lingual gyri [22], and fusiform gyri [48], compared to the Val homozygotes.

In addition to these structural brain differences, there are also differences in functional brain activation observed between Val homozygotes and Met carriers. Hariri et al. [32] found reduced activation of the hippocampus during a declarative memory task among Met carriers as compared with Val homozygotes. Further, Chen et al. [12] found that Met allele carriers showed consistently lower brain activation in the right superior frontal gyrus (SFG) and the middle occipital gyrus during a N-back working memory task. Using resting state MRI, Wei et al. [78] also found reduced functional connectivity between the right hippocampus and left parahippocampal gyrus with cortical regions (middle temporal gyrus, inferior and middle frontal gyrus, fusiform gyrus) in Met carriers compared to Val homozygotes. These differences in brain activation between Met carriers and Val homozygotes generally correspond to observed differences in memory and general cognitive performance in adults [9,24,31,38]. Generally, reduced activation and smaller volume of the hippocampus is associated with poorer memory performance [58,59,75,83]. Indeed, Kambeitz et al. [38]'s meta-analysis of relation between *BDNF* and memory performance and both brain structure and function observed this relationship.

With respect to neural development in humans, there is currently very limited research that has explored this polymorphism in children, and findings to date are not completely consistent with the adult data. For example, in a cohort of Japanese children aged 5–18, Hashimoto et al. [34] found greater gray matter volume in the right cuneus for Met homozygotes (Met/Met) relative to Val homozygotes (a finding not previously observed in adults), whereas they observed greater left insula and left ventromedial prefrontal cortex volumes in Val homozygotes relative to Met homozygotes which is consistent with the adult studies. Further, Marusak et al. [45] reported larger right hippocampal volume among children and adolescents aged 7–15 who were Met carriers, whereas adult studies report larger volumes for Val carriers. Finally, Thomason et al. [71] found that 11–12-year-old children who were Met carriers showed reduced resting state connectivity between the hippocampus and parahippocampal gyrus with cortical regions (middle temporal lobe, posterior cingulate, inferior parietal lobule, precuneus), compared to Val homozygotes, which is consistent with the adult literature and may reflect less robust hippocampal-cortical projections among children who are Met carriers.

In sum, there are demonstrated relationships between the *BDNF* Val^{66}Met polymorphism, and brain structure and function; yet, the effects of this polymorphism on the developing brain are poorly characterized given the limited research on children to date. In the present study, we aimed to bridge this gap in the literature by performing a targeted genetic association study focusing on the role of the *BDNF* Val^{66}Met polymorphism on the structure (cortical

thickness and surface area, and subcortical volume) of developing brain systems in a sample of school-aged children. To this goal, we investigated cortical and subcortical structure in children who were homozygous for the Val allele (Val/Val), as compared with children who were Met allele carriers (Val/Met and Met/Met). We examined cortical surface area, cortical thickness, and subcortical volume differences related to the *BDNF* Val^{66}Met polymorphism because these indices of brain structure are heritable, yet, reflect distinct components of brain maturation [14,53,80]. The present study investigates whether this common genetic variant impacts brain structure in the human developing brain in ways that are relevant for children's emerging cognitive abilities, with the goal of better understanding the complex pathways that link variation in genetic and brain structure during the course of development.

2. Materials and methods

2.1. Experimental subjects

Seventy-eight children between the ages of 6 and 10 (47 males, 31 females, mean age = 8.1, *SD* = 1.2) participated in this study. Participants were part of a larger longitudinal study investigating the genetic underpinnings of structural and functional brain changes over a period in development corresponding to rapid acquisition of reading and other academic skills [42,52]. Participants were divided into two groups based on their *BDNF* genotype: Val homozygotes (Val/Val; $n = 49$) and Met carriers ($n = 29$; this group included Val/Met [$n = 26$] and Met/Met [$n = 3$] individuals). The minor allele frequency (MAF, here for the Met allele) in the sample was 23%. As noted above, given the low frequency of the Met allele, we collapsed Val/Met and Met/Met individuals into one group: Met carriers [55,73,81,85], which is a common practice in the studies of this polymorphism in specific and low-MAF variants in general. But see recent work on differences between Val/Met and Met/Met animal models [51].

There were no significant differences between the Val^{66}Met genotype groups with respect to age, $F(1,76) = 311$, $p = .578$, or gender distribution, χ^2 (1) = 2.098, $p = .07$. Table 1 presents summary of the participants' demographics and genotypic status. Further, given reported associations between the Val^{66}Met polymorphism and cognitive ability in adults, children in our study completed the Weschler Abbreviated Scales of Intelligence (WASI) IQ. Children in this study all had IQ scored in the normal range (Performance IQ: 79–146; Verbal IQ: 70–141) and there were no significant differences in verbal or performance IQ between the two genotype groups (Verbal IQ: $F(1,76) = 0.001$, $p > .05$; Performance IQ: $F(1,76) = 0.705$, $p > .05$).

The study received ethical approval from the Yale University Human Research Protection Program. All child subjects provided informed assent and all parents provided informed consent.

2.2. Procedure

2.2.1. MRI processing and analysis

Structural MRI data were acquired using a Siemens 1.5T Sonata scanner with 8-channel receiver array head coil. We employed the 3D magnetization prepared rapid acquisition gradient echo (MPRAGE) sequence (TR = 2000 ms, TE = 3.65 ms, flip angle = 8°, 160 slices, 256 × 256 matrix), most data were acquired using a 1 mm^3 resolution, however, 14% of the data were acquired using the same sequence under the 1.3 mm^3 resolution, which was resampled to 1 mm^3 for the analysis. Each participant's anatomical scan and resulting segmentation were visually inspected. Image processing and statistical analyses were completed with the software packages Freesurfer version 5.3.0 [21] and R (The R Core Team [70]).

Using Freesurfer, each high-resolution anatomical scan was registered to the Talairach space and voxels were classified as gray or white matter based on intensity and neighborhood constraints. Images were parcellated into specific regions by white and gray matter based on Desikan-Killiany Atlas [15] to examine volumetric, surface area, and cortical thickness differences between groups.

Surface based analysis: Individual cortical reconstructions were smoothed using a Gaussian kernel of 10 mm FWHM. Differences in cortical thickness at each vertex and differences in surface area between Val homozygotes and Met carriers were determined using Freesurfer's QDEC (Query, Design, Estimate, Contrast) and a general linear model (GLM) with a different offset different slope (DODS) design matrix that controlled for age, and for mean cortical thickness and mean surface area by hemisphere respectively. We performed a Monte Carlo simulation with a 2-sided vertex-wise threshold of $p < .05$ to correct for multiple comparisons [29]. Effect size maps were calculated using Cohen's *d* formula whereby the contrast effect size (Freesurfer gamma) was divided by the square root of product of the contrast variance (Freesurfer gammavar) and sample *N*. Surface areas were reported as number of voxels in mm^2. Cortical thickness was computed as the distance between the white and plial surfaces at each vertex as described in Fischl and Dale [20].

Subcortical volume analysis: Subcortical volumes were exported using Freesurfer's "asegstats2table" function for additional analyses in R. We compared subcortical values between Val homozygotes and Met carriers in R using a linear regression model with participant age and overall cortical volume as covariates. Nonparametric permutation testing (1000 permutations) was performed to estimate the significance of each linear model and adjust for multiple statistical tests. Subcortical gray matter volumes were reported as the number of voxels in mm^3 within each segmented region.

2.2.2. DNA collection and analysis

We obtained biological samples from all participants using sterile Oragene™ saliva collection kits (DNA Genotek, Inc). DNA was collected, extracted, and stored according to the manufacturer's protocols. We used the Applied Biosystems Inc. (ABI) TaqMan protocol for SNP genotyping. Specifically, the Assays-on-Demand™ SNP Genotyping Product containing forward and reverse primers as well as the probe for the SNP of interest was utilized. In order to amplify the region of interest, a polymerase chain reaction (PCR) was carried out using MJ Research Tetrad Thermocycler on a 384-well plate format. TaqMan reactions included 100 ng of genomic DNA, 2.5 μl of ABI Taqman® Universal PCR Master Mix, 0.2 μl of ABI 40X Assays-on-Demand™ SNP Genotyping Assay Mix (assay ID C_11592758_10), 2.0 μl of sterile H_2O and 0.5 μl of Bovine Serum Albumin (BSA). The genotyping call rate was 92%; quality was controlled by regenotyping.

Table 1
Summary of participants.

	Val homozygotes	Met carriers
n	49	29
Gender ratio (M:F)	26:23	21:8
Mean age (SD)	8.2 (1.2)	8.0 (1.1)
Verbal IQ	107.2 (14.5)	107.1 (13.7)
Performance IQ	109.2 (16.3)	106.1 (15.9)

3. Results

3.1. Cortical thickness

With respect to cortical thickness, children who were Val homozygotes showed greater thickness than Met carriers in a

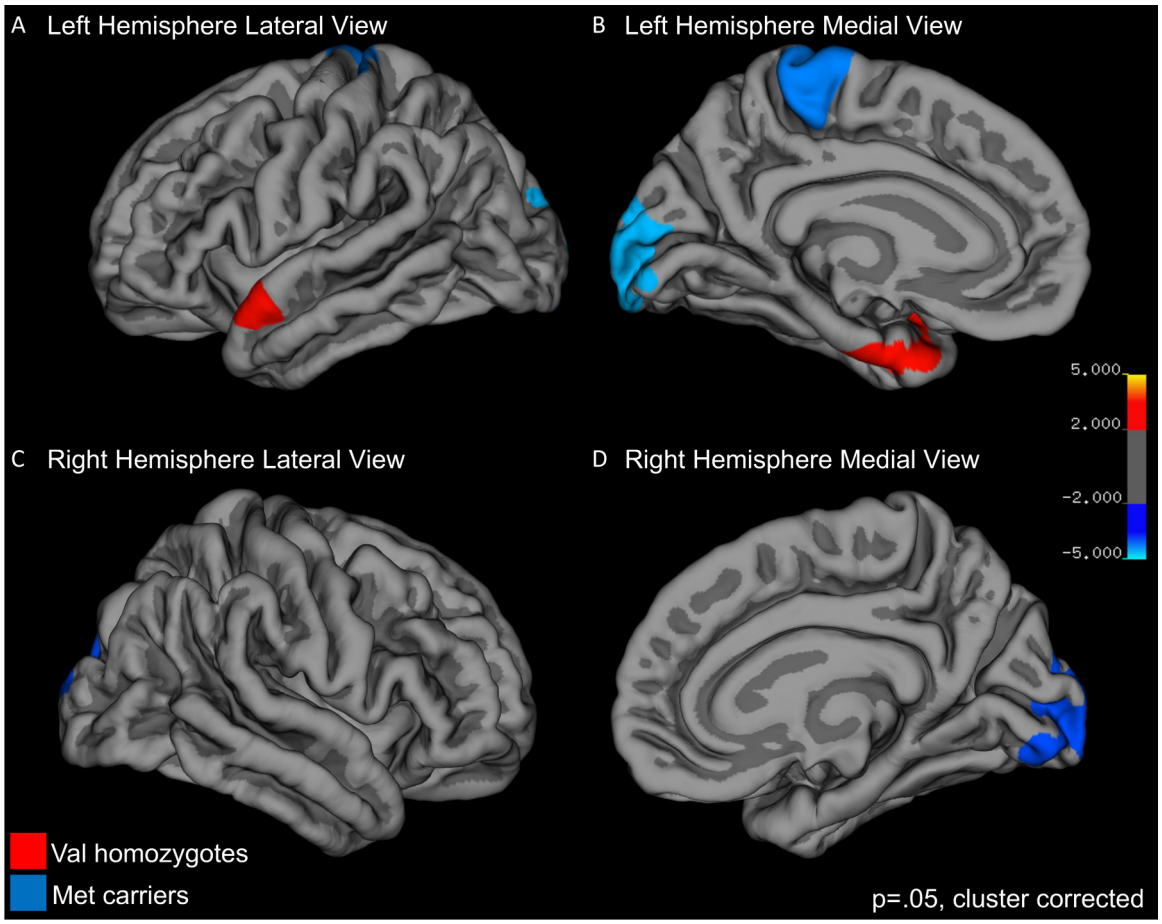

Fig. 1. Group differences in cortical thickness. Greater cortical thickness for Val homozygotes versus Met carriers is noted in red, greater cortical thickness for Met carriers versus Val homozygotes is noted in blue. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

cortical region encompassing the left superior temporal gyrus (STG), anterior temporal pole (ATP) and the entorhinal cortex (EC). On the other hand, children who were Met carriers showed greater cortical thickness relative to Val homozygotes in bilateral lateral occipital/superior parietal gyri, and in a region encompassing the left para-, post-, and precentral gyri (see Fig. 1 and Table 2).

Centroid of significant clusters are reported in MNI coordinates. Cohen's *d* effect sizes are reported. Val and Met notation refer to Val homozygotes (Val/Val) and Met carriers (Val/Met, Met/Met), respectively. Differences in structure between groups for surface areas are reported as number of voxels in mm^2. Cortical thickness was computed as the distance between the white and plial surfaces at each vertex as described in Fischl and Dale [20].

3.2. Cortical surface area

Children who were Met carriers showed greater surface area than Val homozygotes in the right lateral occipital and superior parietal gyri, in bilateral rostral middle frontal gyri, left pars opercularis, and right pars orbitalis (see Fig. 2 and Table 2).

3.3. Subcortical volume

Children who were Met carriers showed greater right hippocampal volume than Val homozygotes (see Table 3). Additionally, we examined whether hippocampal size was related to either verbal or performance IQ and found significant relation with

Table 2
Group mean differences in regional cortical thickness and surface area.

Brain region	Val vs Met	Difference	*X*	*Y*	*Z*	Cohen's *d*
Cortical thickness						
L. Lateral Occipital, Superior Parietal, Pericalcarine, Cuneus	Met > Val	1516	−11.5	−95	7	0.275
L. Paracentral, Postcentral, Precentral	Met > Val	1427	−5	−30	68	0.336
L. Superior Temporal, Temporal Pole, Entorhinal Cortex	Val > Met	869	−54	12	−19	0.303
R. Lateral Occipital, Superior Parietal, Lingual, Pericalcarine	Met > Val	1361	13.4	−87	25.8	0.266
Surface area						
R. Superior Parietal, Lateral Occipital	Met > Val	1591	24	−61	52	0.276
R. Rostral Middle Frontal, Pars Orbitalis	Met > Val	1482	40	41	24	0.276
L. Rostral Middle Frontal, Pars Opercularis	Met > Val	1317	−56	23	16.7	0.267

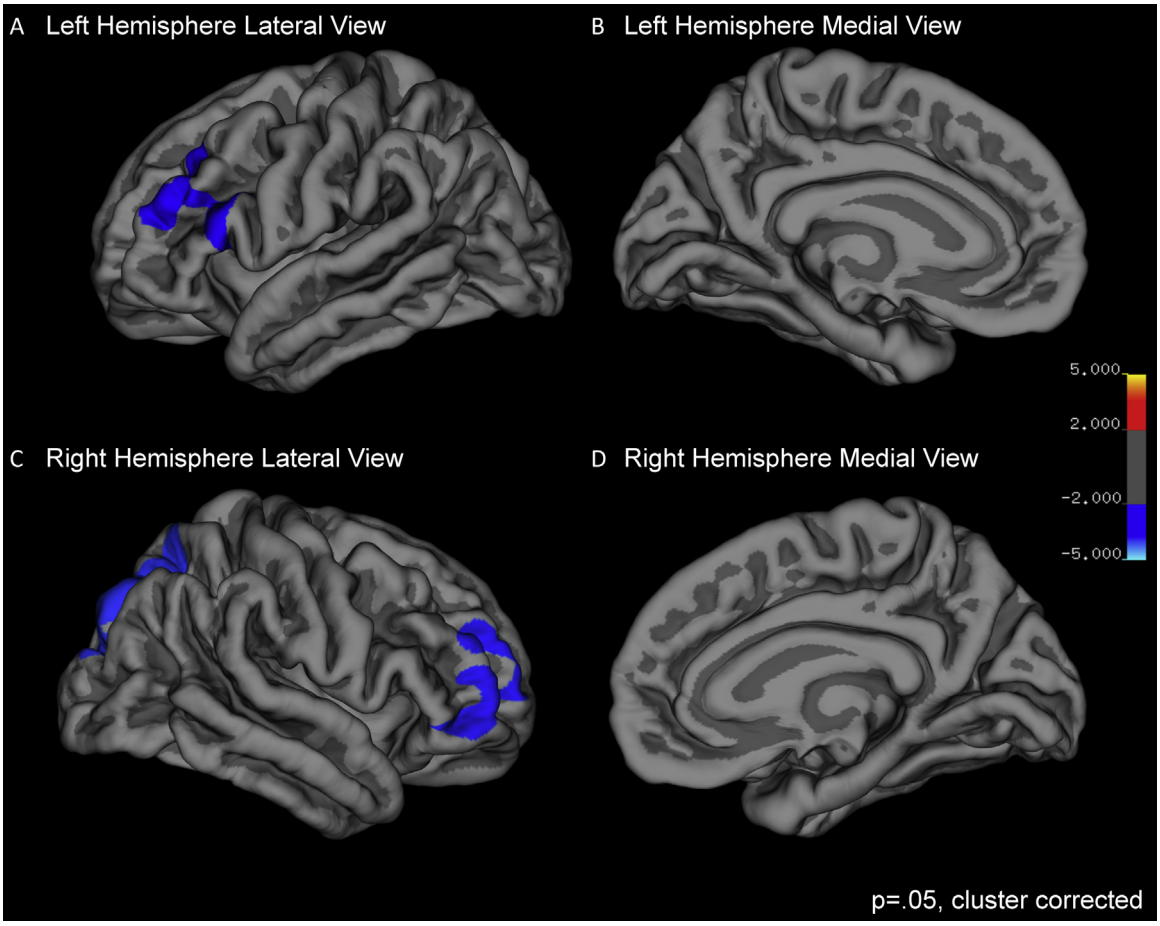

Fig. 2. Group differences in surface area. Greater cortical surface area for Met carriers versus Val homozygotes is noted in blue. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

performance IQ ($F(1,70) = 5.653$, $p < .05$); this finding is discussed below, with particular relevance for future research directions.

4. Discussion

In this study, we asked whether common genetic variation in the *BDNF* gene (specifically, the Val^{66}Met polymorphism) is related to brain structure in children. To this end, we examined cortical surface area, cortical thickness and subcortical volume in children who were Val homozygotes (Val/Val) and Met carriers (Val/Met and Met/Met).

The majority of the published literature on the neural phenotypes associated with the Val^{66}Met *BDNF* polymorphism has focused on hippocampal differences. However, BDNF is widely expressed in the brain – correspondingly, our investigation examined both cortical and subcortical structures, including the hippocampus. Differences in hippocampal and prefrontal regions related to the *BDNF* Val^{66}Met polymorphism have previously been reported, but these findings were largely restricted to patient and adult populations [46], despite findings from the animal and human literatures documenting significant developmental changes in *BDNF* expression [76]. Here, we provide one of the first accounts of *BDNF*-related neuroanatomical differences in school-aged children. Critically, our findings revealed a host of neuroanatomical differences associated with the *BDNF* Val^{66}Met polymorphism, in particular in the prefrontal cortex, parietal lobes, lateral occipital area, and the hippocampus.

Table 3
Group mean differences hippocampal volume.

Group	Mean (mm^3)	Std. error	*p* value	Cohen's *d*
Val homozygotes	3967	50	0.018	0.504
Met carriers	4146	67		

4.1. Cortical thickness and surface area

4.1.1. Cortical thickness

Previous research generally suggests that increased cortical thickness is associated with better cognitive function [40]. Here we find that children who were Val homozygotes have greater cortical thickness in the left anterior temporal lobe/entorhinal cortex – a large region that is involved in semantic processing and declarative memory [7], and is a primary sources of cortical projections to the hippocampus [40]. This finding is consistent with previous adult studies that report superior declarative memory performance in Val homozygotes [19,32].

Interestingly, we also identified several regions where Met carriers showed greater cortical thickness, compared to Val homozygotes, including bilateral lateral occipital/superior parietal gyri, which are involved in comprehension, working memory, and reading [6,13,74], and in a region encompassing the left para-, post-, and precentral gyri (somatosensory cortex and motor cortex).

4.1.2. Cortical surface area

With respect to surface area, all of our findings indicate larger surface area for Met carriers relative to Val homozygotes, which is somewhat unexpected given extant reports of poorer cognitive performance in adult Met carriers. Specifically, children who were Met carriers showed greater surface area relative to Val homozygotes in the right lateral occipital/superior parietal gyri (an overlapping region to that reported above), in bilateral rostral middle frontal gyri, and in a region of the inferior frontal cortex (encompassing IFG [left pars opercularis, and right pars orbitalis] near the dorsolateral prefrontal cortex: DLPFC). This region of inferior frontal cortex is involved in higher-level cognition including attention and executive function as well as language processing, task-switching, attention and working memory [2,8,10,54,57].

Our analysis revealed some regions that showed similar genotype group effects for cortical thickness and cortical surface area (e.g., lateral occipital/superior parietal gyri), whereas other regions did not pattern consistently. Such differences across brain regions are unsurprising given that cortical surface area and cortical thickness reflect unique structural properties of the brain that have been found to be independent of each other and genetically uncorrelated [53,80]. Heritability estimates for cortical surface area and cortical thickness are high in prefrontal regions but heritability estimates for other regions vary considerably between the two measures [36,37,41,44,60]. Further, differing maturational rates of brain structures may interact with heritability, which is likely to influence both the overall pattern of gene–brain associations observed here, as well as the consistency between measures of thickness and surface area. Developmental changes in genetic variance offer support for this view: genetic variance increases in the frontal and temporal lobes until adulthood, which suggests higher initial heritability in early-maturing regions of the brain (e.g., occipital cortex) and higher heritability later in development in later-maturing regions (e.g., frontal cortex) such as those associated with higher cognitive functions [14,44]. This heritability pattern also matches findings from gene-expression studies showing greater variance in expression levels in childhood versus adulthood [68]. Thus, it is expected that changing genetic variability in brain structures and independent measures of those structures (thickness, surface area) may pattern differently over development.

With respect to extant cognitive-behavioral findings associated with the *BDNF* Val^{66}Met polymorphism, our finding of greater cortical thickness for Val homozygotes in a region serving higher cognitive function was expected, given the oft observed superior performance of adult Val homozygotes on cognitive tasks that rely on these networks, and the fact that studies of cortical thickness and cognition typically find greater cortical thickness to be associated with better cognitive performance. On the other hand, regions where we observed greater cortical thickness for Met carriers are also involved in aspects of higher-level cognition, and these findings were unexpected based on existing adult data and relations between thickness and cognitive performance; however, these findings may be specific to children, given both different maturational levels of brain regions and levels of BDNF expression across these regions. For example, Shaw et al. [63] found that thickness shows initial increases throughout the brain in childhood, followed by declines in adolescence until stabilization in early adulthood; higher-order areas (e.g. frontal) reach peak thickness last (late childhood). Likewise, BDNF expression levels follow different trajectories across brain regions. In the DLPFC, BDNF expression increases gradually until adulthood [77]; in the temporal cortex, BDNF expression levels are highest in infancy and decline over childhood [76]; in the occipital cortex, BDNF expression is stable over development [77]. In the present study, Met carriers' greater cortical thickness was observed in regions in parietal and occipital cortex, which show more stable BDNF expression over development. However, Val homozygotes' greater cortical thickness was observed in the temporal cortex, which shows declining BDNF expression over development [62,67]. Thus, these region-specific differences in cortical thickness between Val homozygotes and Met carriers may reflect a combination of developmental changes in BDNF expression and brain maturation across regions. Differences in brain development and BDNF expression highlight the need to interpret gene–brain relationships in a developmental context, as relations between brain structure and genotype are dynamic and developmentally-patterned.

4.2. Hippocampal structure

The results of our study indicated that children who were Val homozygotes had smaller right hippocampi than Met carriers. The adult literature on both healthy/neurotypical and atypical populations typically reports on the opposite pattern: greater hippocampal volumes among Val homozygotes than Met carriers. Further, we observed volumetric differences only in the right hippocampus, which may be a feature of asymmetric hippocampal structure development as young infants have been previously reported to have a larger right hippocampus, an asymmetry not found in adults [72]. Indeed, our finding is consistent with [45], who found larger right (only) hippocampal volume for children, who were Met carriers. Developmental changes in hippocampal volume may reflect general u-shaped developmental trajectories of subcortical volumes which peak in adolescence [27,28,79], as well as, variable expression of BDNF over the lifespan [76]. Differences between our hippocampal volume findings and those of previous studies with adults may be linked to differences in *BDNF* expression and its consequent impact on brain structure over development. The significant relationship between performance IQ and hippocampal size also observed here indicates that the cognitive functions supported by this structure may be related to the BDNF Val66Met polymorphism and require further investigation using additional specific measures of children's cognitive abilities (for example, n-back memory task).

In sum, the juxtaposition of our findings and those from the adult literature, in particular studies by Marusak et al. [45] and Hashimoto et al. [34], suggests that the *BDNF* Val^{66}Met polymorphism exerts a significant influence on the cortical and subcortical structures of the brain, but does so differently in children and adults. These differences are likely driven by developmental differences in both structural brain development and *BDNF* expression, and suggest the need for more research on gene–brain relationships that take a developmental approach.

5. Conclusion

In the current study, we found that the *BDNF* gene Val^{66}Met polymorphism was associated with hippocampal volume and cortical surface area and cortical thickness in frontal, temporal, and occipital cortices in school-aged children. Our findings were partially consistent with previous reports in adults and children but also revealed novel associations between this polymorphism and cortical thickness, surface area, and hippocampal volume. Thus, Val homozygotes showed greater cortical thickness in the anterior temporal pole/entorhinal cortex, consistent with better declarative memory performance observed in adult Val homozygotes. On the other hand, Met carriers showed greater cortical thickness in lateral occipital and somatosensory and motor cortex. Further, Met carriers showed increased surface area in a number of regions that also serve higher level cognitive processes including bilateral prefrontal cortex (left and right IFG and DLPFC), right superior parietal

cortex/lateral occipital gyri, as well as greater right hippocampal volume. Although these findings were somewhat unexpected based on the adult literature, they implicate future regions to be explored in a developmental context and also suggest the need to look at both cortical thickness and surface area, as these neural features have different ontological trajectories and can be associated with different aspects of cognition. The Val/Val homozygotes and Met carriers in this study did show similar performance and verbal IQ scores, which were within a normal range. Future research will be directed at understanding whether the structural differences in observed between these groups have direct relationship to specific cognitive functions beyond IQ measures, particularly memory function. Finally, it is important to note that our findings are limited to associations between brain structure and one SNP on one gene. Complex developmental changes in brain structure, and their relationship to emerging cognition, is governed by multiple genes, gene–gene and gene–environment interactions, and future studies should explore the relation between brain structure and multiple SNPs and SNP interactions on *BDNF* as well as interactions with other genes. Our findings add to an increasingly complex pattern of the relationship between *BDNF* and brain development.

Acknowledgments

This study was supported by NIH grants R01 HD 048830 (K. Pugh, PI); P01 HD052120 (R. Wagner, PI); P01 HD 001994 (C. Fowler, PI); and R03 HD053409 (N. Landi, PI). We also want to thank Beth Eaton and Annie Stutzman for behavioral assessment of children, as well as Teri Hickey, Hedy Serofin and Cheryl McMurray for imaging participants, and Cheryl Lacadie for fMRI preprocessing. We are exceptionally grateful to the families and children who participated in this study, and extend a special thanks to the Windward School for their collaboration. Note that grantees undertaking such projects are encouraged to express freely their professional judgment. This article, therefore, does not necessarily reflect the position or policies of the National Institutes of Health and no official endorsement should be inferred.

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