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Lack of an association of BDNF Val66Met polymorphism and plasma BDNF with hippocampal volume and memory

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Abstract

Brain-derived neurotrophic factor (BDNF) has been shown to be important for neuronal survival and synaptic plasticity in the hippocampus in non-human animals. The Val66Met polymorphism in the BDNF gene, involving a valine (Val) to methionine (Met) substitution at codon 66, has been associated with lower BDNF secretion in vitro. However, there have been mixed results regarding associations between either circulating BDNF or the BDNF Val66Met polymorphism with hippocampal volume and memory in humans. The current study examined the association of BDNF genotype and plasma BDNF with hippocampal volume and memory in two large independent cohorts of middle-aged and older adults (both cognitively normal and early-stage dementia). Sample sizes ranged from 123 to 649. Measures of the BDNF genotype, plasma BDNF, MRI-based hippocampal volume and memory performance were obtained from the Knight Alzheimer Disease Research Center (ADRC) and the Alzheimer's Disease Neuroimaging Initiative (ADNI). There were no significant differences between BDNF Met+ and Met- groups on either hippocampal volume or memory in either cohort. In addition, plasma BDNF was not significantly associated with either hippocampal volume or memory in either cohort. Neither age, cognitive status nor gender moderated any of the relationships. Overall, current findings suggest

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[9]Some data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. A complete listing of ADNI investigators can be found at: http://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf

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that BDNF genotype and plasma BDNF may not be robust predictors for variance in hippocampal volume and memory in middle age and older adult cohorts.

Introduction

Healthy and pathological aging, particularly Alzheimer's disease (AD), are associated with shrinkage of the hippocampus and memory decline (Allen, Bruss, Brown, & Damasio, 2005; Barnes et al., 2009; C. Jack et al., 1997; Martin & Gorenstein, 2010; Raz et al., 2005; Raz, Ghisletta, Rodrigue, Kennedy, & Lindenberger, 2010; Zelinski & Burnight, 1997). Multiple environmental, physiological and genetic factors may influence these age effects. Recent work has suggested that brain derived neurotrophic factor (BDNF) may be a contributing factor. BDNF is a neurotrophin that plays an important role in neurogenesis, neuronal survival and synaptic plasticity (Barnabé-Heider & Miller, 2003; Beck, Lindholm, Castrén, & Wree, 1994; Burke et al., 1994; Kojima et al., 2001; J. Lee, Duan, & Mattson, 2002; Bai Lu, 2003). BDNF is highly expressed in the hippocampus (Murer et al., 1999; Murer, Yan, & Raisman-Vozari, 2001), and has been implicated in hippocampal plasticity and in facilitating hippocampus-dependent memory functions (B Lu & Gottschalk, 2000; Ma, Wang, Wu, Wei, & Lee, 1998; Tyler, Alonso, Bramham, & Pozzo-Miller, 2002).

In humans, a Val66Met polymorphism (rs6265) has been identified in the *BDNF* gene. This single nucleotide polymorphism (SNP) substitutes valine (Val) for methionine (Met) at codon 66. This substitution interferes with intracellular trafficking of BDNF and activity-dependent BDNF secretion (Bath & Lee, 2006; Chen et al., 2004; Egan et al., 2003) in non-human animals. A number of studies have observed smaller hippocampal volumes (Bueller et al., 2006; Frodl et al., 2007; Pezawas et al., 2004; Schofield et al., 2009; but see Richter-Schmidinger et al., 2011; Szeszko et al., 2005) and lower episodic memory performance (Dempster et al., 2005; Egan et al., 2003; Goldberg et al., 2008; Hariri et al., 2003; Ho et al., 2006; Kennedy et al., 2014; Schofield et al., 2009; but see Richter-Schmidinger et al., 2011) in healthy young adult human Met allele carriers.

In contrast, past studies have generally not observed significant associations between the BDNF genotype and hippocampal volume in middle-aged and older adult cohorts (Benjamin et al., 2010; Karnik, Wang, Barch, Morris, & Csernansky, 2010; Miyajima et al., 2008; but see Pezawas et al., 2004). In addition, findings have been inconsistent in regards to episodic memory performance in this age range with some observations of significantly lower performance in Met carriers (Kennedy et al., 2014; Miyajima et al., 2008; Raz, Rodrigue, Kennedy, & Land, 2009), and other reports of no significant differences between Val/Val and Met carrier groups (Benjamin et al., 2010; Harris et al., 2006; Karnik et al., 2010; Tsai et al., 2008). Previous studies have used various methods for determining hippocampal volume, including manual tracing (Bueller et al., 2006; Frodl et al., 2007; Richter-Schmidinger et al., 2011; Szeszko et al., 2005), point counting (Benjamin et al., 2010; Miyajima et al., 2008) and voxel-based morphometry (Pezawas et al., 2004; Schofield et al., 2009). In terms of episodic memory, a variety of measures have been used, but the most commonly used test is the Logical Memory subtest from the Weschler Memory Scales (Dempster et al., 2005; Egan et al., 2003; Harris et al., 2006; Ho et al., 2006; Karnik et al.,

2010). For both hippocampal volume and memory, no consistent pattern has been observed for different methods used and whether or not findings with BDNF genotype are significant. Moreover, sample sizes do not appear to systematically differ between studies finding significant differences and those that did not.

In regards to pathological aging, it appears that the BDNF genotype may not confer a greater risk for Alzheimer's disease (e.g., Bian, Zhang, Zhang, & Zhao, 2005; Combarros, Infante, Llorca, & Berciano, 2004; Desai, Nebes, DeKosky, & Kamboh, 2005; Forlenza et al., 2010; Yu et al., 2008; Zhang et al., 2006; but see Fehér, Juhász, Rimanóczy, Kálmán, & Janka, 2009; Matsushita et al., 2005; Tsai, Hong, Liu, Liu, & Liou, 2006). However, the presence of the Met allele has been associated with a greater risk for cognitive decline in individuals with mild cognitive impairment (MCI;Forlenza et al., 2010), which is considered a potential prodromal stage of AD (Flicker, Ferris, & Reisberg, 1991).

Past work has also examined associations of circulating BDNF (i.e., in serum, plasma or cerebrospinal fluid) with hippocampal volume and memory. A few studies have examined associations between serum BDNF and hippocampal volume or memory in small cohorts of young to middle-aged controls for psychiatric populations, and findings have been mixed (Dias et al., 2009; Eker et al., 2010; Rizos et al., 2011). Notably, advancing age (Erickson et al., 2010; Li et al., 2009; Lommatzsch et al., 2005; Shimada et al., 2014; Ziegenhorn et al., 2007) and Alzheimer disease (Forlenza et al., 2010; Laske et al., 2007; Lee et al., 2009; Li et al., 2009; Yasutake, Kuroda, Yanagawa, Okamura, & Yoneda, 2006; Yu et al., 2008; but see Angelucci et al., 2010; Laske et al., 2006; O'Bryant et al., 2009) have generally been associated with lower circulating BDNF. While positive relationships between circulating BDNF and hippocampal volume in healthy older adults (Erickson et al., 2010) have been reported, other studies have not observed an association (Driscoll et al., 2012). Investigations of the association between circulating BDNF and memory in healthy older adults have demonstrated varying results with reports of positive (Erickson et al., 2010; Komulainen et al., 2008; Li et al., 2009), negative (Forlenza et al., 2010), and non-significant (Driscoll et al., 2012; Gunstad et al., 2008; O'Bryant et al., 2011) correlations. There has also been some limited work demonstrating a positive relationship between circulating BDNF and memory performance in MCI (Yu et al., 2008) and combined cohorts of healthy and MCI individuals (Shimada et al., 2014), but a negative relationship in AD (Forlenza et al., 2010) individuals.

Inconsistent findings in the BDNF and aging literature may relate to a reduced penetrance of BDNF genotype with age. Age-related pathological changes in brain structure and function may take place independent of genetic influence, which then may reduce genetic contribution to variance in hippocampal volume and memory (Erickson, Miller, & Roecklein, 2012). Mixed findings may also be related to limited sample sizes in some investigations that may have increased the likelihood of type II errors, assessment of the memory domain with only one measure of memory, and/or the gender composition of the cohorts. The primary goal of the current study was to assess the associations of the BDNF genotype and plasma BDNF with hippocampal volume and memory in cognitively normal and very mild to mildly demented adults. The present study advances the existing literature by: (1) examining the relationship in two independent cohorts; (2) examining both BDNF

genotype and plasma BDNF within the same cohorts; (3) examining both hippocampal volume and memory within the same cohorts; and (4) use of composite estimates of the memory domain rather than analyses with single tasks.

Methods

Participants

Alzheimer's Disease Neuroimaing Initiative (ADNI)—Data for one cohort used in the current study were obtained from the ADNI database (adni.loni.usc.edu). The ADNI was launched in 2003 by the National Institute on Aging (NIA), the National Institute of Biomedical Imaging and Bioengineering (NIBIB), the Food and Drug Administration (FDA), private pharmaceutical companies and non-profit organizations, as a $60 million, 5-year public-private partnership. The primary goal of ADNI has been to test whether serial magnetic resonance imaging (MRI), positron emission tomography (PET), other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of mild cognitive impairment (MCI) and early Alzheimer's disease (AD). Determination of sensitive and specific markers of very early AD progression is intended to aid researchers and clinicians to develop new treatments and monitor their effectiveness, as well as lessen the time and cost of clinical trials. The Principal Investigator of this initiative is Michael W. Weiner, MD, VA Medical Center and University of California – San Francisco. ADNI is the result of efforts of many co-investigators from a broad range of academic institutions and private corporations, and subjects have been recruited from over 50 sites across the U.S. and Canada. The initial goal of ADNI was to recruit 800 subjects but ADNI has been followed by ADNI-GO and ADNI-2. To date these three protocols have recruited over 1500 adults, ages 55 to 90, to participate in the research, consisting of cognitively normal older individuals, people with early or late MCI, and people with early AD. The follow up duration of each group is specified in the protocols for ADNI-1, ADNI-2 and ADNI-GO. Subjects originally recruited for ADNI-1 and ADNI-GO had the option to be followed in ADNI-2. For up-to-date information, see www.adni-info.org.

Participants were classified using the Clinical Dementia Rating (CDR) scale, a reliable and validated protocol for staging dementia (Morris, 1993). CDR 0 corresponds to cognitively normal, whereas CDR 0.5 and 1 indicate very mild and mild dementia, respectively. 536 ADNI participants had both BDNF genotype (67% Val/Val, 30% Val/Met, 2% Met/Met) data and baseline MRI scans that passed quality control (see Table 1 for demographic information). Among these 536 participants, 355 participants had both baseline plasma BDNF data and baseline MRI scans that passed quality control (see Table 1 for demographic information). For memory analyses, data from the 12-month visit were used in the current report because the 12-month visit included a greater number of participants with available data. 649 participants had both BDNF genotype (66% Val/Val, 31% Val/Met, 3% Met/Met) and episodic memory data (see Table 2 for demographic information). 488 participants had both 12-month visit plasma BDNF and psychometric data (see Table 2 for demographic information).

Washington University Knight Alzheimer Disease Research Center (Knight ADRC)—A second cohort of participants was recruited from the Knight ADRC. Participants were 45 to 100 years of age and were screened for neurological or systemic illnesses (e.g., Huntington's Disease, Parkinson's Disease). In order to compare with ADNI, participants who were CDR 1 or below were selected for analysis. 302 participants had both BDNF genotype (69% Val/Val, 30% Val/Met, 2% Met/Met) data and MRI scans that passed quality control (see Table 3 for demographic information). Among these 302 participants, 142 had plasma BDNF data within two years of their MRI scan (see Table 3 for demographic information). In addition, 331 participants had both BDNF genotype (66% Val/Val, 32% Val/Met, 2% Met/Met) and data from all three memory tests (see Memory Assessment for more detail; see Table 4 for demographic information). Furthermore, 123 participants had both plasma BDNF and data from all three memory tests. All plasma data were within two years of the memory assessment (see Table 4 for demographic information). BDNF genotype, MRI and memory data from a subset of the CDR 0 participants have been previously reported in Karnik et al., 2010. The Human Research Protection Office at Washington University approved the study and written informed consent was obtained from all participants.

Genotyping

ADNI—Detailed procedures for genotyping, including for BDNF Val66Met SNP (rs6265), can be found in previous reports (Saykin et al., 2010; Shen et al., 2010). Briefly, 7mL of blood was taken in EDTA tubes, and genomic DNA was extracted using the QIAamp DNA Blood Maxi Kit (Qiagen, Inc., Valencia, CA). Next, to exclude for any degraded DNA samples, 50ng of genomic DNA was qualitatively analyzed with a 1% Tris-acetate-EDTA agarose gel. Samples were then analyzed using the Illumina Human-610-Quad BeadChip (Illumina, Inc., San Diego, CA). The APOE SNPs (rs429358 and rs7412) were not available on the Illumina Human610-Quad BeadChip. Thus, these SNPs were genotyped separately by polymerase chain reaction amplification and HhaI restriction enzyme digestion. The digested products were ran on a 4% Metaphor Gel and visualized by ethidium bromide staining to analyze the APOE genotype (Potkin et al., 2009; Saykin et al., 2010).

ADRC—Detailed procedures for genotyping in this cohort can be found in previus reports (Cruchaga et al., 2012, 2013). Briefly these DNA samples were genotyped with the Illumina 610 or the Omniexpress chip. Prior to analysis all samples and genotypes underwent stringent QC (Cruchaga et al., 2012). The genotype data for the BDNF val66Met SNP (rs6265) was extracted from the QC'd data. APOE genotyping for these samples was performed using Taqman assays as previously described (Cruchaga et al., 2010).

Plasma BDNF

ADNI—All plasma-based biomarker data were downloaded from the ADNI website (www.loni.ucla.edu/ADNI/) in October 2011. Detailed methods are posted on http://www.adni-info.org/Scientists/ADNIStudyProcedures.aspx. Briefly, blood samples were collected in the morning after an overnight fast, centrifuged to prepare plasma, and frozen on dry ice. Samples underwent an additional freeze-thaw cycle prior to measurement of BDNF. BDNF concentration was analyzed using the multiplex immunoassay panel, which is

based upon Luminex's xMAP Technology by Rules Based Medicine (RBM, Austin, TX). QC was performed on all samples.

ADRC—Similar procedures were performed for the ADRC samples, with the exception that plasma samples underwent only a single free-thaw cycle prior to analysis.

MR Acquisition

ADNI—All MRI data were downloaded from the ADNI website (www.loni.ucla.edu/ADNI/) in October 2011. Detailed methods are posted on http://www.adni-info.org/Scientists/ADNIStudyProcedures.aspx and in a previous report (C. Jack et al., 2008). Imaging was performed using 1.5T scanners (GE, Siemens or Phillips), and T1-weighted sagittal 3D MP-RAGE scans (TR=2400 ms, flip angle=8°, TI=1000 ms, 0.94 × 0.94 × 1.2 mm resolution) were acquired for each participant.

ADRC—Imaging was performed using either a Siemens Vision 1.5T scanner (n=101 for genotype analyses; n=39 for plasma analyses) or a Siemens Trio 3T scanner (n=201 for genotype analyses; n=103 for plasma analyses). For the Vision 1.5 scans, two to four T1-weighted sagittal MP-RAGE scans (TR=9.7 ms, flip angle=10°, TI=20 ms, 1 × 1 × 1.25 mm resolution) were acquired for each participant. For the Trio 3T scans, up to two T1-weighted sagittal MP-RAGE scans (TR=2400ms, flip angle=8°, TI=1000 ms, 1 × 1 × 1 mm resolution) were acquired for each participant.

Regional Volumetry

Hippocampal volume estimates were obtained using the Freesurfer image analysis suite. Total hippocampal volume estimated from the Freesurfer includes roughly the cornu ammonis subfields, dentate gyrus and subiculum. For the ADNI cohort, hippocampal volume estimates were obtained using Freesurfer v4.3. For the ADRC cohort, the Vision 1.5T scans were processed using Freesurfer v5.0, whereas the Trio 3T scans were processed using Freesurfer imaging analysis suite v5.1. The technical details of these procedures are described in prior publications (Dale, Fischl, & Sereno, 1999; Dale & Sereno, 1993; Fischl & Dale, 2000; Fischl, Liu, & Dale, 2001; Fischl et al., 2002; Fischl, Sereno, & Dale, 1999; Fischl, Sereno, Tootell, & Dale, 1999; Fischl et al., 2004). Briefly, this processing includes motion correction and averaging of multiple volumetric T1 weighted images, removal of non-brain tissue using a hybrid watershed/surface deformation procedure, automated Talairach transformation, segmentation of the subcortical white matter and deep gray matter volumetric structures intensity normalization, tessellation of the gray matter white matter boundary, automated topology correction, and surface deformation following intensity gradients to optimally place the gray/white and gray/cerebrospinal fluid borders at the location where the greatest shift in intensity defines the transition to the other tissue class. Once the cortical models are complete, the cerebral cortex is parcellated into units based on gyral and sulcal structure (Desikan et al., 2006; Fischl et al., 2004). Neuroanatomical labels are applied to each voxel based on a probabilistic atlas derived from a manually labeled training set that included older adults (Desikan et al., 2006). This procedure generates anatomical labeling and regional volume estimates with a high correspondence to manually generated labels and its delineation of the hippocampus has been validated in normal aging,

mild cognitive impairment, and AD (Cherbuin, Anstey, Réglade-Meslin, & Sachdev, 2009; Fischl et al., 2002; Sánchez-Benavides et al., 2010; Tae, Kim, Lee, Nam, & Kim, 2008).

While there is evidence of reliability of Freesurfer-derived estimates of volume across scanner upgrades, different manufacturers, and number of MP-RAGE acquisitions, variation in field strength and Freesurfer version may introduce slight bias (e.g., Fennema-Notestine et al., 2007; Gronenschild et al., 2012; Han et al., 2006; Jovicich et al., 2009). To address potential biases, scanner type/Freesurfer version was included as a covariate in the analyses if it showed significant associations with the predictor or outcome variables.

As there were no *a priori* hypotheses regarding laterality effects, hippocampal volumes were summed across hemispheres. Estimated total intracranial volume (ICV; Buckner et al., 2004) was used to adjust hippocampal volumes for body size differences via a formula based on the analyses of covariance approach: Adjusted volume=raw volume-(b x (ICV – mean ICV)), where b is the slope of the regression of the ROI volume on ICV (Jack et al., 1989; Mathalon, Sullivan, Rawles, & Pfefferbaum, 1993). Adjusted hippocampal volume was used as the dependent variable in analyses for both the ADNI and the ADRC cohorts.

Memory Assessment

ADNI—All psychometric data were downloaded from the ADNI website (www.loni.ucla.edu/ADNI/) in October 2011. Detailed methods are posted on http://www.adni-info.org/Scientists/ADNIStudyProcedures.aspx. The episodic memory variables included immediate and delayed recall from the Rey Auditory Verbal Learning Test (Rey, 1964), and immediate and delayed recall from the Wechsler Memory Scale-Revised (WMS-R) Logical Memory subtest (Wechsler, 1987). A composite measure of memory was created by standardizing scores from each task (a total of 4 variables) and averaging the standardized scores.

ADRC—The episodic memory variables included the free recall score from the Free and Cued Selective Reminding Test (Grober, Buschke, Crystal, Bang, & Dresner, 1988), immediate and delayed recall from the WMS-R Logical Memory subtest (Wechsler, 1987), and WMS Associate Learning (Wechsler & Stone, 1973). A composite measure of memory was created by standardizing scores for each task (a total of 4 variables) and averaging the standardized scores.

The psychometric batteries for the ADNI and the ADRC cohorts did not include the exact same set of tests for assessing episodic memory. However, both cohorts included the immediate and delayed recall from the WMS-R Logical Memory subtest. All other memory measures were significantly correlated with this subtest ($rs>.5$, $ps<.0001$), suggesting that these tests are measures of a unitary aspect of episodic memory.

Analytical Approach

Outliers—Univariate outliers were defined as values 3.5 standard deviations from the mean of the cohort. For the ADNI cohort, one individual in the Genotype-MRI analyses had an outlier data point. For the ADRC cohort, one individual in the Plasma-Memory analyses had

an outlier data point. Unless otherwise specified in the Results section, results were unchanged when outliers were removed.

Covariates—To determine the necessity of the inclusion of age (years), education (years), gender (coded as female=0, male=1), APOE genotype (coded as e4 non-carrier=0, e4 carrier=1), and CDR status (coded as CDR 0=0, CDR>0=1) as covariates in the analyses, the zero-order correlations (or t-tests for dichotomous variables) were examined between these variables and the predictors/outcomes. Pearson chi-square test was used to examine two categorical variables (e.g., BDNF genotype versus CDR status). Each analysis controlled for the covariates that were significantly associated with the predictor and/or outcome variables. In addition, the plasma BDNF-MRI assessment interval and scanner type (1.5T vs. 3T) were considered as additional covariates for ADRC MRI analyses. The mean interval between plasma BDNF and MRI assessments was +/− 4.2 months (SD=5.9) for the ADRC cohort and +/− 0.4 months (SD=1.4) for the ADNI cohort. Similarly, the plasma BDNF-memory assessment interval was considered as an additional covariate for ADRC memory analyses. The mean interval between plasma BDNF and memory assessments was +/− 2.3 months (SD=1.7) for the ADRC cohort and +/− 0.0 months (SD=0.6) for the ADNI cohort.

Statistical Analyses—A series of hierarchical regressions were conducted to address the primary questions regarding the main effects of BDNF genotype and plasma BDNF, and the moderating role of CDR on BDNF effects. The dependent variable was either hippocampal volume or memory performance. The predictor variable was either BDNF genotype, which was coded as 0 (Val/Val homozygotes) or 1 (Met allele carriers), or log-transformed plasma BDNF, which was a continuous variable. To correct for non-normality of residuals, a log transformation was applied to plasma BDNF prior to all analyses. In the regression analyses, covariates were entered in the first step. BDNF (i.e., genotype or plasma BDNF) was entered in the second step, and BDNF x CDR was entered in the last step.

The current study included 77 comparisons, including post-hoc analyses. Therefore, a false discovery rate correction was used to adjust all p-values that were below .1 to correct for multiple comparisons. Adjusted p-values were calculated by: (1) ranking the p-value of each comparison from smallest to largest; (2) multiplying the p-value by the total number of comparisons; and (3) dividing the value obtained from step 2 by the rank of p-value obtained from step 1.

Results

BDNF Genotype Analyses

Hippocampus—BDNF genotype was not significantly associated with hippocampal volume in either the ADNI or ADRC cohorts without or with covariates (i.e., ADNI: age, gender, APOE genotype, CDR status; ADRC: age, education, gender, APOE genotype, scanner type, CDR status) included (see Table 5, and Fig. 1A and 1B, respectively). Furthermore, the BDNF genotype x CDR interaction was not significant in either the ADNI or ADRC cohorts without or with covariates. Thus, there was not a significant difference in

the magnitude of the effect between the cognitively normal and the early-stage dementia groups (see Table 5).

Memory—BDNF genotype was not significantly associated with memory in either the ADNI or ADRC cohorts without or with covariates (i.e., ADNI: education, gender, APOE genotype, CDR status; ADRC: age, education, gender, APOE genotype, CDR status) included (see Table 5, and Fig. 2A and 2B, respectively). Furthermore, the BDNF genotype x CDR interaction was not significant in the ADNI cohort without covariates. There was a non-significant trend after controlling for covariates, but this trend was absent after adjusting for multiple comparisons. The BDNF genotype x CDR interaction was not significant in the ADRC cohort without or with covariates. Thus, there was not a significant difference in the magnitude of the effect between the cognitively normal and the early-stage dementia groups (see Table 5).

Plasma BDNF Analyses

Hippocampus—Plasma BDNF was not significantly associated with hippocampal volume in the ADNI cohorts without or with covariates (i.e., age, gender, APOE genotype, CDR status) included. In the ADRC cohort, there was a non-significant trend for an association in the model without covariates, but the trend was absent after adjusting for multiple comparisons, and after controlling for covariates (i.e., age, education, gender, APOE genotype, scanner type, CDR status, time interval between plasma BDNF assessment and MR scans) (see Table 5, Fig. 3A and 3B, respectively). Furthermore, the plasma BDNF x CDR interaction was not significant in either the ADNI or ADRC cohorts without or with covariates. Thus, there was not a significant difference in the magnitude of the effect between the cognitively normal and the early-stage dementia groups (see Table 5).

Memory—Plasma BDNF was not significantly associated with memory in either the ADNI or ADRC cohorts without or with covariates (i.e., ADNI: education, gender, APOE genotype, CDR status; ADRC: age, education, gender, CDR status) included (see Table 5, Fig. 4A and 4B, respectively). Furthermore, the plasma BDNF x CDR interaction was not significant in the ADNI cohort without or with covariates. Thus, there was not a significant difference in the magnitude of the effect between the cognitively normal and the early-stage dementia groups in the ADNI cohort. The plasma BDNF x CDR interaction was significant in the ADRC cohort without and with covariates. However, the BDNF x CDR interaction without covariates became non-significant after adjusting for multiple comparisons (see Table 5). There was a significant negative association between plasma BDNF and memory in the cognitively normal group and a non-significant positive trend in the early dementia group, but both associations became non-significant after adjusting for multiple comparisons.

Post-hoc Analyses: Associate Learning (ADRC cohort)

There were an additional 319 individuals with scores for the WMS Associate Learning task and BDNF genotype data (see Supplementary Table 1 for demographic information). In addition, there were an additional 66 individuals with scores from the WMS Associate Learning task and plasma BDNF data (see Supplementary Table 1 for demographic

information). In addition, Raz and colleagues (2009) observed a significant effect of the BDNF genotype on an associative memory task. Thus, we performed post-hoc analyses controlling for covariates with these increased sample sizes.

BDNF Genotype—BDNF genotype was not significantly associated with associate learning with covariates (i.e., age, education, gender, APOE genotype, CDR status) included. Furthermore, the BDNF genotype x CDR interaction was not significant with covariates (see Supplementary Table 2).

Plasma BDNF—Plasma BDNF was not significantly associated with associate learning with covariates (i.e., age, education, gender, CDR status) included. Furthermore, the plasma BDNF x CDR interaction was not significant with covariates (see Supplementary Table 2).

Post-hoc Analyses: BDNF x Age Interactions

Erickson and colleagues (2012) speculated that there may be lower penetrance of the BDNF genotype effects with advancing age in the context of age effects on brain structure and age-related diseases. Additionally, previous studies have found that circulating BDNF decreases with age in healthy adults (Erickson et al., 2010; Lommatzsch et al., 2005; Ziegenhorn et al., 2007). Thus, we examined whether there were interactive effects between BDNF and age on hippocampal volume and/or episodic memory performance. Hierarchical regressions were conducted to address these questions. In all analyses, the covariates were entered in the first step. Age, CDR status and BDNF (i.e., genotype or plasma) were entered in the second step. The BDNF x age interaction was entered in the third step. The BDNF x CDR and age x CDR interactions were entered in the fourth step. The 3-way interaction was entered in the last step.

BDNF Genotype—The BDNF genotype x age interaction was not significant in the ADNI cohort for hippocampal volume. The BDNF benotype x age interaction was a non-significant trend in the ADRC sample, but the trend was absent after adjusting for multiple comparisons. In addition, the BDNF genotype x age x CDR interaction was not significant in either the ADNI or ADRC cohorts for hippocampal volume.

The BDNF genotype x age interaction was not significant in either the ADNI or ADRC cohorts for memory performance. In addition, the BDNF genotype x age x CDR interaction was not significant in either the ADNI or ADRC cohorts for memory performance (see Table 6).

Plasma BDNF—The plasma BDNF x age interaction was not significant in either the ADNI or ADRC cohorts for hippocampal volume. In addition, the plasma BDNF x age x CDR interaction was not significant in either the ADNI or ADRC cohorts for hippocampal volume (See Table 6).

The plasma BDNF x age interaction was not significant in either the ADNI or ADRC cohorts for memory performance. In addition, the plasma BDNF x age x CDR interaction was not significant in either the ADNI or ADRC cohorts for memory performance (see Table 6).

Post-hoc Analyses: BDNF x Gender Interactions

Gender differences have been observed in serum BDNF levels (Shimada et al., 2014), in associations between plasma BDNF and episodic memory performance (Komulainen et al., 2008, and in BDNF genotype-related risk for AD (Fukomoto et al., 2010). Thus, we examined whether there were interactive effects between BDNF and gender on hippocampal volume and/or episodic memory performance using hierarchical regressions. In all analyses, the covariates were entered in the first step. Gender, CDR status and BDNF (i.e., genotype or plasma) were entered in the second step. BDNF x gender was entered in the third step to examine interactive effects between BDNF and gender. BDNF x CDR and gender x CDR were entered in the fourth step. The 3-way interaction was entered in the last step.

BDNF genotype—The BDNF genotype x gender interaction was not significant in either the ADNI or ADRC cohorts for hippocampal volume. In addition, The BDNF genotype x gender x CDR interaction was not significant in either the ADNI or ADRC cohorts for hippocampal volume (See Table 6).

The BDNF genotype x gender interaction was not significant in either the ADNI or ADRC cohorts for memory performance. In addition, the BDNF genotype x gender x CDR interaction was not significant in either the ADNI or ADRC cohorts for memory performance (see Table 6).

Plasma BDNF—The plasma BDNF x gender interaction was not significant in either the ADNI or ADRC cohorts for hippocampal volume. In addition, the plasma BDNF x gender x CDR interaction was not significant in either the ADNI or ADRC cohorts for hippocampal volume (See Table 6).

The plasma BDNF x gender interaction was not significant in either the ADNI or ADRC cohorts for memory performance. In addition, the plasma BDNF x gender x CDR interaction was a non-significant trend in the ADNI, but the trend was lost after adjusting for multiple comparisons. The plasma BDNF x gender x CDR interaction was not significant in the ADRC cohort. This non-significant interaction became a non-significant trend when an outlier was removed, but the trend was lost after adjusting for multiple comparisons (see Table 6).

Discussion

The current literature on the effects of BDNF, including the Val66Met polymorphism and circulating BDNF, on hippocampal volume and memory in humans has yielded mixed results. In the current study, neither BDNF genotype nor plasma BDNF were significantly associated with either hippocampal volume or memory in cognitively normal and early-stage dementia adults. We performed post-hoc testing to further explore what factors may have contributed to the null findings.

Several studies in young adults have observed significant differences in hippocampal volume and memory based on BDNF genotype (Bueller et al., 2006; Egan et al., 2003; Frodl et al., 2007; Hariri et al., 2003; Schofield et al., 2009). A potential reason for the current null

findings in the cognitively normal cohorts may be the age of the participants. Past studies in healthy middle-aged and older adult cohorts have also failed to find a difference for hippocampal volume (Benjamin et al., 2010; Karnik et al., 2010; Miyajima et al., 2008; but see Pezawas et al., 2004). While two past studies including middle-aged and older adult cohorts observed worse memory performance for Met carriers (Miyajima et al., 2008; Raz et al., 2009), several others failed to find significant group differences (Benjamin et al., 2010; Harris et al., 2006; Karnik et al., 2010; Raz et al., 2008; Tsai et al., 2008). Thus, incorporating current results, the preponderance of investigations suggests minimal effects of the BDNF genotype on memory performance at later age ranges. Indeed, Erickson and colleagues (2012) have speculated that there may be lower penetrance of the BDNF genotype with advancing age, and other factors may have a stronger influence on brain structure and cognition. Furthermore, it has been suggested that the Met allele may be protective in older adults as there have been indications of better performance in older adult Met carriers in other cognitive domains (Erickson et al., 2012; Harris et al., 2006). While post-hoc analyses did not reveal significant interactive effects of BDNF genotype and age on either hippocampal volume or memory in either cohort after correcting for multiple comparisons, this could relate to the lack of younger adults (e.g., no participants <45 years of age) in the analyses.

There is some indication that Met homozygosity is associated with the lowest memory performance (Egan et al., 2003; Schofield et al., 2009), and so the relative proportion of this group in analyses may influence the degree to which significant results are observed. However, it has been estimated that only about 4% of the US population has the Met/Met genotype (Shimizu et al., 2004), and most studies combine the Val/Met and Met/Met groups. In studies with healthy middle-aged and older adults, the proportion of the Met/Met genotype has varied between 0% to 4% with no apparent differences in terms of whether significant BDNF effects are observed (Karnik et al., 2010; Miyajima et al., 2008; Raz et al., 2009). The current cohorts did not have sufficient Met/Met homozygotes to perform a post-hoc analysis (ADNI hippocampus: 2%; ADNI memory: 3%; ADRC hippocampus: 2%; ADRC memory: 2%). Future investigations could attempt to include a large number of Met/Met homozygotes to examine dose-dependent relationships with brain structure and function.

There were also no significant associations between plasma BDNF and hippocampal volume or memory in cognitively normal individuals in either cohort after correcting for multiple comparisons. Circulating BDNF is reduced with aging (e.g., Erickson et al., 2010; Lommatzsch et al., 2005; Ziegenhorn et al., 2007), and BDNF-induced long-term potentiation (LTP) is impaired in aged compared to younger rats (Gooney, Messaoudi, Maher, Bramham, & Lynch, 2004). Thus, there could be differing associations of circulating BDNF with hippocampal volume and memory with aging. The current study observed a significant negative association between age and plasma BDNF in the ADNI – hippocampus cohort only. Furthermore, we did not observe a significant interactive effect between plasma BDNF and age in either cohort. Again, interactive effects may be observed with the inclusion of a young adult group. Notably, conflicting findings have been observed in young adult cohorts as well, although these were predominately relatively small control cohorts (Dias et al., 2009; Eker et al., 2010; Rizos et al., 2011; Ruiz de Azua et al., 2013).

Previous studies have found no significant difference in circulating BDNF between Val homozygote and Met carriers in healthy (Jiang, Wang, Liu, Zhang & Chen, 2009; Li et al., 2009; Terracciano et al., 2009; Zhou et al., 2011) and demented (Li et al., 2009; Yu et al., 2008) middle-aged and older adults. Similarly, in post-hoc analyses there were no significant differences in plasma BDNF level between Val homozygote and Met carriers in our largest cognitively normal (ADRC – hippocampus) and demented (ADNI – memory) samples. These findings suggest that BDNF genotype may not strongly contribute to concentration of circulating BDNF in humans, and that findings with BDNF genotype may be different from those with circulating BDNF.

The role of BDNF in AD risk and pathophysiology has recently received attention (see Diniz & Teixeira, 2011 for a review). Thus far, the majority of previous studies have found no significant differences between AD individuals and healthy controls in terms of BDNF genotype and/or allele frequencies (e.g., Dias et al., 2009; Tsai et al., 2004; Zhang et al., 2006; but see Fukumoto et al., 2010). On the other hand, prior studies have reported a lower circulating BDNF level in AD individuals compared to healthy controls (e.g., Yasutake et al., 2006; Yu et al., 2008; Forlenza et al., 2010), though some work has observed higher BDNF levels in AD individuals (Angelucci et al., 2010; Laske et al., 2006) or no group differences (O'Bryant et al., 2009). In the current study, there were indications of lower plasma BDNF in early-stage dementia (see Tables). However, there were no significant associations of BDNF with hippocampus or memory in the AD groups in either cohort after correcting for multiple comparisons in the current study. These finding are inconsistent with one study that observed associations between circulating BDNF and memory in a cohort with mild cognitive impairment (Yu et al., 2008). This study consisted of a cohort of Chinese Han, and there is evidence of genotype frequency differences between Asian and European populations (e.g., Petryshen et al., 2010; Shimizu, Hashimoto, & Iyo, 2004). Thus, the cohort in Yu and colleagues (2008) had a higher proportion of Met homozygotes than our cohorts, and this may have contributed to the discrepant results. Higher BDNF has also been associated with slower cognitive decline in AD (Laske et al., 2011), and presence of the Met-allele has been associated with faster progression in individuals with mild cognitive impairment (Forlenza et al., 2010) in relatively small cohorts. Thus, further longitudinal work in larger cohorts may be warranted.

The current study measured circulating BDNF in plasma. It is possible that the particular sample analyzed (whole blood, serum, plasma or platelets) could contribute to conflicting findings (Lommatzsch et al., 2005; Trajkovska et al., 2007). However, both plasma and serum BDNF studies have varied in terms of whether or not significant associations with memory or hippocampus are observed in middle-aged to older adult cohorts (Driscoll et al., 2012; Erickson et al., 2010; Gunstad et al., 2008; Kamulainen et al., 2008; O'Bryant et al., 2011; Yu et al., 2008). In addition, positive associations of both serum and plasma BDNF with brain tissue concentrations in the prefrontal cortex and hippocampus have been observed (Elfving et al., 2010; Karege, Schwald, & Cisse, 2002; Klein et al., 2011; Sartorius et al., 2009).

Another potential reason for the null findings in terms of both BDNF genotype and circulating BDNF may be due to the presence of moderators. Multiple factors including

stress (Elzinga et al., 2011; Grassi-Oliveira, Stein, Lopes, Teixeira, & Bauer, 2008; Kauer-Sant'Anna et al., 2007), physical exercise (Ferris, Williams, & Shen, 2007; Gold et al., 2003; Seifert et al., 2010; Zoladz et al., 2008), anti-depressant medications (Chen, Dowlatshahi, MacQueen, Wang, & Young, 2001; Shimizu et al., 2003), weight, gender and menstrual cycle phase (Lommatzsch et al., 2005; Shimada et al., 2014) may influence circulating BDNF concentrations. In addition, gender, exercise and vascular factors (e.g., hypertension) may interact with BDNF genotype (Fukumoto et al., 2010; Kim et al., 2011; Raz et al., 2008, 2009). Furthermore, previous studies have shown an interactive effect between BDNF genotype and early childhood adversity on circulating BDNF in individuals with a history of depression or anxiety (Elzinga et al., 2011) and on hippocampal volume (Carballedo et al., 2013; Gatt et al., 2009). Based on these studies, individuals with Met allele(s) and higher levels of childhood stress may have smaller hippocampal volume or memory performance than those with Met allele(s) but without childhood adversity. The current cohorts did not have data on early life stress experiences. It is possible that there was a mixture of individuals with high and low level of childhood adversity, contributing to null finding when these individuals are examined together. The current study did examine the interactive effect of BDNF and gender, and post-hoc analyses in the current cohorts did not reveal any significant moderating influence of gender. Future investigation could systematically examine the moderating effects of lifestyle and health factors to further elucidate the relationship between BDNF and brain structure and function.

Sample size is another issue to be considered as a contributing factor to the lack of significant effects. The current sample sizes for the BDNF genotype and hippocampus analyses were larger than those in the existing literature (Ns=36–173) (Benjamin et al., 2010; Bueller et al., 2006; Frodl et al., 2007; Karnik et al., 2010; Pezawas et al., 2004; Richter-Schmidinger et al., 2011; Schofield et al., 2009; Szeszko et al., 2005), and the BDNF genotype-memory samples were similar or larger than all but one of the existing studies (Ns=28–475) (Benjamin et al., 2010; Dempster et al., 2005; Egan et al., 2003; Goldberg et al., 2008; Hariri et al., 2003; Hashimoto et al., 2008; Ho et al., 2006; Karnik et al., 2010; Kennedy et al., 2014; Raz et al., 2008 and 2009; Richter-Schmidinger et al., 2011; Schofield et al., 2009; Strauss et al., 2004; Tsai et al., 2008; Yu et al., 2008; but see Miyajima et al., 2008; N=722). In addition, the current sample sizes for the plasma BDNF and hippocampus analyses were similar or larger than in the existing literature (Ns=20–142) (Driscoll et al., 2012; Eker et al., 2010; Erickson et al., 2010; Rizos et al., 2011), and the plasma BDNF-memory cohorts were similar or larger than all but two of the existing studies (Ns=35–429) (Dias et al., 2009; Driscoll et al., 2012; Gunstad et al., 2008; Li et al., 2009; O'Bryant et al., 2010; Ruiz de Azua et al., 2013; Yu et al., 2008; but see Komulainen et al., 2008 (N=1389); Shimada et al., 2014 (N=4463). Importantly, significant associations were not observed in either of the two current cohorts, and the observed beta weights were in the small range (Cohen, Manion, & Morrison, 2007). Prior significant associations were observed in both large (e.g., Komulainen et al., 2008; Shimada et al., 2014) and small (e.g., Bueller et al., 2006; Hariri et al., 2003) sample studies. In a post-hoc analysis with the ADRC cohort, we were able to include additional participants to examine the effects of either BDNF genotype (n=647) or plasma BDNF (n=189) on the Associate Learning task.

However, no significant effects were observed. It appears unlikely that sample size was the major limiting issue in the current study.

Furthermore, the ADNI cohort consisted of three racial groups (White, Black, and Other races), and the ADRC cohort consisted of two racial groups (White and Black) (see Supplementary Tables 3 and 4). Previous studies have demonstrated differences in BDNF allele frequency among different racial populations (e.g., Petryshen et al., 2010; Shimizu et al., 2004). Some cohorts of the current study also showed frequency and/or plasma BDNF differences across racial groups. Thus, we examined BDNF effects in the largest racial group (Whites) and observed no differences in terms of results (data not shown).

There are some limitations in the current study that need to be addressed. First, for the ADRC cohort the scanner field strength and the Freesurfer version varied within the cohort. Although this variation was adjusted for in analyses, this may not have been sufficient to overcome any noise that was introduced into the data. In addition, different memory tests were administered across cohorts, which could have resulted in differing estimates of the episodic memory construct. However, our results also suggest that the failure to find an effect in one cohort was not specific to the particular set of memory tasks used for that cohort, but instead a more general phenonemenon observed across cohorts.

Overall, the current study did not find a significant BDNF effect, in terms of either genotype or plasma, on either hippocampal volume or memory. These null results were observed in two independent cohorts with sample sizes similar or larger than those in the existing literature. Thus, our findings suggest that Val66Met BDNF polymorphism and plasma BDNF may not be robust predictors for variance in hippocampal volume or memory in middle age and older adult cohorts. However, longitudinal investigations, and the incorporation of other brain regions and cognitive domains as well as potential moderators, may reveal protective roles of BDNF.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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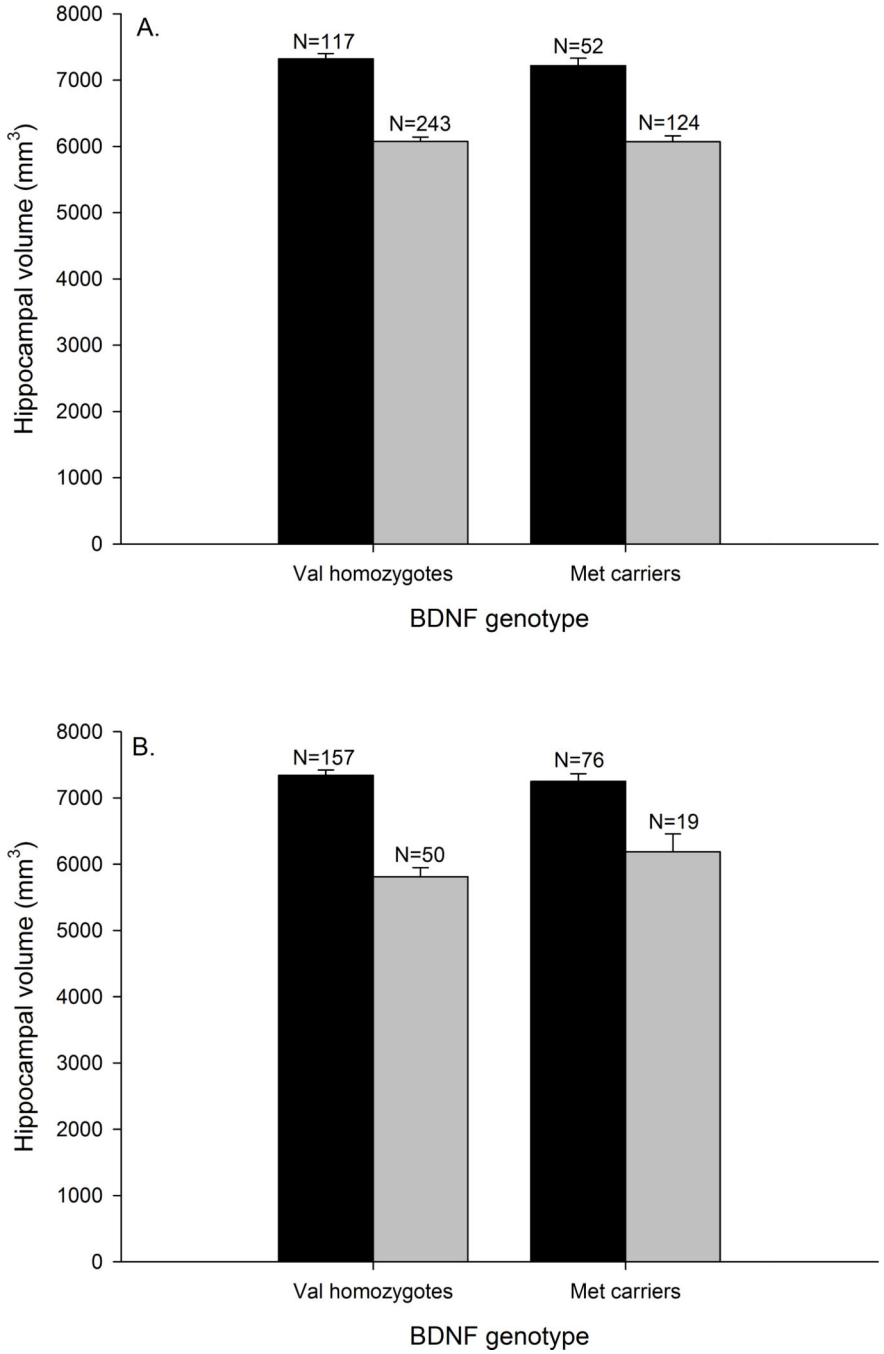

Figure 1.

BDNF genotype and hippocampal volume. A) ADNI cohort (CDR=0: F(1,167)=.520, p=.472; CDR>1: F(1,365)=.001, p=.973); B) ADRC cohort (CDR=0: F(1,231)=.400, p=.528; CDR>1: F(1,67)=1.822, p=.182). Black bars = Cognitively normal, and gray bars = Early-stage dementia. Data represent group means for hippocampal volume, and error bars are standard error of the mean.

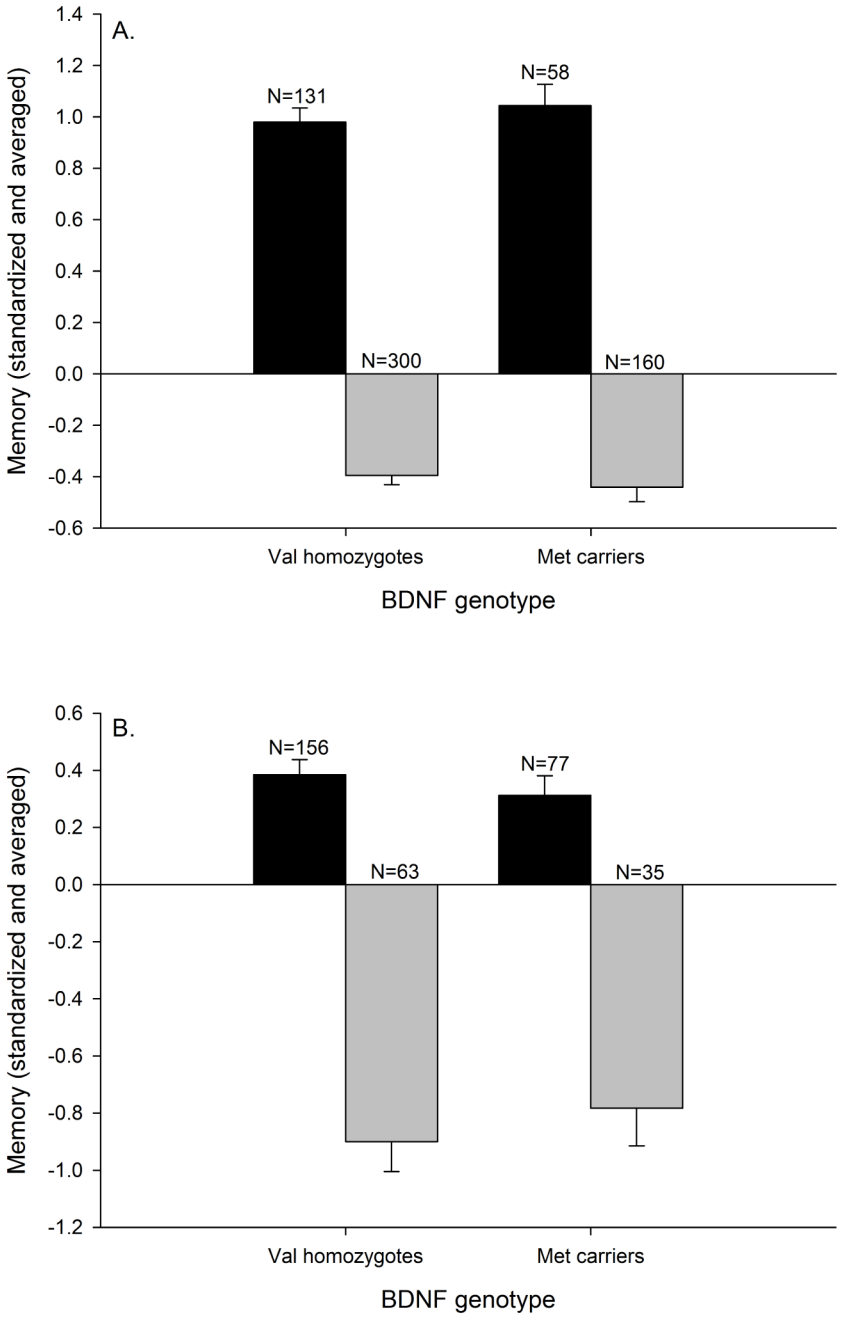

Figure 2.

BDNF genotype and memory. A) ADNI cohort (CDR=0: F(1,187)=.424, p=.516; CDR>1: F(1,458)=.515, p=.473); B) ADRC cohort (CDR=0: F(1,231)=.647, p=.472; CDR>1: F(1,96)=.464, p=.498). Black bars = Cognitively normal, and gray bars = Early-stage dementia. Data represent group means for the standardized memory composite, and error bars are standard error of the mean.

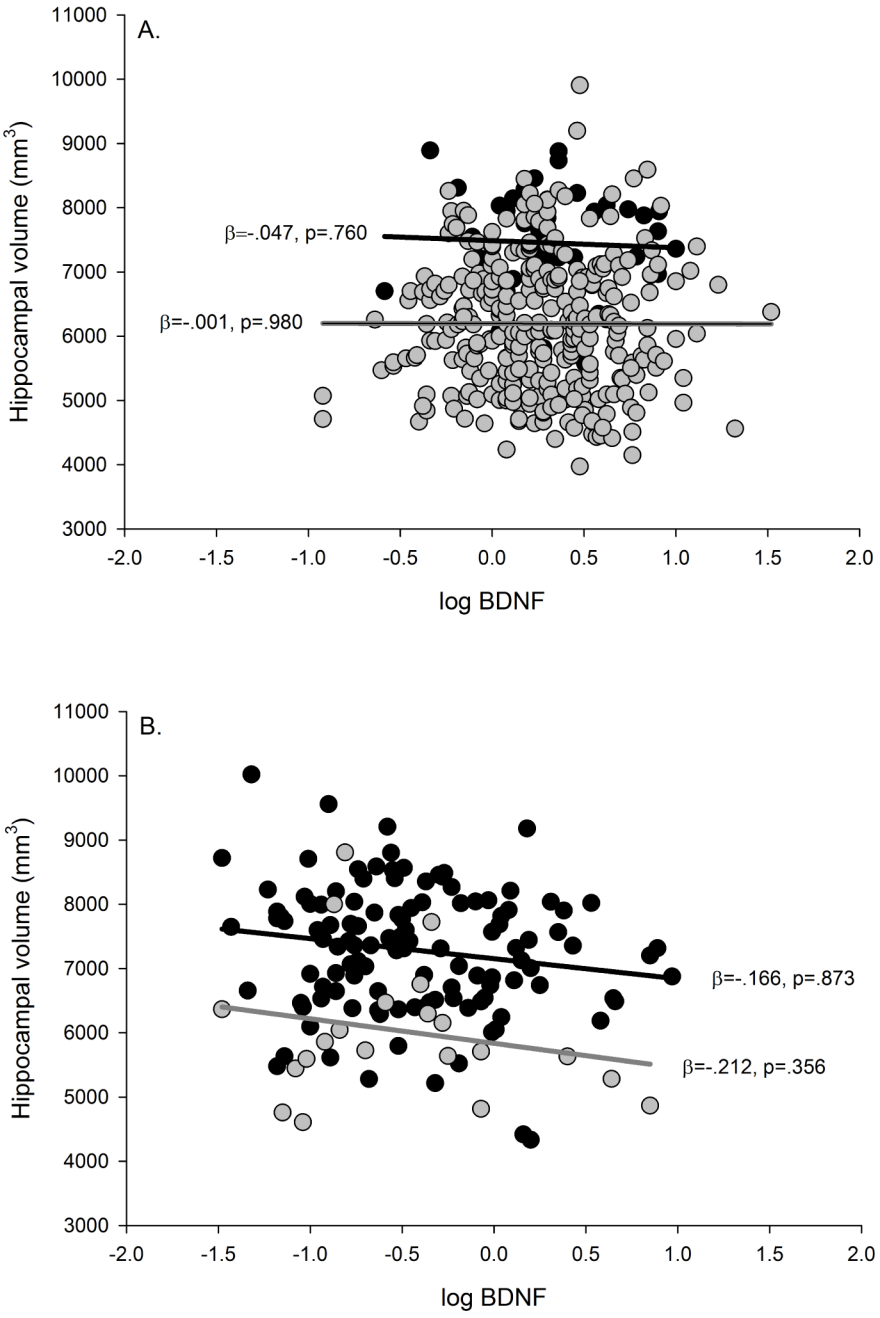

Figure 3.

Plasma BDNF and hippocampal volume. A) ADNI cohort; B) ADRC cohort. Black circles = Cognitively normal, and gray circles = Early-stage dementia. The black line represents the regression line for the cognitively normal group, and the gray line represents the regression line for the early-stage dementia group. P-values are adjusted FDR corrected.

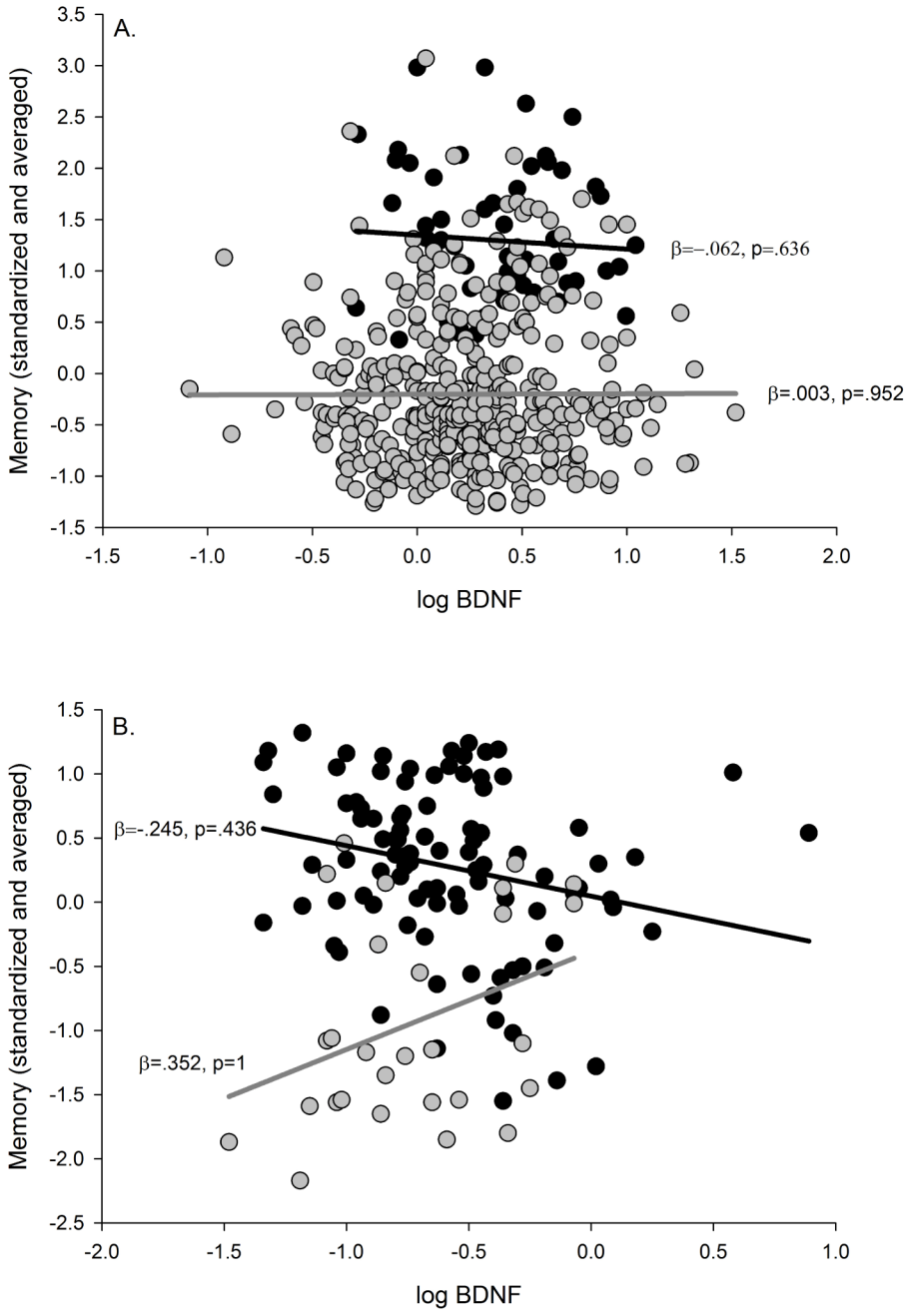

Figure 4.

Plasma BDNF and memory. A) ADNI cohort; B) ADRC cohort. Black circles = Cognitively normal, and gray circles = Early-stage dementia. The black line represents the regression line for the cognitively normal group and the gray line represents the regression line for the early-stage dementia group. P-values are adjusted FDR corrected.

Table 1

Descriptive statistics for the MRI analyses (ADNI)

	Cognitively Normal		Early-Stage Dementia	
	Genotype	**Plasma**	**Genotype**	**Plasma**
N	169	45	367	310
Age, years (mean (SD))	75 (5)	74 (6)	74 (7)$^{+}$	74 (7)
Female, *n* (%)	81 (48)	22 (49)	150 (41)	120 (39)
Education, years (mean (SD))	16 (3)	6 (3)	15 (3)*	16 (3)
*APOE*ε4+, *n* (%)	44 (26)	5 (11)	227 (62)**	187 (60)**
ε2/ε2, *n* (%)	2 (1)	0 (0)	0 (0)	0 (0)
ε2/ε3, *n* (%)	22 (13)	13 (29)	10 (3)	9 (3)
ε2/ε4, *n* (%)	1 (1)	1 (2)	6 (2)	6 (2)
ε3/ε3, *n* (%)	101 (60)	27 (60)	130 (35)	114 (37)
ε3/ε4, *n* (%)	41 (24)	4 (9)	165 (45)	134 (43)
ε4/ε4, *n* (%)	2 (1)	0 (0)	56 (15)	47 (15)
CDR 0.5, *n* (%)	n/a	n/a	314 (86)	281 (91)
MMSE (mean (SD))	29 (1)	29 (1)	26 (3)**	26 (2)**
BDNF met+, *n* (%)	52 (31)	15 (33)	124 (34)	110 (35)
Val/Val, *n* (%)	117 (69)	30 (67)	243 (66)	200 (65)
Val/Met, *n* (%)	48 (28)	15 (33)	115 (31)	101 (33)
Met/Met, *n* (%)	4 (2)	0 (0)	9 (2)	9 (3)
Log plasma BDNF (mean(SD))	n/a	.32 (.34)	n/a	.27 (.39)
Hippocampus, mm^3 (mean (SD))	7291 (846)	7452 (805)	6072 (1037)**	6195 (1035)**

Note:

$^{+}$p<.1;

*p<.05;

**p<.001 for cognitively normal (CDR=0) compared to early-stage dementia (CDR=0.5/1).

Table 2

Descriptive statistics for the cognitive analyses (ADNI)

	Cognitively Normal		Early Stage Dementia	
	Genotype	**Plasma**	**Genotype**	**Plasma**
N	189	60	460	388
Age, years (mean (SD))	77 (5)	76 (6)	76 (7)	76 (7)
Female, *n* (%)	90 (48)	30 (50)	168 (37)*	134 (35)*
Education, years (mean (SD))	16 (3)	15 (3)	16 (3)	16 (3)
APOE ε4+, *n* (%)	51 (27)	7 (12)	266 (58)**	222 (57)**
ε2/ε2, *n* (%)	2 (1)	0 (0)	0 (0)	0 (0)
ε2/ε3, *n* (%)	27 (14)	16 (27)	14 (3)	11 (3)
ε2/ε4, *n* (%)	2 (1)	1 (2)	10 (2)	8 (2)
ε3/ε3, *n* (%)	109 (58)	37 (62)	180 (39)	155 (40)
ε3/ε4, *n* (%)	46 (24)	6 (10)	192 (42)	160 (41)
ε4/ε4, *n* (%)	3 (2)	0 (0)	64 (14)	54 (14)
CDR 0.5, *n* (%)	n/a	n/a	349 (76)	311 (80)
MMSE (mean (SD))	29 (1)	29 (1)	25 (4)**	25 (4)**
BDNF met+, *n* (%)	58 (31)	17 (28)	160 (35)	132 (34)
Val/Val, *n* (%)	131 (69)	43 (72)	300 (65)	256 (66)
Val/Met, *n* (%)	54 (29)	16 (27)	145 (32)	121 (31)
Met/Met, *n* (%)	4 (2)	1 (2)	15 (3)	11 (3)
Log plasma BDNF (mean(SD))	n/a	.36 (.32)	n/a	.25 (.40)*
WMS-R Logical Memory - immediate (mean (SD))	15 (4)	14 (4)	7 (4)**	7 (4)**
WMS-R Logical Memory - delayed (mean (SD))	13 (4)	13 (5)	4 (4)**	4 (4)**
RAVLT - immediate (mean (SD))	44 (10)	42 (9)	27 (10)**	27 (10)**
RAVLT - delayed (mean (SD))	8 (4)	7 (4)	2 (3)**	2 (3)**
Standardized memory composite (mean (SD))	4.00 (2.48)	5.20 (2.79)	−1.64 (2.63)**	−.80 (2.89)**

Note:

+ p<.1;

* p<.05;

** p<.001 for cognitively normal (CDR=0) compared to early-stage dementia (CDR=0.5/1).

WMS-R = Wechsler Memory Scale – Revised; RAVLT = Rey Auditory Verbal Learning Test. WMS-R Logical Memory – immediate: Range 0–25; High score = good; WMS-R Logical Memory – delayed: Range 0–25; High score = good; RAVLT – immediate: Range 0–75; High score = good; RAVLT – delayed: Range 0–15; High score = good.

Table 3

Descriptive statistics for the MRI analyses (ADRC)

	Cognitively Normal		Early Stage Dementia	
	Genotype	**Plasma**	**Genotype**	**Plasma**
N	233	121	69	21
Age, years (mean (SD))	70 (10)	71 (7)	77 (6)**	75 (5)*
Female, *n* (%)	151 (65)	79 (65)	41 (59)	12 (57)
Education, years (mean (SD))	16 (3)	15 (3)	14 (3)**	14 (3)*
APOE ε4+, *n* (%)	75 (32)	32 (26)	39 (57)**	14 (67)**
ε2/ε2, *n* (%)	2 (1)	1 (1)	0 (0)	0 (0)
ε2/ε3, *n* (%)	33 (14)	19 (16)	1 (1)	0 (0)
ε2/ε4, *n* (%)	8 (3)	3 (2)	1 (1)	1 (5)
ε3/ε3, *n* (%)	123 (53)	69 (57)	29 (42)	7 (33)
ε3/ε4, *n* (%)	60 (26)	26 (21)	36 (52)	12 (57)
ε4/ε4, *n* (%)	7 (3)	3 (2)	2 (3)	1 (5)
CDR 0.5, *n* (%)	n/a	n/a	46 (67)	16 (76)
MMSE (mean(SD))	29 (1)	29 (1)	25 (4)**	27 (3)*
BDNF met+, *n* (%)	76 (33)	38 (31)	19 (28)	6 (29)
Val/Val, *n* (%)	157 (67)	83 (69)	50 (72)	15 (71)
Val/Met, *n* (%)	71 (30)	34 (28)	19 (28)	6 (29)
Met/Met, *n* (%)	5 (2)	4 (3)	0 (0)	0 (0)
Log plasma BDNF (mean(SD))	n/a	−.43 (.53)	n/a	−.49 (.60)
Hippocampus, mm^3 (mean (SD))	7310 (1027)	7287 (988)	5915 (1033)**	6024 (1083)**

Note:

+ p<.1;

* p<.05;

** p<.001 for cognitively normal (CDR=0) compared to early-stage dementia (CDR=0.5/1).

Table 4

Descriptive statistics for the cognitive analyses (ADRC)

	Cognitively Normal		Early Stage Dementia	
	Genotype	**Plasma**	**Genotype**	**Plasma**
N	233	95	98	28
Age, years (mean (SD))	75 (8)	72 (6)	79 (8)**	74 (6)
Female, *n* (%)	141 (61)	59 (62)	50 (51)	14 (50)
Education, years (mean (SD))	15 (3)	15 (3)	15 (3)*	15 (3)
APOE ε4+, *n* (%)	68 (29)	30 (32)	48 (49)**	14 (50)+
ε2/ε2, *n* (%)	1 (0)	1 (1)	0 (0)	0 (0)
ε2/ε3, *n* (%)	30 (13)	14 (15)	10 (10)	2 (7)
ε2/ε4, *n* (%)	7 (3)	3 (3)	5 (5)	1 (4)
ε3/ε3, *n* (%)	134 (58)	50 (53)	40 (41)	12 (43)
ε3/ε4, *n* (%)	55 (24)	25 (26)	36 (37)	10 (36)
ε4/ε4, *n* (%)	6 (3)	2 (2)	7 (7)	3 (11)
CDR 0.5, *n* (%)	n/a	n/a	71 (72)	25 (89)
MMSE (mean (SD))	29 (1)	29 (1)	26 (3)**	27 (2)*
BDNF met+, *n* (%)	77 (33)	31 (33)	35 (36)	10 (36)
Val/Val, *n* (%)	156 (67)	64 (67)	63 (64)	18 (64)
Val/Met, *n* (%)	72 (31)	29 (31)	33 (34)	10 (36)
Met/Met, *n* (%)	5 (2)	2 (2)	2 (2)	0 (0)
Log plasma BDNF, (mean(SD))	n/a	−.58 (.40)	n/a	−.73 (.37)+
WMS-R Logical Memory - immediate (mean (SD))	14 (4)	13 (4)	8 (5)**	9 (5)**
WMS-R Logical Memory - delayed (mean (SD))	13 (4)	12 (4)	6 (5)**	6 (5)**
WMS Associate Learning (mean (SD))	15 (4)	14 (3)	10 (4)**	10 (3)**
Free and Cued Selective Reminding Test (mean (SD))	30 (6)	30 (6)	17 (10)**	18 (8)**
Standardized memory composite (mean (SD))	1.44 (2.56)	1.11 (2.60)	−3.43 (3.25)**	−3.75 (3.22)**

Note:

+ p<.1;

* p<.05;

** p<.001 for cognitively normal (CDR=0) compared to early-stage dementia (CDR=0.5/1).

WMS-R = Wechsler Memory Scale – Revised; RAVLT = Rey Auditory Verbal Learning Test. WMS-R Logical Memory – immediate: Range 0–25; High score = good; WMS-R Logical Memory – delayed: Range 0–25; High score = good; WMS Associate Learning: Range 0–21; High score = good; Free and Cued Selective Reminding Test: Range 0–48; High score = good.

Table 5

BDNF genotype and plasma BDNF analyses statistics

	Hippocampus				Memory			
	Genotype		*Plasma*		*Genotype*		*Plasma*	
	ADNI	**ADRC**	**ADNI**	**ADRC**	**ADNI**	**ADRC**	**ADNI**	**ADRC**
Unadjusted								
R-sq	.001	.001	.000	.020	.001	.001	.003	.000
F	.448	.199	.048	2.848	.832	.186	1.333	.025
Beta	−.029	.026	.012	−.141	−.036	−.024	.055	.014
p-value	.504	.655	.826	.094***	.362	.667	.249	.876
Adjusted								
R-sq	.000	.000	.001	.002	.000	.000	.000	.001
F	.203	.182	.601	.375	.057	.001	.015	.232
Beta	−.016	.017	−.035	−.053	−.006	−.001	.005	−.033
p-value	.653	.670	.439	.541	.811	.978	.901	.631
Unadjusted BDNFxCDR								
R-sq	.000	.006	.000	.000	.001	.002	.000	.045
F	.249	2.216	.051	.027	.839	1.151	.212	9.025
Beta	.037	.096	.036	−.014	−.052	.065	.059	.244
p-value	.618	.138	.821	.869	.360	.284	.645	.003**
Adjusted BDNFxCDR								
R-sq	.000	.001	.000	.000	.003	.003	.000	.054
F	.251	.869	.161	.086	3.561	1.760	.343	13.930
Beta	.034	.048	−.058	−.021	−.103	.078	.072	.271
p-value	.617	.352	.689	.769	.060+	.186	.559	.000*

*False discovery rate adjusted p=.023;

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** False discovery rate adjusted p=.116;

*** False discovery rate adjusted p=.724;

+ False discovery rate adjusted p=.924

Table 6

Post-hoc analyses statistics

	Hippocampus				Memory			
	Genotype		***Plasma***		***Genotype***		***Plasma***	
	ADNI	**ADRC**	**ADNI**	**ADRC**	**ADNI**	**ADRC**	**ADNI**	**ADRC**
BDNFxAge								
R-sq	.002	.006	.004	.008	.000	.004	.000	.004
F	1.520	3.662	1.817	1.945	.409	2.401	.094	.868
Beta	.052	−.090	.062	.093	−.021	−.074	.011	.063
p-value	.218	.057**	.179	.166	.523	.122	.759	.353
BDNFxAgexCDR								
R-sq	.001	.002	.000	.005	.000	.000	.002	.001
F	.635	1.277	.143	1.165	.035	.237	1.591	.136
Beta	−.081	−.060	−.076	−.111	.015	.029	−.190	.030
p-value	.426	.259	.706	.282	.851	.627	.208	.713
BDNFxGender								
R-sq	.003	.002	.000	.006	.000	.000	.001	.001
F	2.524	1.481	.175	1.564	.012	.269	.600	.195
Beta	−.099	.068	−.031	−.100	−.005	.032	−.050	.039
p-value	.113	.225	.676	.213	.911	.604	.439	.660
BDNFxGenderxCDR								
R-sq	.002	.002	.000	.002	.001	.000	.004	.010
F	1.331	1.271	.004	.379	.788	.012	2.895	2.611
Beta	−.137	.074	.016	−.052	−.084	.010	−.375	−.163
p-value	.249	.261	.947	.539	.375	.914	.090*	.109

*False discovery rate adjusted p=.770;

**False discovery rate adjusted p=1

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