

Research report

The BDNF Val⁶⁶Met polymorphism is associated with structural neuroanatomical differences in young children



Kaja K. Jasińska^{a,b,*}, Peter J. Molfese^{b,c}, Sergey A. Kornilov^{b,e,f,g,h}, W. Einar Mencl^{b,d}, Stephen J. Frost^b, Maria Lee^d, Kenneth R. Pugh^{b,c,d}, Elena L. Grigorenko^{b,d,e,f,g,h,i}, Nicole Landi^{b,c,d}

^a University of Delaware, Newark, DE, USA

^b Haskins Laboratories, New Haven, CT, USA

^c University of Connecticut, Storrs, CT, USA

^d Yale University, New Haven, CT, USA

^e University of Houston, Houston, TX, USA

^f Baylor College of Medicine, Houston, TX, USA

^g Moscow State University, Moscow, Russian Federation

^h Saint-Petersburg State University, Saint-Petersburg, Russian Federation

ⁱ Moscow State University for Psychology and Education, Moscow, Russian Federation

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) Val⁶⁶Met 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 Val⁶⁶Met 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 Val⁶⁶Met 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 Val⁶⁶Met polymorphism on the structure of the developing brain therefore reflects regionally-specific developmental changes in BDNF expression and cortical maturation trajectories.

© 2017 Elsevier B.V. All rights reserved.

1. Introduction

Multiple genes and gene by environment interactions regulate the emerging cognitive abilities in the child's developing brain.

* Corresponding author at: University of Delaware, Linguistics and Cognitive Science, 125 E Main Street, Newark, DE 19716, USA.
E-mail address: jasińska@udel.edu (K.K. Jasińska).

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

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* Val⁶⁶Met 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 Val⁶⁶Met, affects production of the *BDNF* protein [19]. Specifically, this polymorphism results in a single amino acid substitution (valine to methionine) in the pro*BDNF* 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* Val⁶⁶Met 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 Val⁶⁶Met 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 Val⁶⁶Met 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 Val⁶⁶Met 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 Val⁶⁶Met 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* Val⁶⁶Met 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* Val⁶⁶Met 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* Val⁶⁶Met 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 Val⁶⁶Met genotype groups with respect to age, $F(1,76) = 311$, $p = .578$, or gender distribution, $\chi^2(1) = 2.098$, $p = .07$. Table 1 presents summary of the participants' demographics and genotypic status. Further, given reported associations between the Val⁶⁶Met 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 mm³ resolution, however, 14% of the data were acquired using the same sequence under the 1.3 mm³ resolution, which was resampled to 1 mm³ 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 mm². Cortical thickness was computed as the distance between the white and pial 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 mm³ within each segmented region.

2.2.2. DNA collection and analysis

We obtained biological samples from all participants using sterile OrageneTM 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-DemandTM 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-DemandTM SNP Genotyping Assay Mix (assay ID C_11592758_10), 2.0 µl of sterile H₂O and 0.5 µl of Bovine Serum Albumin (BSA). The genotyping call rate was 92%; quality was controlled by regenotyping.

3. Results

3.1. Cortical thickness

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

Table 1
Summary of participants.

	Val homozygotes	Met carriers
<i>n</i>	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)

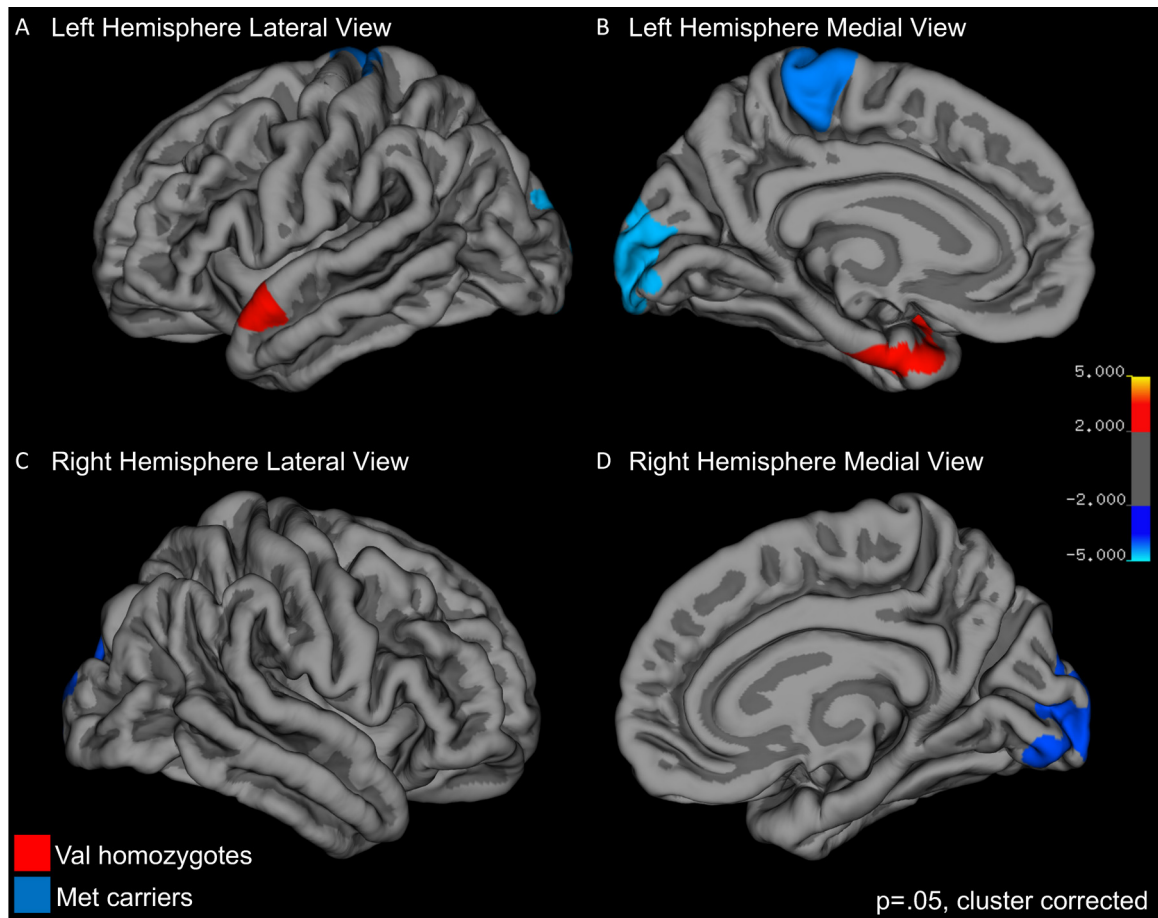


Fig. 1. Group differences in cortical thickness. Greater cortical thickness for Val homozygotes versus Met carriers is noted in red, greater cortical thickness for Met carriers versus Val homozygotes is noted in blue. (For interpretation of the references to color in this figure legend, the reader is 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 mm². Cortical thickness was computed as the distance between the white and pial 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 <i>d</i>
<i>Cortical thickness</i>						
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
<i>Surface area</i>						
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

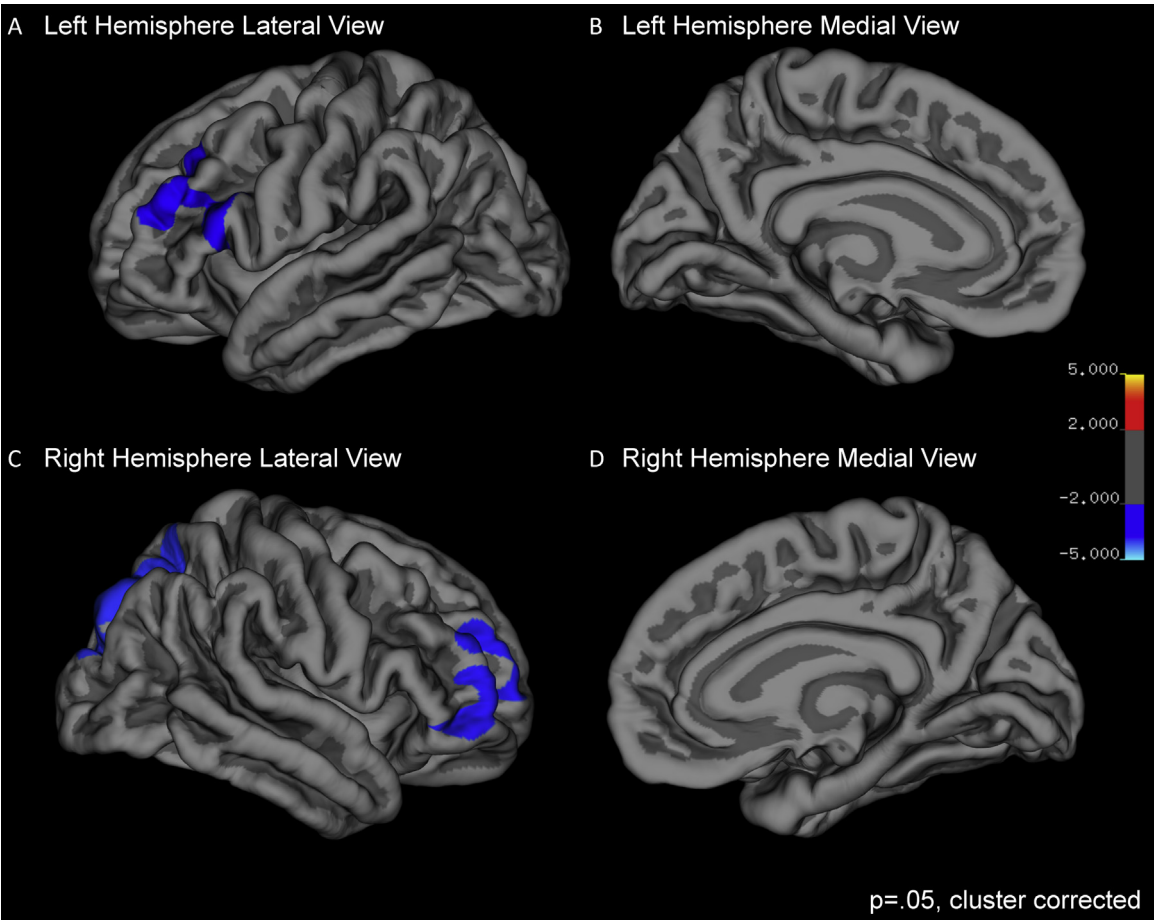


Fig. 2. Group differences in surface area. Greater cortical surface area for Met carriers versus Val homozygotes is noted in blue. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

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 Val⁶⁶Met 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 Val⁶⁶Met *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* Val⁶⁶Met 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* Val⁶⁶Met polymorphism, in particular in the prefrontal cortex, parietal lobes, lateral occipital area, and the hippocampus.

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).

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		

4.1.2. 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* Val⁶⁶Met 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* Val⁶⁶Met 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 Val⁶⁶Met 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 HD001994 (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.

References

- [1] M.V. Alfimova, G.I. Korovaitseva, T.V. Lezheiko, V.E. Golimbet, Effect of *BDNF* Val66Met polymorphism on normal variability of executive functions, *Bull. Exp. Biol. Med.* 152 (2012) 606–609.
- [2] M. Balconi, Dorsolateral prefrontal cortex, working memory and episodic memory processes: insight through transcranial magnetic stimulation techniques, *Neurosci. Bull.* 29 (2013) 381–389.
- [3] Z.C. Baquet, J.A. Gorski, K.R. Jones, Early striatal dendrite deficits followed by neuron loss with advanced age in the absence of anterograde cortical brain-derived neurotrophic factor, *J. Neurosci.* 24 (2004) 4250–4258.
- [4] T. Bartsch, S. Arzy, Human Memory: Insights into Hippocampal Networks in Epilepsy, 2014.
- [5] K.G. Bath, F.S. Lee, Variant *BDNF* (Val66Met) impact on brain structure and function, *Cognit. Affect. Behav. Neurosci.* 6 (2006) 79–85.
- [6] J.R. Binder, R.H. Desai, W.W. Graves, L.L. Conant, Where is the semantic system? A critical review and meta-analysis of 120 functional neuroimaging studies, *Cereb. Cortex* 19 (2009) 2767–2796.
- [7] M.F. Bonner, A.R. Price, Where is the anterior temporal lobe and what does it do? *J. Neurosci.* 33 (2013) 4213–4215.
- [8] S. Bookheimer, Functional MRI of language: new approaches to understanding the cortical organization of semantic processing, *Annu. Rev. Neurosci.* 25 (2002) 151–188.
- [9] S.J. Brooks, E.K. Nilsson, J.A. Jacobsson, D.J. Stein, R. Fredriksson, L. Lind, H.B. Schiöth, *BDNF* polymorphisms are linked to poorer working memory performance, reduced cerebellar and hippocampal volumes and differences in prefrontal cortex in a Swedish elderly population, *PLOS ONE* 9 (2014).
- [10] D. Caplan, Functional neuroimaging studies of syntactic processing, *J. Psycholinguist. Res.* 30 (2001) 297–320.
- [11] C.C. Chen, C.J. Chen, D. Wu, N.F. Chi, P.C. Chen, Y.P. Liao, H.W. Chiu, C.J. Hu, *BDNF* Val66Met polymorphism on functional MRI during n-back working memory tasks, *Medicine (Baltimore)* 94 (2015) e1586.
- [12] J. Chen, T. Kitanishi, T. Ikeda, N. Matsuki, M.K. Yamada, Contextual learning induces an increase in the number of hippocampal CA1 neurons expressing high levels of *BDNF*, *Neurobiol. Learn. Mem.* 88 (2007) 409–415.
- [13] H. Chertkow, D. Bub, C. Deaudo, V. Whitehead, On the status of object concepts in aphasia, *Brain Lang.* 58 (1997) 203–232.
- [14] F. Chouinard-Decorte, D.R. McKay, A. Reid, B. Khundrakpam, L. Zhao, S. Karama, P. Rioux, E. Sprooten, E. Knowles, J.W. Kent Jr., J.E. Curran, H.H. Goring, T.D. Dyer, R.L. Olvera, P. Kochunov, R. Duggirala, P.T. Fox, L. Almasy, J. Blangero, P. Bellec, A.C. Evans, D.C. Glahn, Heritable changes in regional cortical thickness with age, *Brain Imaging Behav.* 8 (2014) 208–216.
- [15] C. Destrieux, B. Fischl, A. Dale, E. Halgren, Automatic parcellation of human cortical gyri and sulci using standard anatomical nomenclature, *Neuroimage* 53 (2010) 1–15.
- [16] V.V. Dias, S. Brissos, B.N. Frey, A.C. Andreazza, C. Cardoso, F. Kapczynski, Cognitive function and serum levels of brain-derived neurotrophic factor in patients with bipolar disorder, *Bipolar Disord.* 11 (2009) 663–671.
- [17] I. Dincheva, C.E. Glatt, F.S. Lee, Impact of the *BDNF* Val66Met polymorphism on cognition: implications for behavioral genetics, *Neuroscientist* 18 (2012) 439–451.
- [18] C.M. Dodds, R.N. Henson, J. Suckling, K.W. Miskowiak, C. Ooi, R. Tait, F. Soltész, P. Lawrence, G. Bentley, K. Maltby, A. Skeggs, S.R. Miller, S. McHugh, E.T. Bullmore, P.J. Nathan, Effects of the *BDNF* Val66Met polymorphism and met allele load on declarative memory related neural networks, *PLOS ONE* 8 (2013) e74133.
- [19] M.F. Egan, M. Kojima, J.H. Callicott, T.E. Goldberg, B.S. Kolachana, A. Bertolino, E. Zaitsev, B. Gold, D. Goldman, M. Dean, B. Lu, D.R. Weinberger, The *BDNF* Val66Met polymorphism affects activity-dependent secretion of *BDNF* and human memory and hippocampal function, *Cell* 112 (2003) 257–269.
- [20] B. Fischl, A.M. Dale, Measuring the thickness of the human cerebral cortex from magnetic resonance images, *Proc. Natl. Acad. Sci. U. S. A.* 97 (2000) 11050–11055.
- [21] B. Fischl, D.H. Salat, E. Busa, M. Albert, M. Dieterich, C. Haselgrove, A. van der Kouwe, R. Killiany, D. Kennedy, S. Klaveness, A. Montillo, N. Makris, B. Rosen, A.M. Dale, Whole brain segmentation: automated labeling of neuroanatomical structures in the human brain, *Neuron* 33 (2002) 341–355.
- [22] N.J. Forde, L. Ronan, J. Suckling, C. Scanlon, S. Neary, L. Holleran, A. Leemans, R. Tait, C. Rua, P.C. Fletcher, B. Jeurissen, C.M. Dodds, S.R. Miller, E.T. Bullmore, C. McDonald, P.J. Nathan, D.M. Cannon, Structural neuroimaging correlates of allelic variation of the *BDNF* Val66Met polymorphism, *Neuroimage* 90 (2014) 280–289.
- [23] H. Frieledsdorf, K.G. Bath, F. Soliman, J. Difede, B.J. Casey, F.S. Lee, Variant brain-derived neurotrophic factor Val66Met endophenotypes: implications for posttraumatic stress disorder, *Ann. N. Y. Acad. Sci.* 1208 (2010) 150–157.
- [24] E.M. Galloway, N.H. Woo, B. Lu, Persistent neural activity in the prefrontal cortex: a mechanism by which *BDNF* regulates working memory? *Essen. Mem.* 169 (2008) 251–266.
- [25] J.M. Gatt, C.B. Nemeroff, C. Dobson-Stone, R.H. Paul, R.A. Bryant, P.R. Schofield, E. Gordon, A.H. Kemp, L.M. Williams, Interactions between *BDNF* Val66Met polymorphism and early life stress predict brain and arousal pathways to syndromal depression and anxiety, *Mol. Psychiatry* 14 (2009) 681–695.
- [26] L. Gerritsen, I. Tendolkar, B. Franke, A.A. Vasquez, S. Kooijman, J. Buitelaar, G. Fernandez, M. Rijpkema, *BDNF* Val66Met genotype modulates the effect of childhood adversity on subgenual anterior cingulate cortex volume in healthy subjects, *Mol. Psychiatry* 17 (2012) 597–603.
- [27] J.N. Giedd, J. Blumenthal, N.O. Jeffries, F.X. Castellanos, H. Liu, A. Zijdenbos, T. Paus, A.C. Evans, J.L. Rapoport, Brain development during childhood and adolescence: a longitudinal MRI study, *Nat. Neurosci.* 2 (1999) 861–863.
- [28] J.N. Giedd, J.L. Rapoport, Structural MRI of pediatric brain development: what have we learned and where are we going? *Neuron* 67 (2010) 728–734.
- [29] D.J. Hagler Jr., A.P. Saygin, M.I. Sereno, Smoothing and cluster thresholding for cortical surface-based group analysis of fMRI data, *Neuroimage* 33 (2006) 1093–1103.
- [30] J.L. Hanover, Z.J. Huang, S. Tonegawa, M.P. Stryker, Brain-derived neurotrophic factor overexpression induces precocious critical period in mouse visual cortex, *J. Neurosci.* 19 (1999) Rc40.
- [31] N.K. Hansell, M.R. James, D.L. Duffy, A.J. Birley, M. Luciano, G.M. Geffen, M.J. Wright, G.W. Montgomery, N.G. Martin, Effect of the *BDNF* Val66Met polymorphism on working memory in healthy adolescents, *Genes Brain Behav.* 6 (2007) 260–268.
- [32] A.R. Hariri, T.E. Goldberg, V.S. Mattay, B.S. Kolachana, J.H. Callicott, M.F. Egan, D.R. Weinberger, Brain-derived neurotrophic factor Val66Met polymorphism affects human memory-related hippocampal activity and predicts memory performance, *J. Neurosci.* 23 (2003) 6690–6694.
- [33] F. Harrisberger, K. Spalek, R. Smieskova, A. Schmidt, D. Coynel, A. Milnik, M. Fastenrath, V. Freytag, L. Gschwind, A. Walter, T. Vogel, K. Bendfeldt, D.J. de Quervain, A. Papassotiropoulos, S. Borgwardt, The association of the *BDNF* Val66Met polymorphism and the hippocampal volumes in healthy humans: a joint meta-analysis of published and new data, *Neurosci. Biobehav. Res.* 42 (2014) 267–278.
- [34] T. Hashimoto, H. Fukui, H. Takeuchi, S. Yokota, Y. Kikuchi, H. Tomita, Y. Taki, R. Kawashima, Effects of the *BDNF* Val66Met polymorphism on gray matter volume in typically developing children and adolescents, *Cereb. Cortex* 26 (2016) 1795–1803.
- [35] Z.J. Huang, A. Kirkwood, T. Pizzorusso, V. Porciatti, B. Morales, M.F. Bear, L. Maffei, S. Tonegawa, *BDNF* regulates the maturation of inhibition and the critical period of plasticity in mouse visual cortex, *Cell* 98 (1999) 739–755.
- [36] H.E. Hulshoff Pol, H.G. Schnack, D. Posthuma, R.C.W. Mandl, W.F. Baaré, C. van Oel, N.E. van Haren, D.L. Collins, A.C. Evans, K. Amunts, U. Bürgel, K. Zilles, E.

- de Geus, D.I. Boomsma, R.S. Kahn, Genetic contributions to human brain morphology and intelligence, *J. Neurosci.* 26 (2006) 10235–10242.
- [37] A.A. Joshi, N. Lepore, S.H. Joshi, A.D. Lee, M. Barysheva, J.L. Stein, K.L. McMahon, K. Johnson, G.I. de Zubicar, N.G. Martin, M.J. Wright, A.W. Toga, P.M. Thompson, The contribution of genes to cortical thickness and volume, *Neuroreport* 22 (2011) 101–105.
- [38] J.P. Kambeitz, S. Bhattacharyya, L.M. Kambeitz-Ilanovic, I. Valli, D.A. Collier, P. McGuire, Effect of BDNF val(66)met polymorphism on declarative memory and its neural substrate: a meta-analysis, *Neurosci. Biobehav. Rev.* 36 (2012) 2165–2177.
- [39] K. Kauppi, L.G. Nilsson, R. Adolfsson, A. Lundquist, E. Eriksson, L. Nyberg, Decreased medial temporal lobe activation in BDNF (66)Met allele carriers during memory encoding, *Neuropsychologia* 51 (2013) 2462–2468.
- [40] J.J. Knierim, J.P. Neunuebel, S.S. Deshmukh, Functional correlates of the lateral and medial entorhinal cortex: objects, path integration and local–global reference frames, *Philos. Trans. R. Soc. Lond. B: Biol. Sci.* 369 (2014).
- [41] W.S. Kremen, E. Prom-Wormley, M.S. Panizzon, L.T. Eyler, B. Fischl, M.C. Neale, C.E. Franz, M.J. Lyons, J. Pacheco, M.E. Perry, A. Stevens, J.E. Schmitt, M.D. Grant, L.J. Seidman, H.W. Thermenos, M.T. Tsuang, S.A. Eisen, A.M. Dale, C. Fennema-Notestine, Genetic and environmental influences on the size of specific brain regions in midlife: the VETSA MRI study, *Neuroimage* 49 (2010) 1213–1223.
- [42] N. Landi, S.J. Frost, W.E. Mencl, R. Sandak, K.R. Pugh, Neurobiological bases of reading comprehension: insights from neuroimaging studies of word-level and text-level processing in skilled and impaired readers, *Read. Writ. Q.: Overcom. Learn. Difficult.* 29 (2013) 145–167.
- [43] J.Y. Lau, D. Goldman, B. Buzas, C. Hodgkinson, E. Leibenluft, E. Nelson, L. Sankin, D.S. Pine, M. Ernst, BDNF gene polymorphism (Val66Met) predicts amygdala and anterior hippocampus responses to emotional faces in anxious and depressed adolescents, *Neuroimage* 53 (2010) 952–961.
- [44] R.K. Lenroot, J.E. Schmitt, S.J. Ordaz, G.L. Wallace, M.C. Neale, J.P. Lerch, K.S. Kendler, A.C. Evans, J.N. Giedd, Differences in genetic and environmental influences on the human cerebral cortex associated with development during childhood and adolescence, *Hum. Brain Mapp.* 30 (2009) 163–174.
- [45] H.A. Marusak, N. Kuruvadi, A.M. Vila, D.W. Shattuck, S.H. Joshi, A.A. Joshi, P.K. Jella, M.E. Thomason, Interactive effects of BDNF Val66Met genotype and trauma on limbic brain anatomy in childhood, *Eur. Child Adolesc. Psychiatry* (2015).
- [46] K. Matsuo, C. Walss-Bass, F.G. Nery, A.M. Nicoletti, J.P. Hatch, B.N. Frey, E.S. Monkul, G.B. Zunta-Soares, C.L. Bowden, M.A. Escamilla, J.C. Soares, Neuronal correlates of brain-derived neurotrophic factor Val66Met polymorphism and morphometric abnormalities in bipolar disorder, *Neuropsychopharmacology* 34 (2009) 1904–1913.
- [47] M.L. Molendijk, B.A. Bus, P. Spinhoven, A. Kaimatzoglou, R.C. Oude Voshaar, B.W. Penninx, I.M.H. van, B.M. Elzinga, A systematic review and meta-analysis on the association between BDNF val(66)met and hippocampal volume – a genuine effect or a winners curse? *Am. J. Med. Genet. B, Neuropsychiatr. Genet.: Off. Publ. Int. Soc. Psychiatr. Genet.* 159b (2012) 731–740.
- [48] C. Montag, B. Weber, K. Fließbach, C. Elger, M. Reuter, The BDNF Val66Met polymorphism impacts parahippocampal and amygdala volume in healthy humans: incremental support for a genetic risk factor for depression, *Psychol. Med.* 39 (2009) 1831–1839.
- [49] S.J. Mowla, H.F. Farhadi, S. Pareek, J.K. Atwal, S.J. Morris, N.G. Seidah, R.A. Murphy, Biosynthesis and post-translational processing of the precursor to brain-derived neurotrophic factor, *J. Biol. Chem.* 276 (2001) 12660–12666.
- [50] S.C. Mueller, A. Aouidad, E. Gorodetsky, D. Goldman, D.S. Pine, M. Ernst, Gray matter volume in adolescent anxiety: an impact of the brain-derived neurotrophic factor Val(66)Met polymorphism? *J. Am. Acad. Child Adolesc. Psychiatry* 52 (2013) 184–195.
- [51] M.J. Notaras, R.A. Hill, J.A. Gogos, M. van den Buuse, BDNF Val66Met genotype interacts with a history of simulated stress exposure to regulate sensorimotor gating and startle reactivity, *Schizophr. Bull.* (2016).
- [52] D. Palejev, W. Hwang, N. Landi, M. Eastman, S.J. Frost, R.K. Fulbright, J.R. Kidd, K.K. Kidd, G.F. Mason, W.E. Mencl, C. Yrigollen, K.R. Pugh, E.L. Grigorenko, An application of the elastic net for an endophenotype analysis, *Behav. Genet.* 41 (2011) 120–124.
- [53] M.S. Panizzon, C. Fennema-Notestine, L.T. Eyler, T.L. Jernigan, E. Prom-Wormley, M. Neale, K. Jacobson, M.J. Lyons, M.D. Grant, C.E. Franz, H. Xian, M. Tsuang, B. Fischl, L. Seidman, A. Dale, W.S. Kremen, Distinct genetic influences on cortical surface area and cortical thickness, *Cereb. Cortex* 19 (2009) 2728–2735.
- [54] M. Petrides, Lateral prefrontal cortex: architectonic and functional organization, *Philos. Trans. R. Soc. Lond. Ser. B, Biol. Sci.* 360 (2005) 781–795.
- [55] T.L. Petryshen, P.C. Sabeti, K.A. Aldinger, B. Fry, J.B. Fan, S.F. Schaffner, S.G. Wagoner, A.R. Tahl, P. Sklar, Population genetic study of the brain-derived neurotrophic factor (BDNF) gene, *Mol. Psychiatry* 15 (2010) 810–815.
- [56] L. Pezawas, B.A. Verchinski, V.S. Mattay, J.H. Callicott, B.S. Kolachana, R.E. Straub, M.F. Egan, A. Meyer-Lindenberg, D.R. Weinberger, The brain-derived neurotrophic factor val66met polymorphism and variation in human cortical morphology, *J. Neurosci.* 24 (2004) 10099–10102.
- [57] C.J. Price, A review and synthesis of the first 20 years of PET and fMRI studies of heard speech, spoken language and reading, *Neuroimage* 62 (2012) 816–847.
- [58] M.M. Rahman, C.K. Callaghan, C.M. Kerskens, S. Chatterji, S.M. O'Mara, Early hippocampal volume loss as a marker of eventual memory deficits caused by repeated stress, *Sci. Rep.* 6 (2016) 29127.
- [59] T. Riggins, S.L. Blankenship, E. Mulligan, K. Rice, E. Redcay, Developmental differences in relations between episodic memory and hippocampal subregion volume during early childhood, *Child Dev.* 86 (2015) 1710–1718.
- [60] L.M. Rimol, M.S. Panizzon, C. Fennema-Notestine, L.T. Eyler, B. Fischl, C.E. Franz, D.J. Hagler, M.J. Lyons, M.C. Neale, J. Pacheco, M.E. Perry, J.E. Schmitt, M.D. Grant, L.J. Seidman, H.W. Thermenos, M.T. Tsuang, S.A. Eisen, W.S. Kremen, A.M. Dale, Cortical thickness is influenced by regionally specific genetic factors, *Biol. Psychiatry* 67 (2010) 493–499.
- [61] C. Scassellati, R. Zanardini, A. Tiberti, M. Pezzani, V. Valenti, P. Efferdi, E. Filippini, S. Conte, A. Ottolini, M. Gennarelli, L. Bocchio-Chiavetto, Serum brain-derived neurotrophic factor (BDNF) levels in attention deficit-hyperactivity disorder (ADHD), *Eur. Child Adolesc. Psychiatry* 23 (2014) 173–177.
- [62] P. Shaw, D. Greenstein, J. Lerch, L. Clasen, R. Lenroot, N. Gogtay, A. Evans, J. Rapoport, J. Giedd, Intellectual ability and cortical development in children and adolescents, *Nature* 440 (2006) 676–679.
- [63] P. Shaw, N.J. Kabani, J.P. Lerch, K. Eckstrand, R. Lenroot, N. Gogtay, D. Greenstein, L. Clasen, A. Evans, J.L. Rapoport, J.N. Giedd, S.P. Wise, Neurodevelopmental trajectories of the human cerebral cortex, *J. Neurosci.* 28 (2008) 3586–3594.
- [64] S.H. Shim, Y. Hwangbo, Y.J. Kwon, H.Y. Jeong, B.H. Lee, H.J. Lee, Y.K. Kim, Increased levels of plasma brain-derived neurotrophic factor (BDNF) in children with attention deficit-hyperactivity disorder (ADHD), *Prog. Neuro-Psychopharmacol. Biol. Psychiatry* 32 (2008) 1824–1828.
- [65] D.J. Smith, M. Wilkie, G. Smith, R. Wolff, I.C. Reid, W.J. Muir, D.H.R. Blackwood, The Val66Met polymorphism of BDNF is associated with impaired frontal executive function in young adults with recurrent depression, *J. Psychopharmacol. (Oxf.)* 18 (2004) A18.
- [66] X. Song, M. Qian, L. Lv, X. Li, L. Pang, D. Kennedy, S. Hodge, A. Harrington, D. Ziedonis, X. Fan, Decreased cortical thickness in drug naive first episode schizophrenia: in relation to serum levels of BDNF, *J. Psychiatr. Res.* 60 (2015) 22–28.
- [67] E.R. Sowell, P.M. Thompson, C.M. Leonard, S.E. Welcome, E. Kan, A.W. Toga, Longitudinal mapping of cortical thickness and brain growth in normal children, *J. Neurosci.* 24 (2004) 8223–8231.
- [68] K.N. Sterner, A. Weckle, H.T. Chugani, A.L. Tarca, C.C. Sherwood, P.R. Hof, C.W. Kuzawa, A.M. Boddy, A. Abbas, R.L. Raaum, L. Grégoire, L. Lipovich, L.I. Grossman, M. Uddin, M. Goodman, D.E. Wildman, Dynamic gene expression in the human cerebral cortex distinguishes children from adults, *PLoS ONE* 7 (2012) e37714.
- [69] P.R. Szeszkó, R. Lipsky, C. Mentschel, D. Robinson, H. Gunduz-Bruce, S. Sevy, M. Ashtari, B. Napolitano, R.M. Bilder, J.M. Kane, D. Goldman, A.K. Malhotra, Brain-derived neurotrophic factor val66met polymorphism and volume of the hippocampal formation, *Mol. Psychiatry* 10 (2005) 631–636.
- [70] The R Core Team, R: A Language and Environment for Statistical Computing, R Foundation for Statistical Computing, Vienna, Austria, 2013.
- [71] M.E. Thomason, D.J. Yoo, G.H. Glover, I.H. Gotlib, BDNF genotype modulates resting functional connectivity in children, *Front. Hum. Neurosci.* 3 (2009) 55.
- [72] D.K. Thompson, S.J. Wood, L.W. Doyle, S.K. Warfield, G.F. Egan, T.E. Inder, MR-determined hippocampal asymmetry in full-term and preterm neonates, *Hippocampus* 19 (2009) 118–123.
- [73] H. Tost, T. Alam, M. Geramita, C. Rebsch, B. Kolachana, D. Dickinson, B.A. Verchinski, H. Lemaitre, A.S. Barnett, J.W. Trampush, D.R. Weinberger, S. Marengo, Effects of the BDNF Val66Met polymorphism on white matter microstructure in healthy adults, *Neuropsychopharmacology* 38 (2013) 525–532.
- [74] H. Ullman, R. Almeida, T. Klingberg, Structural maturation and brain activity predict future working memory capacity during childhood development, *J. Neurosci.* 34 (2014) 1592–1598.
- [75] N.M. van Strien, N.L. Cappaert, M.P. Witter, The anatomy of memory: an interactive overview of the parahippocampal-hippocampal network, *Nat. Rev. Neurosci.* 10 (2009) 272–282.
- [76] M.J. Webster, M.M. Herman, J.E. Kleinman, C. Shannon Weickert, BDNF and trkB mRNA expression in the hippocampus and temporal cortex during the human lifespan, *Gene Expr. Patterns* 6 (2006) 941–951.
- [77] M.J. Webster, C.S. Weickert, M.M. Herman, J.E. Kleinman, BDNF mRNA expression during postnatal development, maturation and aging of the human prefrontal cortex, *Dev. Brain Res.* 139 (2002) 139–150.
- [78] S.M. Wei, D.P. Eisenberg, P.D. Kohn, J.S. Kippenhan, B.S. Kolachana, D.R. Weinberger, K.F. Berman, Brain-derived neurotrophic factor Val(66)Met polymorphism affects resting regional cerebral blood flow and functional connectivity differentially in women versus men, *J. Neurosci.* 32 (2012) 7074–7081.
- [79] L. Wierenga, M. Langen, S. Ambrosino, S. van Dijk, B. Oranje, S. Durston, Typical development of basal ganglia, hippocampus, amygdala and cerebellum from age 7 to 24, *Neuroimage* 96 (2014) 67–72.
- [80] A.M. Winkler, P. Kochunov, J. Blangero, L. Almasy, K. Zilles, P.T. Fox, R. Duggirala, D.C. Glahn, Cortical thickness or grey matter volume? The importance of selecting the phenotype for imaging genetics studies, *Neuroimage* 53 (2010) 1135–1146.
- [81] X. Yang, P. Liu, J. Sun, G. Wang, F. Zeng, K. Yuan, J. Liu, M. Dong, K.M. von Deneen, W. Qin, J. Tian, Impact of brain-derived neurotrophic factor Val66Met polymorphism on cortical thickness and voxel-based morphometry in healthy Chinese young adults, *PLoS ONE* 7 (2012) e37777.

- [82] Y. Yin, Z. Hou, X. Wang, Y. Sui, Y. Yuan, The BDNF Val66Met polymorphism, resting-state hippocampal functional connectivity and cognitive deficits in acute late-onset depression, *J. Affect. Disord.* 183 (2015) 22–30.
- [83] A.P. Yonelinas, The hippocampus supports high-resolution binding in the service of perception, working memory and long-term memory, *Behav. Brain Res.* 254 (2013) 34–44.
- [84] C.P. Zeni, S. Tramontina, B.W. Aguiar, A. Salatino-Oliveira, G.F. Pheula, M. Hutz, F. Kapczinski, L.A. Rohde, Brain-Derived Neurotrophic Factor in Juvenile Bipolar Disorder and Attention-Deficit Hyperactivity Disorder: differentiation using BDNF serum levels, and Val66Met, *Bipolar Disord.* 14 (2012) 48.
- [85] E. Ziegler, A. Foret, L. Mascetti, V. Muto, A. Le Bourdieu-Shaffii, J. Stender, E. Balteau, V. Dideberg, V. Bours, P. Maquet, C. Phillips, Altered white matter architecture in BDNF met carriers, *PLOS ONE* 8 (2013) e69290.