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Hippocampal Volumes and the BDNF val66met Polymorphism in Geriatric Major Depression

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Abstract

Objectives—Structural abnormalities in the hippocampus have been implicated in the pathophysiology of major depressive disorder (MDD). The brain derived neurotrophic factor (*BDNF*) val66met polymorphism may contribute to these abnormalities and therefore confer vulnerability to MDD. This study examined whether there is a relationship among *BDNF* genotype, hippocampal volumes, and MDD in older adults.

Methods—Thirty-three older adults with MDD and 23 psychiatrically normal comparison subjects were studied. Structural MRI analysis was used to quantify hippocampal volumes. A repeated measures ANCOVA examined the relationships among *BDNF* val66met (val/val, met carrier), diagnosis (depressed, non-depressed), and hippocampal volumes (right, left). Age, gender, education, and whole brain volume were included as covariates.

Results—Elderly MDD *BDNF* val/val homozygotes had significantly higher right hippocampal volumes compared with non-depressed val/val subjects. However, there was no difference between the depressed and healthy non-depressed met carriers. Additionally, depressed met carriers had an earlier age of onset of depressive illness than val/val homozygotes but age of onset did not moderate the relationship between hippocampal volumes and MDD diagnosis.

Conclusion—These results provide preliminary evidence of a neuroprotective role of the val/val genotype, suggesting neurotrophic factor production protects against pathophysiological processes triggered by depression in older adults with later age of onset of MDD. The *BDNF* val66met polymorphism may play a salient role in structural alterations of the hippocampus in older adults with MDD.

Keywords

Geriatric depression; BDNF val66met; hippocampus; older adults

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INTRODUCTION

Geriatric major depression is often accompanied by brain alterations, particularly in structures implicated in mood regulation. Magnetic resonance imaging (MRI) has identified structural abnormalities hypothesized to be relevant to the pathophysiology of geriatric depression, including small volumes in the prefrontal cortex, (1–3), the anterior cingulate gyrus (3,4), the amygdala (5), and the hippocampus (4,6–8).

The hippocampus is a critical component of the distributed network critical for affect regulation, which includes the thalamus, the basal ganglia, the prefrontal cortex, the amygdala, and the cingulate gyrus (9,10). The hippocampus plays an important role in verbal and visual memory deficits that often accompany geriatric major depression (11,12) and is sensitive to the effects of aging (13,14) and to ischemic changes (15). For these reasons, hippocampal abnormalities are of particular interest in geriatric depression.

Structural changes in the aging hippocampus may influence its function. Smaller hippocampal volume is related to poorer verbal memory in healthy elderly individuals (16) and in older persons with major depression (12). Further, smaller hippocampal volume is associated with lower memory scores of depressed patients after antidepressant treatment (7). Hippocampal abnormalities may therefore predispose to, or interact with depression in older adults and contribute to cognitive impairment.

To date, studies of hippocampal volume in geriatric depression have yielded conflicting reports. Although some studies have shown that older depressed patients have smaller hippocampal volumes than controls (6,8), others have found no differences (17,18). Laterality differences in studies of hippocampal volumes in geriatric depression are inconsistent, with some detecting smaller hippocampal volume on the right (4,7), whereas others report smaller hippocampal volume on the left (19). Clinical heterogeneity and/or genetic variations may account for some of the discrepant results.

Hippocampal volume may also be influenced by neurotrophic factors (20). One such neurotrophin is brain derived neurotrophic factor (BDNF), which is widely distributed in the adult brain and has been implicated in structural abnormalities of the human hippocampus (21,22). A single nucleotide polymorphism in the *BDNF* gene has been identified causing a valine (val) to methionine (met) substitution at codon 66 in the prodomain (*BDNF*_{met}) (23,24). Cultured rat hippocampal neurons transfected with the met allele have impaired BDNF production and distribution in the hippocampus compared to rats with the val/val allele (24). The val/val *BDNF* allele may be associated with higher dendritic complexity and increased number of both neuronal and glia cells, the mechanism of which may be attributable to enhancing neurogenesis or decreasing cell death (23).

BDNF may be relevant to the pathophysiology of major depression. Prolonged exposure to chronic stress may ultimately decrease BDNF production in the hippocampus and predispose an individual to depressive symptoms (9). The *BDNF* met allele has been associated with smaller hippocampal volumes in both depressed and non-depressed younger adults relative to val/val homozygotes (25), although these results have not been replicated (26). There is some evidence that older individuals with the *BDNF* met allele may be at an increased risk for depressive syndromes (27) although negative findings also exist (28).

In healthy older adults, the *BDNF* met allele appears to be associated with reduced performance in several cognitive domains (29) including fluid intelligence, processing speed, and memory. Furthermore, older non-depressed *BDNF* met allele carriers with increased vascular risk exhibit declines in memory performance (30). Therefore it is possible

that *BDNF* allele status may interact with cognitive status and age-related vascular changes to predispose individuals to geriatric depression.

The relationship among *BDNF* val66met allele status, hippocampal volumes, aging, and depression is complex and has not been fully explored. One recent study of older adults examining the interaction between *BDNF* val66met allele status, hippocampal volume, and major depression in older adults found no association (31). However, the dearth of studies in this area warrants the need for further investigation.

The objective of the present study was to compare hippocampal volumes of depressed older adults and non-depressed comparison subjects and examine the relationship with the *BDNF* val66met polymorphism. We hypothesized that 1) depressed subjects would have abnormal hippocampal volumes relative to non-depressed comparison subjects, and that 2) this relationship would be influenced by presence of the *BDNF* val66met allele.

METHODS

Subjects

Thirty-three older adults (age ≥ 60 years) with a DSM-IV diagnosis of Major Depressive Disorder and 23 community dwelling non-psychiatric comparison subjects participated in this study. Depressed subjects were recruited through radio and print advertisement in community radio stations and newspapers. Non-depressed comparison subjects were recruited through print advertisements community newspapers. All study subjects included in this analysis were Caucasian; African-American ($n=6$) and Asian subjects ($n=1$) were excluded due to the small number of subjects recruited and the ethnicity differences in the distribution of *BDNF* polymorphisms (23) in these groups. Written informed consent, approved by the Weill Cornell Institutional Review Board, was obtained for all participants.

The depressed group met DSM- IV-TR criteria for unipolar major depression without psychotic features according to the SCID-R interview and had a score of 18 or greater on the 24-item Hamilton Depression Rating Scale (HDRS) after a 15 day placebo lead-in antidepressant wash-out phase subsequent to which an escitalopram treatment trial was started. Exclusion criteria for the depressed group included: 1) History or presence of other axis I psychiatric disorders before the onset of depression; 2) neurological disorders (i.e., presence of delirium, history of stroke, head trauma, multiple sclerosis, and brain degenerative diseases); 3) major medical illness (i.e. metastatic cancer, brain tumors, unstable cardiac, hepatic or renal disease, myocardial infarction, or stroke) within the 3 months preceding the study; 4) conditions often associated with depression (i.e. endocrinopathies other than diabetes, lymphoma, pancreatic cancer); 5) use of drugs that may be associated with development of depressive symptoms (i.e. treatment with steroids, alpha-methyl- dopa, clonidine, reserpine, tamoxifen, and cimetidine); 6) significant cognitive compromise as determined by a Mini-Mental State Examination score <25 and 7) the presence of metal implants. Exclusion criteria for healthy non-depressed subjects was the same as above with the additional criteria of absence of any history of psychiatric illness, the diagnosis of depression, and an HDRS score lower than 7.

MRI Procedures

Image Acquisition—Scanning took place on a 1.5T Siemens Vision Scanner (Erlangen, Germany) housed at the Nathan Kline Institute (NKI) Center for Advanced Brain Imaging. Depressed subjects were scanned after the antidepressant wash-out phase but prior to onset of escitalopram treatment trial. Non-depressed comparison subjects were not on psychotropic drugs at the time of scanning. All subjects received a magnetization prepared

rapidly acquired gradient echo (MPRAGE) scan (TR=11.6ms, TE=4.0 ms, matrix=256×256, FOV=320mm, NEX=1, slice thickness = 1.25 mm, 172 slices, no gap), as well as a turbo dual spin echo scan (TSE; TR=ms, TE=22/90 ms, matrix=256×256, FOV=240 mm, slice thickness=5mm, 26 slices, no gap).

MR Image Processing: After acquisition, all MR images were processed using MEdX 3.23 (Sensor Systems, Sterling, VA). The MPRAGE images were reformatted off-line and corrected for undesirable effects of head tilt, pitch and rotation using standard neuroanatomical landmarks. The realignment process consisted of the following steps: First, to correct for head pitch, the axial plane was tilted so it passed through the anterior and posterior commissures (incorporating the AC-PC line). In the next step, head tilt was adjusted using the coronal plane, which was fixed interactively by forcing it through the orbits in such a way that the coronal cross section of the orbits on the right and left side of the head was level and of equal diameter. After correcting for head tilt, the mid-sagittal plane was moved to pass along the straight line drawn through the interhemispheric fissure.

Volumetric Image analysis: Images were displayed on a 21-inch monitor and each region of interest (ROI) was traced manually. All questionable cases were resolved by consulting the corresponding images in neuroanatomy atlases. Intra-rater reliability was computed from measures obtained by comparing tracings of 10 random brains to re-tracings at a follow-up timepoint. The intra-rater correlation for intra-rater reliability was used and the resulting reliability estimates for all ROIs exceeded $r=0.90$. The hippocampus was measured separately for each hemisphere. The hippocampus ROI was modified from guidelines established by Rodrigue and Raz (32). Examples of traced ROIs are depicted in Figure 1. Manual tracing of subregions was performed on every coronal slice of the hippocampus, starting from the most anterior slice, and moving posteriorly according to the following boundaries: The rostral boundary was defined as the slice at which the mamillary bodies appeared and were fully connected; the caudal boundary was the slice at which the fornices appeared to be rising from the fimbria; the lateral border was defined by the inferior horn of the lateral ventricles while the medial border was delineated by cerebrospinal fluid from the cisterns. Next, to obtain gray matter volumes, each ROI was multiplied by the individual subject's whole brain gray matter mask that was created using FSL's Brain Extraction Tool (BET) and FMRI's Automated Segmentation Tool (FAST) software (33). Whole brain volume brain volume was calculated for each subject by summing the total white matter, gray matter, and cerebrospinal fluid volumes that were obtained using (FAST).

Genotyping

Genomic DNA was isolated from whole blood samples using the QIAamp DNA blood kit (Qiagen) according to the manufacturer's standard protocol. DNA samples were genotyped at *BDNF* val66met (rs6265) using a commercially available Taqman 5' exonuclease assay (ABI). All genotype data was visually inspected to ensure clear allelic discrimination. All samples whose initial genotype was not clear were re-genotyped in duplicate and all such samples provided clear concordant genotypes on rerun.

Data Analysis

The Hardy-Weinberg Equilibrium was tested using chi-square tests. Chi-square tests were also used to compare the allele frequencies between depressed and comparison subjects. Independent group t-tests were used to examine differences in demographic and clinical variables between the diagnostic groups and between alleles within each group. The relationship of diagnosis, *BDNF* genotype and hippocampus volumes was examined using a repeated measures analysis of covariance (ANCOVA), with left and right hippocampus volumes as the within-subjects variable. Diagnosis (depressed, comparison) and *BDNF*

genotype (val/val, met carrier) were categorical between-subjects factors. Age, gender, education, and whole brain volume, were entered as covariates to statistically control for their influence. Post-hoc ANCOVAs were conducted to test hippocampal differences between diagnosis groups. The Statistical Package for Social Sciences (SPSS) version 14 was used for all statistical analyses.

RESULTS

A total of 56 subjects were included in this analysis. Of these, 33 met criteria for major depression after a 15-day antidepressant washout phase, and 23 were non-psychiatric comparison subjects that were not on any psychotropic medication. There were no significant differences between depressed and non-depressed comparison subjects in age (depressed *mean*: 72.3, *SD*: 6.8 vs. non-depressed *mean*: 70.7, *SD*: 5.7, $t = -0.9$, $df=54$, $p=0.374$), gender (depressed 36.4% male vs non-depressed 39.1% male, $\chi^2=0.4$, $df=1$, $p=0.833$), education (depressed *mean*: 16.1, *SD*: 2.9 vs. non-depressed *mean*: 16.9, *SD*: 2.5, $t=1.0$, $df=54$, $p=0.314$) or cognitive impairment (MMSE) (depressed *mean*: 28.6, *SD*: 1.3 vs. non-depressed *mean*: 28.7, *SD*: 1.2, $t=0.32$, $df=54$, $p=0.753$). *BDNF* genotypes were similarly distributed between depressed and non-depressed comparison subjects ($\chi^2=2.3$, $df=2$, $p=0.3$) and were in Hardy-Weinberg equilibrium. There were three met/met homozygotes among depressed subjects, and none among comparison subjects. Due to the scarcity of met/met homozygotes, those subjects were combined with the val/met allele subjects to form a “met carriers” category.

There were no differences between depressed and non-depressed comparison subjects in memory [HVLT Immediate Recall Total Correct (Mann Whitney U (51) = 314.5, $Z = -0.143$, $p=0.887$), Delayed Recall Correct (Mann Whitney U (51) = 320.5, $Z = -0.029$, $p=0.977$)], or DRS scores (DRS Total: Mann Whitney U (55) = 361, $Z = -0.12$, $p=0.905$]. Furthermore, there were no differences between *BDNF* alleles within non-depressed or depressed subjects in memory or DRS scores (Table 1).

BDNF met carriers and val/val homozygotes did not significantly in sex, age, years of education, or cognitive impairment or whole brain volume in either the depressed or non-depressed comparison groups (Table 1). In the depressed group, there were no significant differences by *BDNF* allele in depression severity, number of previous episodes, or length of illness or anxiety as measured by the Clinical Anxiety Scale (34) (Table 1). Furthermore, there were no differences in lifetime history of antidepressant use between depressed val/val and met carriers prior to study entry ($\chi^2=0.20$, $df=1$, Fisher's exact $p=0.722$) or in use of antidepressants in the year prior to study entry between these groups ($\chi^2=2.0$, $df=1$, Fisher's exact $p=0.257$). Depressed met carriers, however, had a significantly younger mean age at onset of MDD when compared to depressed val/val subjects (Table 1).

Repeated measures ANCOVA indicated that the relationship between *BDNF* genotype and diagnostic group varied across left and right hippocampi, as indicated by significant interaction between diagnosis, *BDNF* genotype, and hemisphere ($F_{(1,48)}=6.25$, $p=0.02$). To further explore this relationship, post-hoc ANCOVAs were conducted to test differences in hippocampal volume of diagnosis by genotype in each hemisphere. Depressed val/val subjects had greater right hippocampal volume than non-depressed val/val comparison subjects (depressed val/val *mean*=2.34, *SD*=0.3; non-depressed *mean*=2.0, *SD*=0.2, $F_{(1,23)}=5.3$, $p=0.03$; Figure 2). There were no significant differences in left hippocampal volume between depressed and normal comparison subjects with the val/val genotype ($F_{(1,23)}=2.1$, $p=0.23$). Furthermore, there were no significant differences in hippocampal volumes between depressed and comparison met carriers (Left: $F_{(1,21)}=2.5$, $p=0.13$; Right: $F_{(1,21)}=0.03$, $p=0.88$).

To explore the relationship between *BDNF* and age of onset of depression, we conducted a multiple regression analysis with *BDNF* allele status (met carrier vs. val/val) and hippocampal volume as predictors of age of onset. We found that *BDNF* allele significantly predicts age of onset ($F_{(1,30)}=10.97, p=0.002$, Adjusted $R^2=0.25$). Addition of either adjusted right hippocampal volume ($R^2=0.257$) or adjusted left hippocampal volume ($R^2=0.38$) did not significantly account for any additional variance in this model.

To examine the possibility that *BDNF* may be related to hippocampal function in the subgroup of depressed older adults, we examined the relationship between *BDNF* allele (met carrier vs. val/val homozygote) and HVLT delayed recall total and found that *BDNF* allele did not predict memory performance ($F_{(1,27)}=0.613, p=0.441$). Furthermore, hippocampal volume (adjusted for whole brain volume, age, education, and gender as in our original model) on both the left ($F_{(5,27)}=1.692, p=0.178$) and right ($F_{(5,27)}=0.169, p=0.178$) was unrelated to delayed recall. In order to test whether a hippocampal volume may have influenced the relationship between *BDNF* allele and delayed recall, we examined whether adding hippocampal volume changed the regression results. We found that neither right hippocampal volume ($F_{(6,27)}=1.403, p=0.260$) nor left hippocampal volume ($F_{(6,27)}=1.439, p=0.247$) influenced the relationship between *BDNF* allele and delayed recall in this model.

CONCLUSIONS

The main finding of this study is that elderly depressed val/val individuals had higher right, but not left hippocampal volumes when compared to healthy non-depressed comparison val/val homozygotes. There was no difference in hippocampal volumes between depressed and non-depressed comparison met carriers. These findings are consistent with the view that the *BDNF* val66met polymorphism is associated with hippocampal volume (25) and suggest a potential interaction between this polymorphism and resultant hippocampal volume in an older adult population. These results were specific to val/val homozygotes and to the right hippocampus, as there was no hippocampal volume difference from non-depressed comparison subjects among met carriers, or for the left hippocampus, regardless of *BDNF* polymorphism status.

To our knowledge, this is the first study to demonstrate an association between *BDNF* val66met allele status and hippocampal volume in geriatric depression. The only other published report that examined this association in older adults reported negative findings (31). In our study, elderly depressed val/val homozygotes had larger right hippocampal volumes than their non-depressed counterparts. Previous reports of hippocampal volume differences in geriatric depression have been inconclusive (4,6,8,19). The results of our study support the view that these inconsistent findings may be partially explained by the *BDNF* polymorphism.

The effects of the *BDNF* val66met polymorphism may vary across the lifespan. An allele that was previously a risk factor during one stage of development may be a protective factor during another stage (35). Indeed, lower hippocampal volumes for met carriers regardless of depression diagnosis have been reported in younger adults (25). We did not find similar differences in hippocampal volumes within our older sample of *BDNF* met carriers. Rather, our results indicate that elderly depressed *BDNF* val/val homozygotes had larger right hippocampal volumes than their non-depressed val/val counterparts. This difference which could not be attributed to diffuse brain atrophy as whole brain volumes did not differ between *BDNF* val/val and met carriers or between depressed and non-depressed subjects.

It is unclear what mechanism, biological, environmental or otherwise accounts for our finding. However, it is possible that moderating variables may have influenced the relationship between *BDNF* val66met and hippocampal volume in our sample. In order to investigate this possibility, we examined variables related to hippocampal volume and function, namely 1) antidepressant use prior to study entry, and 2) episodic memory, a cognitive domain related to hippocampal function. One possible interpretation of our findings is that differences in history of antidepressant use by depressed subjects influenced hippocampal volume. Antidepressant administration enlarges hippocampal volume by increasing neural progenitor cell numbers in the dentate gyrus, an area that continues to produce new neurons throughout adult life (36,37). However, in our sample, there were no differences in lifetime use of antidepressants or use in the year prior to study entry between depressed *BDNF* met allele carriers and val/val homozygotes. Furthermore, there were no differences in episodic memory between depressed and non-depressed comparison subjects, or between *BDNF* alleles within each group.

Hippocampal volume may be affected by longer exposure to major depressive illness. A greater number of depressive episodes has been associated with low hippocampal volume in depressed young adults, usually on the right (38). In our sample of older adults, however, there was no significant association between number of depressive episodes and right or left hippocampal volume. Thus the difference in hippocampal volume between depressed and non-depressed comparison subjects could not be attributed to differences in the overall exposure to and accumulation of pathophysiological changes occurring during depressive states. In this sample, val/val individuals had a later age of onset of depressive illness than met carriers. A potential explanation is that *BDNF* val/val may exert a neuroprotective effect delaying the onset of depressive illness. Nonetheless, hippocampal volume did not seem to significantly contribute to the relationship between *BDNF* allele and age of onset of major depression.

An ethnic stratification effect cannot be excluded and may influence the findings of a study using a small sample. Allelic frequencies vary across ethnic groups, (39) and subjects may differ in ethnicity even though we limited our sample to Caucasians in order to minimize this effect. Another limitation may be that the study focused only on the effect of a single *BDNF* polymorphism and did not investigate other causes of brain structure changes in elderly individuals. Volume reductions occur as a result of neuronal body loss, decrease in dendritic processes, or loss of overall neuron size. Although *BDNF* may influence these processes, other genetic and non-genetic factors likely influence hippocampal volume. Lastly, we were only able to test one neuropsychological function related to hippocampal function. It is possible that a more thorough evaluation of cognition could uncover specific cognitive functions related to *BDNF* allele status and hippocampal volumes.

The principal finding of this study is that the *BDNF* gene plays a role in hippocampal volumes in depressed older adults. Further research is needed to clarify this role in the etiology of geriatric depressive illness. Recent evidence suggests that the val66met allele may confer neuroprotection when interacting with the S allele of the serotonin transporter gene, indicating possible epigenetic interactions (40). Additional studies are needed to explore the potentially complex genetic interactions and their influence on hippocampal volume and vulnerability to geriatric depression.

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Figure 1.

Manual tracing of subregions was performed on every coronal slice of the hippocampus, starting from the most anterior and advancing to the most posterior slice. Boundaries were as follows: Rostral: slice at which mamillary bodies appear and are fully connected; Caudal: slice at which the fornices appeared to be rising from the fimbria; Lateral: inferior horn of the lateral ventricles; Medial: cerebrospinal fluid from the cisterns.

Figure 2. Covariate adjusted mean values for Left and Right Hippocampus values in by *BDNF* allele for 33 Depressed Older Adults and 23 Normal Controls.

TABLE 1

Difference in Demographic and Clinical Data by BDNF allele (val/val vs Met Carrier) for 33 Depressed Older Adults and 23 Normal Controls.

	Non-Depressed					Depressed				
	Met Carrier (n=11)	Val/Val (n=12)	Statistics			Met Carrier (n=16)	Val/Val (n=17)	Statistics		
Sample Characteristics	M(SD)		t	df	p	M (SD)		t	df	p
Gender (% male)	27%	50%			$\chi^2=1.3, df=1, p=0.27$	25%	47%			$\chi^2=1.7, df=1, p=0.19$
Age (years)	72(4.6)	69.8(6.6)	1.0	21	0.32	72.0(6.4)	72.6(7.4)	-0.3	31	0.80
Education (years)	16.9(2.3)	16.8(2.7)	0.07	21	0.94	16.6(2.6)	15.7(3.1)	0.9	31	0.40
Intracranial Volume	1328.1(100.6)	1305.9(97.8)	0.536	21	0.60	1325.3(147.9)	1375.4(132.24)	-1.03	31	0.312
HDRS [†] at Baseline	1.8(2.1)	1.8(1.7)	-0.02	21	0.99	19.3(4.7)	19.4(4.4)	-0.1	31	0.95
Mint Mental State Exam Total	28.5(1.2)	28.8(1.1)	-0.8	21	0.44	28.6(1.1)	28.5(1.5)	0.3	31	0.74
DRS [†] + Total Score	138.1(3.2)	136.3(3.6)	1.3	21	0.21	137.1(3.8)	136.6(4.9)	0.3	31	0.76
HVLT [‡] Immediate Recall Correct Total	24.6 (3.5)	26.9(3.5)	-1.6	21	0.12	25.6(3.7)	25.1(5.0)	0.3	26	0.75
HVLT [‡] Delayed Recall	9.0 (1.7)	9.3 (1.8)	-0.5	21	.65	9.2 (2.2)	8.4 (3.2)	0.8	26	0.44
Snaith Anxiety Scale Tot	-	-	-	-	-	2.9 (2.2)	5.1 (3.9)	-1.9	30	0.07
Age of Onset (years)	-	-	-	-	-	51.1(18.1)	67.5(6.7)	-3.3	29	0.00
Number of Previous Episodes	-	-	-	-	-	3.8(3.4)	2.2(1.3)	1.7	29	0.11
Length of illness (months)	-	-	-	-	-	23.7 (19.8)	20.1 (19.6)	0.5	29	0.61

[†] HDRS = 24-item Hamilton Depression Rating Scale;

[‡] Mattis Dementia Rating Scale

[§] HVLT = Hopkins Verbal Learning Test

Comparisons between Depressed and Non-Depressed groups in age ($t=-0.9$, $df=54$, $p=0.4$), Gender (39.1% male, $\chi^2=0.4$, $df=1$, $p=0.8$), Education ($t=1.0$, $df=54$, $p=0.3$), MMSE total ($t=0.32$, $df=54$, $p=0.8$), and HVLT Delayed Recall ($t=0.58$, $df=49$, $p=0.56$), or intracranial volume ($t=-1.02$, $df=54$, $p=0.3$) revealed no significant differences.