Published in final edited form as:

Psychogeriatrics. 2013 December ; 13(4): . doi:10.1111/psyg.12013.

Brain-Derived Neurotrophic Factor Val66Met Polymorphism and Cognitive Function in Persons with Cardiovascular Disease

Ashley J. Szabo, M.A.¹, Michael L. Alosco, B.A.¹, Lindsay A. Miller, M.A.¹, John E. McGeary, Ph.D.^{2,3}, Athena Poppas, M.D.⁴, Ronald A. Cohen^{2,5}, and John Gunstad, Ph.D.¹

¹Department of Psychology, Kent State University, Kent, OH, USA

²Department of Psychiatry and Human Behavior, Brown Medical School, Providence, RI

³Research Service, Providence VA Medical Center, Providence, RI

⁴Department of Cardiology, Rhode Island Medical Center, Providence, RI

⁵Departments of Neurology Psychiatry and the Institute on Aging, Center for Cognitive Aging and Memory, University of Florida

Abstract

Background—Cognitive impairment is common among persons with cardiovascular disease (CVD) and several potential etiological mechanisms have been described, including contributions of genetic markers such as variations in the brain-derived neurotrophic (*BDNF*) gene. The current study examined the associations of *BDNF* genotype with cognitive function among individuals with CVD.

Methods—110 participants with CVD completed a comprehensive neuropsychological battery that assessed global cognitive function, attention/executive function, memory, language, and visuospatial abilities. All participants also underwent blood draw to provide a DNA sample that was used to determine *BDNF* genotype. Carriers of either one or two copies of the MET allele of *BDNF* were categorized into one group (N = 33), while non-carriers were categorized into a second group (N = 77).

Results—After adjustment for demographic and medical characteristics, hierarchical regression analyses revealed persons with one or more Met alleles displayed better performance than Val/Val individuals for attention/executive function ($\beta = .22, p = .047$), memory ($\beta = .25, p = .03$) and a trend for language ($\beta = .19, p = .08$) and visuospatial abilities ($\beta = .21, p = .06$).

Conclusions—*BDNF* VAL66MET had little impact on cognitive functioning in a sample of older adults with CVD and significant findings were actually opposite of that predicted by past work. Future work is much needed to clarify the mechanisms for these findings, particularly studies examining both circulating *BDNF* levels and genetic variation in the *BDNF* gene and cognitive function over time.

Keywords

BDNF; cardiovascular disease; cognitive function; genetics; MET allele

1. Introduction

Cardiovascular disease (CVD) is the second leading cause of disability in older adults and is associated with reduced functional independence.¹ An identified contributor to poor outcomes in this population is cognitive impairment.² Indeed, CVD is an independent risk factor for significant neurological conditions including stroke, dementia, and Alzheimer's disease.³ Preceding these conditions, CVD patients also display milder deficits across multiple cognitive domains, including attention, executive function, and memory.⁴⁻⁶

Several mechanisms for the relationship between CVD and cognitive impairment in non-demented populations have been described, including structural brain changes, reduced cerebral perfusion, and systemic inflammation.⁷⁻¹⁶ However, these mechanisms do not fully explain this relationship and new potential mechanisms need to be examined.

Recent work has identified genetic factors that may contribute to cognitive impairment in CVD, including the brain-derived neurotrophic factor (*BDNF*) gene, which has been implicated in neurological and medical conditions such as Alzheimer's disease, schizophrenia, bipolar disorder, and type 2 diabetes.¹⁷ *BDNF*, located on chromosome 11p13 (NCBI), produces a small dimeric protein that is a nerve growth factor commonly found in the hippocampus.¹⁸ Egan and colleagues (2003)¹⁹ showed that the Val66Met substitution impacted activity-dependent serum levels of BDNF, such that the MET allele produces lower amounts of serum BDNF than the VAL allele. Furthermore, the MET allele creates a BDNF protein that is less effective than the VAL allele and thus cannot provide the level of neuronal support necessary.^{17,20} Carriers of the MET allele showed reduced secretion of BDNF over time and poorer cognitive functioning.²⁰ Persons with one or two MET alleles also have reduced cognitive functioning on various tasks, including processing speed, delayed recall, general intelligence, episodic memory, digital working memory, spatial localization, and verbal recall.^{19,21-23}

Beyond these findings, there also appears to be possible sex differences in the effect of BDNF on cognitive function. Indeed, there is extant evidence demonstrating women to exhibit elevated levels of BDNF compared to men.^{24,25} This is noteworthy, as one study found that women but not men with higher BDNF plasma levels demonstrate deficits on neuropsychological tests of global cognitive function, memory, and language.²⁵ Consistent with this pattern, past work has also found a significant association between the BDNF MET allele and Alzheimer's disease risk for women, but not men.²⁶

Based on the above findings, the investigation of the possible contribution of the *BDNF* gene to cognitive function in CVD is warranted. It was hypothesized that individuals with one or two MET alleles would have overall lower cognitive functioning than VAL/VAL individuals, particularly on tests of general cognition, memory, attention, and language. Exploratory analyses were also conducted to identify possible sex differences.

2. Methods

These study methods were approved by the appropriate Internal Review Boards and all participants provided written informed consent prior to participation.

2.1 Participants

110 participants were recruited from outpatient cardiology clinics. Individuals were eligible if they were between the ages of 55 and 85, were native English speakers, and had one or more of the following: myocardial infarction, cardiac surgery, heart failure, coronary artery disease, or hypertension. Prior to study entry, all patients were screened for neurological and

psychiatric conditions that may influence cognitive function. Specifically, individuals were precluded from study entry if they had a history of neurological disorders, such as a stroke or Alzheimer's disease, or major psychological disorders such as schizophrenia to minimize potential confounds.

Of these participants, 59.1% (N = 65) were male. The mean age of participants was 68.03 (SD = 7.55) and the mean years of education was 14.33 (SD=2.61). Participants were separated into two groups based on BDNF genotype: Val/Val homozygotes (N=77) and those with one or more Met alleles (Val/Met and Met/Met; N=33). See Table 1 for demographic and medical characteristics.

2.2 Procedure

Participants underwent a blood draw to obtain a DNA sample that was used assess *BDNF* genotype and a comprehensive battery of neuropsychological tests. Medical and demographic characteristics were ascertained through self-report and medical record review.

2.3 Measures

2.3.1 Genotyping

Single nucleotide polymorphism (SNP) Genotyping: All SNP determinations were performed using the fluorogenic 5'nuclease (Taqman, Applied Biosystems, Foster City, CA) method using reagents (VIC(tm) and FAM(tm) labeled probes and TaqMan® Universal PCR Master Mix without AMPerase® UNG) obtained from Applied Biosystems (ABI). Unlabeled forward and reverse primers were purchased from ABI or Integrated DNA Technologies (Coralville, IA). All reactions were performed in an ABI Prism 7300 Sequence Detection System using both absolute quantification and allelic discrimination modes as described by Livak (1995).²⁷ The assay ID number for rs6265 (*BDNF*) is C_11592758. Genotype distributions did not significantly vary from Hardy Weinberg equilibrium ($X^2 = 0.31$, $p = 0.58$).

2.3.2 Neuropsychological Tests—All neuropsychological tests used in the current study demonstrate strong psychometric properties, including excellent reliability and validity. The domains and neuropsychological tests administered are as follows:

- Global Cognitive Function: Mini-Mental Status Exam,²⁸ Dementia Rating Scale²⁹
- Attention/executive function: Trail Making Test B,³⁰ Digit Symbol Coding,³¹ Stroop Color-Word Test^{32,33}
- Memory: Complex Figure Test Immediate and Long Delay Recall³⁴
- Language: Boston Naming Test,³⁵ Controlled Oral Word Association Test,^{36,37} Animal Naming³⁸
- Visuospatial: Hooper Visual Organization Test,³⁹ Block Design,³¹ Complex Figure Test-Copy³⁴

2.4 Statistical Analyses

Composite scores for global functioning, attention/executive function, memory, language, and visuospatial ability were created and consisted of the means of the raw scores within each cognitive domain. To maintain directionality for attention/executive function, scores for neuropsychological tests measured in units of time (i.e., Trail Making Test B) were multiplied by -1 so that lower scores reflect worse performance. Demographic variables and medical conditions were compared across Val66Met groups to identify possible confounds

using t-tests or chi-square analyses. Results indicated no between group differences (see Table 1).

To examine the independent association between *BDNF* polymorphism (0 = ValVal homozygote; 1 = ValMet/MetMet) on cognitive function a series of multivariable hierarchical regression analyses was performed with composite scores for global functioning, attention/executive function, memory, language, and visuospatial ability as the dependent variables. To account for the known influence of demographic and medical factors on cognitive function, age, sex (1 = male; 2 = female), years of education, and diagnostic history of arrhythmia, hypertension, and elevated total cholesterol were entered in block 1. Finally, the *BDNF* polymorphism was entered into the second block of each model to determine whether persons with one or more copy of the Met allele (ValMet or MetMet) performed worse on neuropsychological test performance than those with the ValVal homozygote. Finally, exploratory MANOVAs were then conducted to examine whether there are sex differences in *BDNF* and cognitive function in persons with CVD. In light of the exploratory nature of these analyses, they were not adjusted for demographic and medical factors.

3. Results

Neuropsychological Differences Between *BDNF* Groups

Table 2 displays raw neuropsychological test performance in the current sample. After controlling for age, sex, years of education, and history of cardiac arrhythmia, hypertension, and elevated total cholesterol the *BDNF* genotype demonstrated significant associations with attention/executive function ($\beta = .22, p = .047$) and memory ($\beta = .25, p = .03$) and a trend for language ($\beta = .19, p = .08$) and visuospatial abilities ($\beta = .21, p = .06$). Contrary to expectations and past work, persons with one or more MET alleles performed better on measures assessing these domains than Val/Val individuals. No such pattern emerged for global functioning. Table 3 displays a full summary of hierarchical regression analyses, including the effect of demographic and medical characteristics on cognitive function.

Sex Differences in *BDNF*-related cognitive differences

To examine the possibility of gender effects in the current sample, MANOVA analyses were conducted separately for men and women to examine differences on neuropsychological test performance between ValVal persons and those with at least one copy of the Met allele (ValMet or MetMet). No group differences emerged for women for global functioning [$\lambda = 0.10, F(2, 42) = 2.37, p = 0.11$], attention/executive function [$\lambda = 0.09, F(3, 41) = .96, p = 0.27$], memory [$\lambda = 0.08, F(2, 42) = 1.81, p = 0.18$], language [$\lambda = 0.43, F(3, 41) = 0.61, p = 0.61$], or visuospatial ability [$\lambda = 0.05, F(3, 41) = 0.69, p = 0.57$].

There were also no between group differences for any of the cognitive domain for males: Global functioning, [$\lambda = 0.03, F(2, 62) = 0.86, p = 0.43$], memory [$\lambda = 0.88, F(2, 62) = 3.01, p = 0.06$], attention/executive function [$\lambda = 0.07, F(3, 61) = 1.56, p = 0.21$], language [$\lambda = 0.09, F(3, 61) = 2.07, p = 0.11$], or visuospatial ability [$\lambda = 0.04, F(3, 61) = 0.75, p = 0.52$].

4. Discussion

When comparing CVD patients with and without the *BDNF* MET allele, significant group differences emerged for attention/executive function and memory. However, contrary to predictions and past studies, persons with at least one copy of the MET allele actually performed better on these measures. Our results also revealed that there were no sex

differences for the effect of the MET allele on cognitive test performance. Several aspects of these findings warrant discussion.

Previous studies have shown that individuals with one or two MET alleles show reduced performance in multiple cognitive abilities, including episodic memory, processing speed, delayed recall, general intelligence, digital working memory, spatial localization, and verbal recall.^{19,21–23} As no such pattern emerged in the current sample, it appears likely that the *BDNF* genotype does not produce the same effects in older adults with CVD as it does for others. There are several possible explanations for this finding. One possibility is that the MET allele interacts with the cognitive changes associated with either CVD or aging, as both CVD and normal aging are linked to deficits in memory and psychomotor speed and may thus obscure any possible influence of *BDNF* genotype.⁴⁰ Consistent with this possibility, Miyajima and Colleagues (2008)²³ observed that the Met allele was associated with only nominally poorer performance on tests of processing speed, delayed recall, and general intelligence in a sample of older adults.

Another potential explanation is that CVD impacts circulating levels of BDNF in some way, which is noteworthy given that BDNF is permeable to the blood brain barrier.⁴¹ Thus, the relationship between the genetic BDNF and circulating BDNF is less straightforward than typically believed. Circulating BDNF is associated with several risk factors related to CVD, such as body mass index and cholesterol in females, triglycerides in males, elevated plasma leptin, and diastolic blood pressure in both sexes.^{42,43} The causal relationship among these factors is unknown, as either BDNF or the cardiac variables may be driving this association. However, it is possible that CVD, or processes related to CVD, may alter the levels of circulating BDNF. If so, it would be very difficult to anticipate the association between BDNF genotype and cognitive function in persons with CVD without also direct quantification of circulating BDNF levels. Future studies should examine circulating BDNF, genetic variation in the *BDNF* gene, and cognitive functioning to disentangle this relationship, especially in samples of individuals with chronic medical diseases.

Exploratory analyses examined whether sex differences emerged in cognitive function in *BDNF* genotype groups. Past studies had shown that women have higher levels of circulating BDNF than men and that BDNF is a marker of impaired memory and general cognition in older women.^{24,25} In the current study, there were no group differences when the sample was restricted to only men or women. As above, this finding is contrary to past work, which typically shows the MET allele is associated with poorer cognitive function and such deficits have frequently been found in women but not men.^{19,21–26} Clearly, much additional work in this area is needed.

The current study is limited in several ways and may not generalize to all samples. One potential limitation is the unequal sample sizes between those with and without a MET allele. However, as reported in Bath & Lee (2006),⁴⁴ about 30% of the population of the United States is a carrier for the MET allele, and only 4% of the population has the MET/MET genotype. This is consistent with our study, where 28% of the 110 individuals in the study were carriers of the MET allele, and just 1.8% of the sample had the MET/MET genotype. However, this means that most of the MET group in our sample was comprised of heterozygotes, or persons with the VAL/MET genotype. This genotype may produce a smaller effect size on circulating BDNF and neurocognitive outcome, as MET/MET individuals may demonstrate more severe cognitive changes and have bigger effects. However, the relatively small sample does not appear to directly impact the current findings. Few effects were found in the current study and all were actually in the opposite of the predicted direction, with the MET group actually performing better than Val/Val participants. Such findings suggest that the effects of BDNF genotype differ in older persons

with CVD, rather than inadequate statistical power. It is also important for future studies to examine the possible contribution of BDNF genotype in persons with more severe cognitive impairment, including mild cognitive impairment and dementia. Persons with the MET allele are known to be at higher risk for dementia⁴⁵ and our exclusion of such persons may influence the current findings. Similarly, future studies with larger more diverse samples are needed to confirm our findings. Future studies would also benefit from the inclusion of brain imaging to clarify how BDNF might affect brain structure and function in this population. Previous research has examined schizophrenia and major depressive patients, and found that carriers of the Met allele typically have smaller hippocampal volume and reduced prefrontal cortexes.^{46,47} It would be beneficial to see if these effects may interact with aging process in both healthy and medically ill populations.

In conclusion, BDNF VAL66MET had little impact on cognitive functioning in a sample of older adults with CVD and significant findings were actually opposite of that predicted by past work. Based on these findings, it appears likely that CVD and/or cognitive aging moderates the relationship between BDNF and cognition. Future work is needed to clarify the mechanisms for these findings, particularly studies examining both circulating and the *BDNF* gene and cognitive function over time.

Acknowledgments

Indirect support for this work included National Institutes of Health (NIH) grants DK075119 and HL089311 and grant 1S10RR023457-01A1 and Shared equipment grants (ShEEP) from the Medical Research Service of the Department of Veteran Affairs were used for genotyping (J. E. McGeary).

References

1. Yazdanyar A, Newman AB. The burden of cardiovascular disease in the elderly: morbidity, mortality, and costs. *Clin Geriatr Med*. 2009; 25:563–577. (2009). [PubMed: 19944261]
2. Zuccala G, Pedone C, Cesari M, et al. The effects of cognitive impairment on mortality among hospitalized patients with heart failure. *Am J Med*. 2003; 115:97–103. [PubMed: 12893394]
3. Peila R, White L, Masaki K, Petrovitch H, Launer L. Reducing the risk of dementia: efficacy of long-term treatment of hypertension. *Stroke*. 2006; 37:1165–1170. [PubMed: 16601212]
4. Vogels R, Scheltens P, Schroeder-Tanka J, Weinstein H. Cognitive impairment in heart failure: a systematic review of the literature. *Eur J Heart Fail*. 2007; 9:440–449. [PubMed: 17174152]
5. Solomon A, Kareholt I, Ngandu T, et al. Serum cholesterol changes after midlife and late-life cognition: twenty-one-year follow-up study. *Neurology*. 2007; 68:751–756. [PubMed: 17339582]
6. Hogue CW, Hershey T, Dixon D, et al. Preexisting cognitive impairment in women before cardiac surgery and its relationship with C-reactive protein concentrations. *Anesth Analg*. 2006; 102:1602–1608. [PubMed: 16717295]
7. DeCarli C. Prevention of white-matter lesions through control of cerebrovascular risk factors. *Int Psychogeriatr*. 2003; 15:147–151. [PubMed: 16191232]
8. Gianaros PJ, Greer PJ, Ryan CM, Jennings JR. Higher blood pressure predicts lower regional grey matter volume: Consequences on short-term information processing. *Neuroimage*. 2006; 31:754–765. [PubMed: 16488626]
9. Raz N, Rodrigue K, Kennedy K, Head D, Gunning-Dixon F, Acker J. Differential aging of the human striatum: Longitudinal evidence. *AJNR Am J Neuroradiol*. 2003; 24:1849–1856. [PubMed: 14561615]
10. Dufouil C, de Kersaint-Gilly A, Besançon V, et al. Longitudinal study of blood pressure and white matter hyperintensity: The EVA MRI Cohort. *Neurology*. 2001; 56:921–926. [PubMed: 11294930]
11. Veldnick J, Scheltens P, Jonker C, Launer L. Progression of cerebral white matter hyperintensities on MRI is related to diastolic blood pressure. *Neurology*. 1998; 51:319–320. [PubMed: 9674838]

12. Haley A, Forman D, Poppas A, et al. Carotid artery intima-media thickness and cognition in cardiovascular disease. *Int J Cardiol.* 2007; 121:148–154. [PubMed: 17196687]
13. Moser DJ, Robinson RG, Hynes SM, et al. Neuropsychological performance is associated with vascular function in patients with atherosclerotic vascular disease. *Arterioscler Thromb Vasc Biol.* 2007; 27:141–146. [PubMed: 17068287]
14. Jefferson A, Poppas A, Paul R, Cohen R. Systemic hypoperfusion is associated with executive dysfunction in geriatric cardiac patients. *Neurobiol Aging.* 2007; 28:477–483. [PubMed: 16469418]
15. Jefferson AL, Massaro JM, Wolf A, et al. Inflammatory biomarkers are associated with total brain volume: The Framington Heart Study. *Neurology.* 2007; 68:1032–1038. [PubMed: 17389308]
16. Price JM, Hellermann A, Hellermann G, Sutton ET. Aging enhances vascular dysfunction induced by the Alzheimer's peptide beta-amyloid. *Neurol Res.* 2004; 26:305–311. [PubMed: 15142324]
17. Connor B, Dragunow M. The role of neuronal growth factors in neurodegenerative disorders of the human brain. *Brain Res Brain Res Rev.* 1998; 27:1–39. [PubMed: 9639663]
18. Akatsu H, Yamagata H, Kawamata J, et al. Variations in the BDNF gene in autopsy-confirmed Alzheimer's disease and dementia with Lewy bodies in Japan. *Dement Geriatr Cogn Disord.* 2006; 22:216–222. [PubMed: 16899999]
19. Egan MF, Kojima M, Callicott JH, et al. The BDNF val66met polymorphism affects activity-dependent secretion of BDNF and human memory and hippocampal function. *Cell.* 2003; 112:257–269. [PubMed: 12553913]
20. Erickson K, Kim J, Suever B, Voss M, Francis B, Kramer A. Genetic contributions to age-related decline in executive function: a 10-year longitudinal study of COMT and BDNF polymorphisms. *Front Hum Neurosci.* 2008; 2:11. [PubMed: 18958211]
21. Schofield PR, Williams LM, Paul RH, et al. Disturbances in selective information processing associated with the BDNF Val66Met polymorphism : Evidence from cognition, the P300 and fronto-hippocampal systems. *Biol Psychol.* 2009; 80:176–188. [PubMed: 18838100]
22. Gong P, Zheng A, Chen D. Effect of BDNF Val66Met Polymorphism on Digital Working Memory and Spatial Localization in a Healthy Chinese Han Population. *J Mol Neurosci.* 2009; 38:250–256. [PubMed: 19424874]
23. Miyajima F, Ollier W. Brain-derived neurotrophic factor polymorphism Val66met influences cognitive abilities in the elderly. *Genes Brain Behav.* 2008; 7:411–417. [PubMed: 17973920]
24. Li G, Peskind ER, Millard SP, et al. Cerebrospinal Fluid Concentration of Brain-Derived Neurotrophic Factor and Cognitive Function in Non-Demented Subjects. *PLoS One.* 2009; 4:1–5.
25. Komulainen P, Pedersen M, Hänninen T, et al. BDNF is a novel marker of cognitive function in ageing women: The DR's EXTRA Study. *Neurobiol Learn Mem.* 2008; 90:606–613.
26. Fukumoto N, Fujii T, Combarros O, et al. Sexually dimorphic effect of the Val66Met Polymorphism on susceptibility to Alzheimer's disease: New data and meta-analysis. *Am J Med Genet B Neuropsychiatr Genet.* 2010; 153b:235–242. [PubMed: 19504537]
27. Livak KJ, Marmaro J, Todd JA. Towards fully automated genome-wide polymorphism screening. *Nat Genet.* 1995; 9:341–342. [PubMed: 7795635]
28. Teng E, Chui H. The Modified Mini-Mental State (3MS) examination. *J Clin Psychiatry.* 1987; 48:314–318. [PubMed: 3611032]
29. Mattis, S. Dementia Rating Scale (DRS). Odessa, FL: Psychological Assessment Resources; 1988.
30. Reitan, R.; Wolfson, D. The Halstead-Reitan Neuropsychological Test Battery: Theory and Clinical Interpretation. Tucson, AZ: Neuropsychology Press; 1993.
31. Wechsler, D. Wechsler Adult Intelligence Scale-III. San Antonio: The Psychological Corporation; 1997.
32. Jensen AR, Rohwer WD. The Stroop Color-Word Test: a review. *Acta Psychologica.* 1966; 25:36–93. [PubMed: 5328883]
33. Stroop JR. Studies of interference in serial verbal reactions. *Journal of Experimental Psychology.* 1935; 18:643–662.

34. Fastenau P, Denburg N, Hufford B. Adult norms for the Rey-Osterrieth Complex Figure Test and for supplemental recognition and matching trials from the Extended Complex Figure Test. *Clin Neuropsychol.* 1999; 13:30–47. [PubMed: 10937646]
35. Hawkins KA, Sledge WH, Orleans JE, Quinlan DM, Rakfeldt J, Huffman RE. Normative implications of the relationship between reading vocabulary and Boston Naming Test performance. *Arch Clin Neuropsychol.* 1993; 8:525–537. [PubMed: 14591992]
36. Benton, AL.; Hamsher, K. *Multilingual Aphasia Examination*. 3rd ed.. Iowa City: AJA; 1989.
37. Spreen, O.; Strauss, E. *A Compendium of Neuropsychological Tests*. New York: Oxford University Press; 1991.
38. Morris J, Heyman A, Mohs R, et al. The Consortium to Establish a Registry for Alzheimer's Disease (CERAD). Part I. Clinical and neuropsychological assessment of Alzheimer's disease. *Neurology.* 1989; 39:1159–1165. [PubMed: 2771064]
39. Lezak, MD. The test-retest stability and reliability of some tests commonly used in neuropsychological assessment. Paper presented at the 5th European conference of the International Neuropsychological Society; Deauville, France. 1982.
40. Lezak, MD.; Howieson, DB.; Loring, DW. *Neuropsychological Assessment*. 4th ed.. New York: Oxford University Press; 2004.
41. Pan W, Banks WA, Fasold MB, Bluth J, Kastin AJ. Transport of brain-derived neurotrophic factor across the blood-brain barrier. *Neuropharmacology.* 1998; 37:1553–1561.
42. Golden E, Emiliano A, Maudsley S, et al. Circulating brain-derived neurotrophic factor and indices of metabolic and cardiovascular health: Data from the Baltimore Longitudinal Study of Aging. *PLoS One.* 2010; 5:e10099. [PubMed: 20404913]
43. Chaldakov GN, Fiore M, Stankulov IS. Neurotrophin presence in human coronary atherosclerosis and metabolic syndrome: a role for NGF and BDNF in cardiovascular disease? *Prog Brain Res.* 2004; 146:279–289. [PubMed: 14699970]
44. Bath KG, Lee FS. Variant BDNF (Val66Met) impact on brain structure and function. *Structure.* 2006; 6:79–85.
45. Hashimoto R, Hirata Y, Asada T. Effect of brain-derived neurotrophic factor and the apolipoprotein E polymorphisms on disease progression in preclinical Alzheimer's disease. *Genes Brain Behav.* 2009; 8:43–52. [PubMed: 18786162]
46. Frodl T, Moller HJ, Meisenzah E. Neuroimaging genetics: new perspectives in research on major depression? *Acta Psychiatr Scand.* 2008; 118:363–372. [PubMed: 18644006]
47. van Haren NE, Bakker SC, Kahn RS. Genes and structural brain imaging in schizophrenia. *Curr Opin Psychiatry.* 2008; 21:161–167. [PubMed: 18332664]

Table 1Demographic and Medical Characteristics of 110 Adults with Cardiovascular Disease by *BDNF* genotype

Demographic or Medical Variable	Val/Val (N=77)	Val/Met or Met/Met (N=33)	Test Statistic	<i>p</i>
Age, yrs.	69.42±7.32	68.12±8.10	-0.82	0.41
Education, yrs.	14.11±2.44	14.84±2.96	1.34	0.19
Female, %	42.9	36.4	0.40	0.53
High Blood Pressure, %	76.6	72.7	0.19	0.66
CABG, %	37.7	39.4	0.06	0.81
Heart Failure, %	19.5	15.2	0.31	0.58
Type II Diabetes, %	20.8	18.2	0.06	0.81
High Cholesterol, %	45.5	48.5	0.74	0.39
Heart Attack, %	45.5	48.5	0.14	0.71

Note. 'Test Statistic' includes Chi-square analyses for dichotomous variables and t-tests for continuous variables.

Table 2**Neuropsychological Test Performance**

Raw Test Performance, mean (SD)	
<i>Global Function</i>	
MMSE	28.43(1.81)
Total DRS	137.01(4.97)
<i>Attention/Executive Function</i>	
TMTB (seconds)	98.96(44.18)
Digit Symbol	56.04(13.36)
Stroop Color Word Test	30.58(8.65)
<i>Memory</i>	
CFT Immediate	14.17(7.37)
CFT Delay	14.08(7.09)
<i>Language</i>	
Boston Naming Test	54.53(4.51)
Animals	19.66(5.35)
COWA	39.28(3.44)
<i>Visuospatial</i>	
Block Design	32.19(10.80)
HVOT	23.68(3.44)
CFT Copy	30.45(5.38)

MMSE = Mini Mental State Examination; DRS = Dementia Rating Scale; TMTB = Trail Making Test B; CFT = Complex Figure Test; COWA = Controlled Oral Word Association; HVOT = Hooper Visual Organization Test

Table 3

The independent association of *BDNF* genotype on cognitive function in individuals with CVD ($N = 110$)

Variable	Global β (SE b)	Attn/EF β (SE b)	Memory β (SE b)	Language β (SE b)	Visuospatial β (SE b)
<i>Block 1</i>					
Age	-.19(.05)	-.33(.25)*	-.11(.11)	-.21(.08)	-.14(.08)
Sex	.16(.69)	.14(3.78)	-.10(1.59)	.12(1.27)	-.11(1.18)
Education	.30(.12)*	.13(.66)	.25(.28)*	.35(.22)*	.27(.21)
Arrhythmia	-.13(.84)	-.01(4.63)	.02(1.94)	.14(1.56)	-.12(1.45)
Hypertension	.20(.77)	-.01(4.23)	-.02(1.78)	.14(1.42)	.03(1.32)
Cholesterol	-.14(.69)	-.04(3.80)	.08(1.59)	.03(1.28)	.00(1.19)
R^2	.22	.16	.10	.23	.11
F	3.16*	2.20	1.22	3.42*	1.45
<i>Block 2</i>					
BDNF	.18(.73)	.22(4.01)*	.25(1.68)*	.19(1.36)	.22(1.26)
R^2	.25	.21	.15	.26	.16
F for ΔR^2	2.71	4.10*	4.70*	3.26($p=.08$)	3.55($p=.06$)

Note.

* $p < .05$;

Global = Global functioning; Attn/EF = Attention/Executive function; BDNF = Brain Derived Neurotrophic Factor (0 = ValVal homozygote; 1 = ValMet/MetMet)