The *BDNF* Val66Met Polymorphism, Hippocampal Volume and Cognitive Function in Geriatric Depression

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Abstract

Objective—The Val66Met polymorphism of the brain-derived neurotrophic factor (*BDNF*) gene is associated with geriatric depression. In studies of younger adults without depression, met allele carriers exhibit smaller hippocampal volumes and have poorer performance on neuropsychological tests. We examined the relationship between the *BDNF* gene and hippocampal volumes in depressed and non-depressed older individuals and its relationship with memory functions mediated by the hippocampus.

Design—One hundred seventy-six elderly depressed Caucasian participants and eighty-eight non-depressed participants completed clinical assessments, neuropsychological testing and provided blood samples for genotyping. One hundred seventy-three participants also underwent brain Magnetic Resonance Imaging (MRI). Statistical modeling tested the relationship between genotype and hippocampal volume and function while controlling for diagnosis and other covariates.

Results—*BDNF* genotype was not associated with a difference in performance on tests mediated by the hippocampus, including word-list learning, prose recall, non verbal memory, or digit span. After controlling for covariates, *BDNF* genotype was not significantly associated with hippocampal volume ($F_{1, 171} = 1.10$, p=0.30).

Conclusion—Despite different findings in younger populations, the *BDNF* Val66Met polymorphism is not significantly associated with hippocampal volume or function in a geriatric population. We hypothesize that other factors may have a stronger effect on hippocampal structure in older individuals, and that the association between the Val66Met polymorphism and geriatric depression is mediated through other mechanisms.

Keywords

genetic polymorphism; magnetic resonance imaging; depression; hippocampus

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INTRODUCTION

The etiology of depression remains unexplained. In general, depression may be driven by altered neural and emotional response to environmental stimuli, coupled with decreased ability to regulate that emotional response. Neuroimaging studies have revealed structural (1) and functional (2) differences between depressed and normal populations. This work is accompanied by studies investigating contributing factors at the molecular level, such as the neurotrophic model of depression (3), and research at the genetic level that has identified single nucleotide polymorphisms (SNPs) that may be linked with vulnerability to depression (3,4). Since none of these elements on their own has provided a comprehensive understanding of the pathophysiology of depression, exploration of the interplay among neuroanatomic, molecular and genetic factors might be a more productive approach.

Depressed individuals exhibit smaller hippocampal volumes when compared with non-depressed individuals (5), a finding also observed in elderly populations (6), although not always replicated (7,8). Smaller hippocampal volumes in depressed subjects are associated as adverse antidepressant outcomes including a failure to remit (9,10) and greater likelihood of relapse (11). It is possible that genetic differences may explain part of the discrepancy in results of studies examining hippocampal volume in depression. One potentially important contributor is the valine (val) to methionine (met) substitution in the 5' pro-region of the human Brain Derived Neurotropic Factor protein, a result of a functional SNP (Val66Met). The met allele is more common in late life depression (LLD) (12,13) and is associated with smaller hippocampal volumes in healthy adults (14). Studies that have examined the association between the *BDNF* genotype and hippocampal volumes in major depression among younger adults have yielded conflicting results (15,16). A three-way interaction between the *BDNF* genotype, hippocampal volumes and LLD has not yet been studied in a geriatric sample. Besides its relationship with hippocampal volume, *BDNF* genotype is associated with cognitive function, specifically, episodic memory (17–19). These findings are consistent with the role of the hippocampus in memory performance.

Since both hippocampal volume loss and memory deficits are observed in LLD (20,21), we examined if the *BDNF* genotype had an effect on these measures in a mixed population of depressed and healthy elderly subjects. Based on work in younger adult populations, we hypothesized that: 1) depressed elderly who are met allele carriers will have smaller hippocampal volumes; and 2) in a mixed cohort of depressed and healthy elderly participants, those with the val/val genotype will have better cognitive performance on tests specific for hippocampal memory.

METHODS

Sample and clinical evaluation

Subjects were participants in the National Institute of Mental Health Conte Center for the Neuroscience of Depression in Late Life, located at Duke University, Durham, NC. Eligibility was limited to age 60 years or older with a diagnosis of unipolar major depressive disorder. Exclusion criteria included 1) another major psychiatric illness; 2) history of alcohol or drug abuse or dependence; 3) primary neurologic illness, including dementia; 4) illness or medication precluding cognitive testing; and 5) metal in the body precluding magnetic resonance imaging (MRI).

Non-depressed comparison subjects were recruited from the community though the Aging Center Subject Registry at Duke University. Eligible control subjects had a non-focal neurologic examination, no report of neurologic illness, and no evidence of a diagnosis of depression based on the National Institute of Mental Health Diagnostic Interview Schedule

(22). The study protocol was approved by the Duke University Medical Center institutional review board. All subjects provided written informed consent before beginning study procedures.

As we have previously reported differences in Val66Met allele frequency between Caucasian and minority subjects (12), this analysis was limited only to Caucasian subjects. This study included data utilized in other analyses examining the relationship between the *BDNF* Val66Met polymorphism, geriatric depression, and other clinical and neuroimaging findings (12,23). Subjects that did not have either cognition data or hippocampal volume data were not included in these analyses.

A trained interviewer administered the Duke Depression Evaluation Schedule (DDES) (24) to each subject. The DDES, a composite diagnostic interview instrument, includes sections of the National Institute of Mental Health Diagnostic Interview Schedule (22) assessing depression, enriched with items assessing sleep problems and the clinical features of melancholia and psychosis, dysthymia, mania, and alcohol abuse or dependence. Depressed subjects were evaluated by a geriatric psychiatrist. If they had a diagnosis of dementia or met criteria for dementia on clinical exam, they were excluded from the study. Additionally, all participants completed the Mini Mental State Examination (25). Participants with a MMSE <25 were excluded from the study to further rule out possible dementia.

Genotyping

Fresh blood samples were obtained from all participants and DNA was extracted and stored according to methods and quality checks previously reported (26). An aliquot of DNA was used for genotyping of the *BDNF* Val66Met polymorphism. DNA samples were placed in 96-well plates together with no-template controls and four sample duplicates in an asymmetric pattern to avoid unintended plate switching. DNA was polymerase chain reaction-amplified applying a Taqman by-design assay (Applied Biosystems) that recognized the single nucleotide polymorphism, which defines the Val66Met polymorphism (rs6265). The samples were examined with an ABI7900 DNA analyzer (Applied Biosystems) and the genotypes determined with the SDS software package (Applied Biosystems). Greater than 95% genotyping efficiency was required before data were submitted for further analysis.

Neuropsychological testing

We selected measures that we expected to be relatively specific for hippocampal function. These tests were part of a larger neuropsychological battery that is described in detail elsewhere (27). Neuropsychological tests included Word List Memory and Delayed Constructional Praxis from the Consortium to Establish a Registry in Alzheimer's disease (CERAD) battery (28,29). Word List Memory composed of immediate recall of three learning trials of a 10-item word list, delayed recall of the list, and recognition/ discrimination of target words from non-target foils. In addition to the variables that were directly assessed, we also calculated a percent retained variable (delayed trial / trial 3×100), and a summary score of words provided during recall trials that were not actually presented, which were labeled as intrusion errors. Delayed Praxis Recall assesses memory for 4 drawings copied prior to an intervening task. Immediate and delayed prose recall was assessed with the Logical Memory subtest of the Wechsler Memory Scale-Revised (30), including percent retained (Logical Memory delayed / Logical Memory immediate $\times 100$). Visual immediate memory was assessed by the Benton Visual Retention Test (31), and short-term working memory span was assessed by the Digit Span subtest of the Wechsler Adult Intelligence Scale-Revised (32).

MRI acquisition and analysis

All subjects were screened for any condition where MRI was contraindicated, then imaged with a 1.5-T, whole body MRI system (Signa; GE Medical Systems, Milwaukee, Wis) using the standard head (volumetric) radiofrequency coil. Two sets of dual-echo, fast spin-echo acquisitions were obtained: one in the axial plane for morphometry of cerebral structures and another in a coronal oblique plane for segmentation of the hippocampus. The pulse sequence parameters were repetition time = 4000 milliseconds, echo time = 30 and 135 milliseconds, 32-kHz (±16-kHz) full-imaging bandwidth, echo train length = 16, a 256_256 matrix, 3-mm section thickness, 1 number of excitations, and a 20-cm field of view. The images were acquired in 2 separate acquisitions with a 3-mm gap between sections for each acquisition. The second acquisition was offset by 3-mm from the first so that the resulting data set consisted of contiguous sections. For the near coronal acquisition, the localizer scan was used to prescribe oblique, near coronal images perpendicular to the axis of the temporal pole, covering the entire brain from just anterior of the temporal lobe to a plane posterior to the lateral ventricles.

Methods for delineating the hippocampus and anatomic boundaries of the hippocampus and the GRID program used to quantify the volume of the hippocampus have been previously described (6). The GRID program allows for semi automated determination of region of interest volumes and was based on a manual point-counting method (33). Methods for measuring total cerebral volume have also been previously reported (34), and this composite measure was defined as total white matter, total gray matter, and cerebrospinal fluid volumes in both cerebral hemispheres.

Our primary outcome measure in the MRI scans was the total hippocampal volume in right and left hemispheres. We corrected for side and cerebral volume in the analysis stage. Three image analysts received extensive training and completed reliability assessments before being approved to process study data. Reliability procedures included repeated processing of scans (n=9 for hippocampus; n=10 for cerebrum) no less than one week apart. Intraclass correlation coefficients attained were: left hippocampus = 0.8, right hippocampus = 0.7, and total cerebral volume = 0.997.

Analytic Strategy

Due to the small number of Met66 homozygous individuals (12), Met66 carriers were grouped together and compared with Val66 homozygotes. All analyses were conducted using SAS 9.1 (Cary, NC). Diagnosis-based and genotype-based differences in demographic variables were tested using pooled, two-tailed t tests for continuous variables and chi square tests for categorical variables. Satterthwaite t-tests were used for continuous variables with unequal variances. The relationship between BDNF genotype and hippocampal volume was analyzed using a mixed model with hippocampal volume as the dependent variable and hemisphere (left or right) as a covariate. In this model, we also adjusted for cerebral volume, diagnosis of depression, age and sex.

To examine the interaction between the genotype and cognitive function, we created models for each neuropsychological test measure where the test result was the dependent variable and Val66Met genotype, presence or absence of depression, education and age were independent variables. For all of these models, we initially tested for a gene-diagnosis interaction, and this interaction term was removed and the model rerun if it did not reach statistical significance. In a subset of the participants who had both neuropsychological test measures as well as hippocampal volume data, we tested for a relationship between hippocampal volume and test performance. For this approach, we added total hippocampal volume as an additional independent variable to the model described above.

RESULTS

Sample Characteristics

A total of 264 subjects were included in the analyses. 176 had a diagnosis of depression and 88 were non-depressed control subjects. Diagnostic groups did not differ by age or sex, however non-depressed subjects were more educated and had higher MMSE scores (Table 1). The depressed group had a mean Montgomery-Asberg Depression Rating score of 26.2 (SD = 7.31; range 6–53) and a mean age of onset of first depressive episode of 44.73.

In this sample, 171 subjects were val/val homozygotes, while the other 93 subjects were met allele carriers. There were no significant differences between genotypes in age, sex, education or MMSE scores on univariate analysis. As previously reported (12), depressed subjects were more likely than non-depressed subjects to be Met66 allele carriers. Comparisons of hippocampal volumes not adjusted for cerebral volume found no difference between either diagnostic or genotype groups.

BDNF Genotype and Cognitive Function

All 264 subjects underwent neuropsychological testing, but not all of them completed every test. The number of participants for each test and test results by genotype are displayed in Table 2. In general, depressed subjects performed more poorly than nondepressed subjects. Table 2 displays statistically analyses testing for differences in cognition based on genotype and diagnoses. These are derived from models examining each cognitive measure as the dependent variable, with age, education, *BDNF* genotype, and depression diagnosis as independent variables.

After controlling for these covariates, none of the test results were significantly associated with *BDNF* genotype (Table 2). Although we present data from models without interaction terms, we initially included a genotype by diagnosis interaction within each model. This was removed from the models as it did not reach statistical significance in any model, with one exception. This interaction reached statistical significance for only one test: word list intrusions ($F_{1, 263} = 7.00$, p = 0.0087). To further explore this interaction, we compared covariate adjusted means across groups. The only statistically significant difference observed was between the met carrier depressed subjects and met carrier nondepressed subjects (met/depressed = 0.84; met/nondepressed = 0.21; p = 0.0209). None of the other group comparisons (val/depressed = 0.73, val/nondepressed = 0.53) reached a level of statistical significance. We applied a Bonferroni correction for the multiple neuropsychological test comparisons, which lowered the alpha to 0.0042. At that alpha, the interaction was no longer statistically significant.

BDNF Genotype and Hippocampal Volume

173 study participants had hippocampal volume data. This lower number is because the MR sequence required for measurement of hippocampal volume was inadvertently omitted during a specific study interval, and because some subjects had MRI scans that were not processable. Of these 173 participants, 116 were depressed and 57 were non-depressed subjects, and 106 were val/val homozygous while 67 were met allele carriers.

There was no significant difference in the total hippocampal volume among the val/val homozygous individuals when compared with the met allele carriers (t = −1.39, p = 0.17). In a mixed model procedure with cerebral volume, diagnosis of depression, age and sex as cofactors, *BDNF* was not significantly associated with hippocampal volume ($F_{1, 171} = 1.10$, p = 0.30). In this model, there was no significant interaction between depression and

hippocampal volume ($F_{1, 171} = 0.66$, $p = 0.42$) however, age was significantly related to hippocampal volume ($F_{1, 171} = 4.91$, $p = 0.03$).

We also incorporated hippocampal volume into models examining genotype effects on task performance. After controlling for presence of depression, *BDNF* genotype, age, education and cerebral volume, and correcting for multiple comparisons, there were no statistically significant relationships between hippocampal volume and the neuropsychological measures (data not shown). *BDNF* test performance relationships did not change after adding hippocampal volume to the models.

DISCUSSION

Our study examined the effect of the *BDNF* Val66Met genotype on hippocampal structure and function in an elderly cohort of depressed and nondepressed subjects. After controlling for covariates and accounting for the number of comparisons, we did not find a statistically significant relationship between this polymorphism and either hippocampal volume or hippocampally-mediated cognitive function.

To our knowledge, this is the first study examining the relationship between the *BDNF* genotype, hippocampal volume, cognition, and depression in an elderly cohort. In healthy populations, the met allele has been shown to be associated with significantly smaller hippocampal volumes (14,35). In a mixed cohort of depressed and nondepressed individuals in a younger population, a significant interaction was found between the genotype and hippocampal volumes; however, this was independent of the diagnosis of depression (15). A more recent study that attempted to replicate these results in a larger sample did not show an interaction between the *BDNF* genotype, hippocampal volume and depression (16). Further, this study did not find a significant difference in hippocampal volumes among the healthy populations unlike some other studies. However, the other studies looked at non depressed populations (35) or those with other psychiatric illnesses like schizophrenia (36).

Similar to Jessen et al., we did not find a difference in hippocampal volumes based on *BDNF* genotype (16). An explanation for such mixed results could be differences in the etiologies of depression, some of which may not be associated with hippocampal changes through *BDNF*. Alternatively, comorbid conditions observed in LLD may obfuscate this relationship, so *BDNF* genotype may be related to hippocampal volume, but this effect may become less apparent in older individuals due to age related changes or co-morbid diseases affecting the morphology of the brain (37). Examples of such confounding issues include stroke, which is also associated with depression, (38,39) and Alzheimer's disease. Though we excluded those with AD at entry, neuroanatomic changes can precede clinical symptoms which will be picked up only in longitudinal studies.

Another potential confounding factor is concomitant antidepressant use. In our study, all depressed subjects exhibited depressive symptoms and met diagnostic criteria for Major Depressive Disorder at the time of enrollment. They were treated after enrollment by a study algorithm. We do not have specific information about antidepressant use at study entry and this is a limitation. Antidepressant treatment has been shown to be associated with increased *BDNF* expression in the hippocampus (40) and may by itself prevent a decrease in hippocampal volume (41) and the relationship between depression and hippocampal volume could be lost with lifetime exposure to antidepressants. The ability of the hippocampal cells to regenerate might even be a mechanism which predicts response to antidepressants (10). It is unclear if ineffective antidepressant treatment affects hippocampal volume, as recent work suggests that nonremission is associated with greater decreases in hippocampal volume, even in context of antidepressant use (42). The theories of *BDNF* expression are related to

serum BDNF however, a direct relationship between the *BDNF* gene and serum BDNF levels has been negative (43). Although antidepressants can increase serum BDNF levels (44), so can diet and exercise (45). These relationships should be examined further in future studies.

Performance on memory tests was not significantly different by *BDNF* genotype. This is inconsistent with other studies conducted among healthy individuals, in which met allele carriers performed poorly in all cognitive domains (19). Functional neuroimaging during declarative memory tasks revealed decreased hippocampal activity during encoding and retrieval in healthy met allele carriers (46). Since both emotional stress, such as depression, and antidepressant treatments are tied with the regulation of *BDNF* and hippocampal activity, the differences between the genotypes might be lost in this cohort of mixed depressed and healthy participants. Another explanation could be differences produced by variation in the cognitive measures used in different studies. Like the current study, most cognitive studies of BDNF have focused on the links between memory and the hippocampus; however, recent studies suggest that other cognitive domains may be adversely affected by the *BDNF* genotype (19,47). Additional studies are needed to replicate the relationship of this polymorphism to broader cognitive deficits, with attention to the neural pathways that account for these associations.

Other genes associated with differences in cognition such as apolipoprotein E (*APOE*) (48,49) and Catechol-o-methyl transferase (*COMT*) (50) might also alter results, though these interactions were not examined in this study. Potential gene-gene interactions need to be considered, as one gene's effect may be modulated by other genes. For example, a recent study found that the *5HTTLPR* gene's effect on the amygdala and the subgenual portion of the anterior cingulate volume was observed only in individuals who were *BDNF* val/val homozygous (51).

Unlike findings in non-geriatric adult populations, we did not find the hypothesized differences in hippocampal volumes and memory performance based on *BDNF* Val66Met genotype. Based on our results, we postulate that factors other than the *BDNF* gene might play a greater role in modulating both of the above. Further, the association between the *BDNF* genotype and LLD might be mediated through other phenomenon. One such mechanism has been illustrated by the association between the incidence of depression and stroke being found to increase incrementally with increasing numbers of met alleles (39). The direct effects of the *BDNF* gene on depression have been inconsistent and it has been suggested that the neurotrophic model like the monoamine model before it, be reexamined as its effects might be more divergent than we currently accept (52). Further research into more widespread effects of this polymorphism is warranted, including genetic influences on psychosocial realms (23) which also play an important role in mood disorders.

One of the limitations of this study is its case-control model with unequal numbers of gene frequencies. We could not test for a dose-dependent relationship between the Val66Met polymorphism and all three genotype groups; given the lower frequency of the homozygous met/met genotype, such a strategy will require a larger sample. We also considered the diagnosis of depression as a categorical rather than continuous variable, as MADRS data were not available for nondepressed subjects, whereby we might have lost some information. We included only a Caucasian sample for analysis in this study to due differences in gene frequencies in different racial populations, thus limiting its generalizability. This however, is not unique to our study and future studies should examine the differences between common ethnicities in the US. Further, the imaging protocol used on this study is relatively old and there may be some heterogeneity of data due to multiple

analysts. Another possible explanation for the negative finding is the lack of power to detect a difference; however, this may be less likely given this study's relatively large sample size.

In this case-control study of elderly subjects, we found no relationship between Val66Met genotype and hippocampal structure or cognitive performance thought to be mediated by the hippocampus. Though both hypotheses proposed at the beginning of the study were rejected in our analyses, this study adds significantly to the current literature by systematically exploring possible interactions that might play a role in the pathophysiology of geriatric depression. Future studies should explore other mechanisms through which BDNF genotype regulates mood as our study like others found that more participants in the met allele cohort were depressed.

Acknowledgments

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Table 1

Demographic and clinical characteristics by diagnosis and genotype

	Depressed N=176	Non depressed N=88	df	Test Statistic	p value
BDNF genotype			1	$x^2=7.47$	0.01
Val/Val	104	67			
Val/Met and Met/met	72	21			
Age, y	69.07(7.02)	70.13(5.60)	212	t=1.32	0.19
Sex (percent female)	62.50	70.45	1	$x^2=1.64$	0.20
Education	14.44(3.13)	16.13(2.35)	223	t=4.89	<0.0001
MMSE	28.24(2.15)	29.13(1.02)	247	t=4.46	<0.0001
Left Hippocampal Volume $_{n=173}$	2.99(0.43)	2.98((0.46)	171	t=−0.19	0.85
Right Hippocampal Volume $_{n=173}$	3.10((0.39)	3.14((0.45)	171	t= 0.70	0.49
Total Cerebral volume $_{n=173}$	1158.1(135.95)	1150.8(121.96)	171	t=−0.35	0.73
BDNF Genotype					
	Val/Val N= 171	Val/met and Met/met N=93	df	Test statistic	p value
Percent depressed	60.82(104/171)	70.42(72/93)	1	$x^2=7.47$	0.01
Age	69.84(6.72)	68.67(6.31)	262	t= 1.38	0.17
Sex (percent female)	62.57	69.89	1	$x^2=1.42$	0.23
Education	15.16(2.91)	14.72(3.14)	262	t= 1.13	0.26
MMSE $_{n = 251}$	28.63(1.84)	28.39(1.98)	249	t= 0.96	0.34
Age of onset of depression $_{n=173}$	46.06 (19.99)	43.39 (20.52)	171	t= 0.85	0.39
Left Hippocampal volume $_{n=173}$	2.94 (0.43)	3.05 (0.44)	171	t= −1.69	0.09
Right Hippocampal volume $_{n=173}$	3.09 (0.43)	3.15 (0.39)	171	t= −0.85	0.40
Total cerebral volume $_{n=173}$	1146.7 (128.33)	1169.9 (135.36)	171	t=−1.13	0.26

Data presented as mean (SD). Age and education presented in years, MRI measures in milliliters. All comparisons between categorical variables made using the x2 test, and comparisons of continuous variables made using pooled, two-tailed t-tests except for comparisons of age, MMSE, and education between depressed and non-depressed subjects, which required the Satterthwaite t-test for unequal variances.

Table 2

Effect of *BDNF* Val66Met genotype and Depression on neuropsychological test measures.

Task n	Mean test score by genotype		Effect of *BDNF* genotype		Effect of Depression	
	Val/Val n=171	Val/Met n=93	F	p	F	p
Word recall -immediate	19.52(4.53)	18.88 (5.15)	0.06	0.80	31.4	<0.0001
Word recall - delayed	6.49(2.22)	6.40(2.54)	0.18	0.67	26.5	<0.0001
Word recall % retained 169/90	82.93 (22.55)	83.15(28.53)	0.12	0.73	4.27	0.04
Word recall intrusions	0.60(1.05)	0.70(1.18)	0.34	0.56	0.04	0.851
Word List Recognition	19.37(1.27)	19.22(1.63)	0.20	0.66	11.3	0.0009
Logical Memory Immediate 170/93	25.58(8.29)	24.47(9.11)	0.09	0.76	20.33	<0.0001
Logical Memory Delayed 170/92	21.61(9.21)	20.37(10.24)	0.11	0.74	18.24	<0.0001
Logical Memory % retained 170/92	80.17(21.30)	78.21(21.78)	0.04	0.84	7.07	0.0083
Visual Retention Test 170/90	6.05(1.96)	5.60 (2.13)	2.82	0.94	18.81	<0.0001
Praxis Recall 171/92	8.29(2.53)	8.09(2.63)	0.01	0.92	12.71	0.0004
Digit Span Forward 149/78	8.80(2.34)	8.42(2.32)	1.53	0.22	0.78	0.378
Digit Span Backward 149/77	7.11(2.25)	7.45(2.69)	0.86	0.36	3.06	0.081

n= number of people who completed each task, listed as val/val homozygotes / met allele carriers. If no value is listed, then the entire sample of 171 val/val homozygous individuals and 93 met allele carriers had data for that task. Data presented as mean (standard deviation). Statistical results derived from models where task performance was the dependent variable and *BDNF* genotype an independent variable, also controlling for diagnosis of depression, age, and education. The effect of depression was controlled for age, education and *BDNF*.