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## Apolipoprotein E $\epsilon$ 4 genotype status is not associated with neuroimaging outcomes in a large cohort of HIV+ individuals

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### Abstract

Previous neuroimaging studies suggest a negative relationship between the apolipoprotein (ApoE)  $\epsilon$ 4 allele and brain integrity in HIV-infected (HIV+) individuals, although the presence of this relationship across adulthood remains unclear. The purpose of this study is to clarify the discrepancies using a large, diverse group of HIV+ individuals and multiple imaging modalities sensitive to HIV. The association of ApoE  $\epsilon$ 4 with structural neuroimaging and magnetic

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resonance spectroscopy (MRS) was examined in 237 HIV+ individuals in the CNS HIV Anti-Retroviral Therapy Effects Research (CHARTER) study. Cortical and subcortical gray matter, abnormal and total white matter, ventricles, sulcal cerebrospinal fluid (CSF), and cerebellar gray matter, white matter, and CSF volumes) and MRS concentrations of myo-inositol, creatine, N-acetyl-aspartate, and choline in the frontal white matter (FWM), frontal gray matter (FGM) and basal ganglia) were examined. Secondary analyses explored this relationship separately in individuals  $\geq 50$  years old (n= 173) and  $< 50$  years old (n=63). No significant differences were observed between ApoE  $\epsilon 4+$  (ApoE  $\epsilon 3/\epsilon 4$  & ApoE  $\epsilon 4/\epsilon 4$ ) individuals (n=69) and ApoE  $\epsilon 4-$  (ApoE  $\epsilon 2/\epsilon 3$  & ApoE  $\epsilon 3/\epsilon 3$ ) individuals (n=167). When individuals were further divided by age, no significant genotype group differences were identified in individuals  $< 50$  or  $\geq 50$  years of age on any neuroimaging outcome. The ApoE  $\epsilon 4$  allele did not affect brain integrity in this large, diverse sample of HIV+ individuals. The effects of ApoE  $\epsilon 4$  may not be apparent until more advanced ages, and may be more prominent when present along with other risk factors for neuronal damage.

## Keywords

HIV/AIDS; genetics; magnetic resonance spectroscopy; brain volumetrics

Changes in brain structure and function have been well documented in individuals infected with human immunodeficiency virus (HIV+). HIV infection has been associated with cognitive impairment (Heaton et al., 2010; Heaton et al., 2011), smaller brain volumes (Stout et al., 1998; Jernigan et al., 2011; Ances et al., 2012; Heaps et al., 2012), altered brain metabolites (Ernst et al., 2003; Harezlak et al., 2011; Anderson et al., 2015), and altered white matter integrity (Pomara et al., 2001; Gongvatana et al., 2009; Wright et al., 2012; Fennema-Notestine et al., 2013), even after implementation of highly active anti-retroviral therapy (HAART; Sacktor et al., 2002; Ernst et al., 2003; Stebbins et al., 2007; Cohen et al., 2010; Ances et al., 2012). The continued prevalence of these abnormalities varies among HIV+ individuals, suggesting that additional host and/or viral factors influence outcomes after HAART initiation (Tozzi et al., 2007; Heaton et al., 2010).

A host genetic factor that may contribute to changes in brain integrity is the apolipoprotein E (ApoE)  $\epsilon 4$  allele. ApoE  $\epsilon 4$  is associated with neuroimaging abnormalities in patients with neurodegenerative disorders (e.g. Alzheimer's disease (AD; Martins et al., 2005; Schuff et al., 2009) and is associated with abnormal brain structure and function independent of clinical dementia (Fennema-Notestine et al., 2011). Previous studies of ApoE  $\epsilon 4$  and HIV neuropathogenesis have produced mixed results. Several investigations report no significant effect of ApoE  $\epsilon 4$  on cognitive function in HIV+ individuals (Burt et al., 2008; Joska et al., 2010; Sun et al., 2010; Morgan et al., 2013; Becker et al., 2014), while others identified significant relationships between ApoE  $\epsilon 4$  and cognitive impairment or increased prevalence of HIV-associated neurocognitive disorders (HAND; Valcour et al., 2004; Spector et al., 2010; Chang et al., 2011; Hoare et al., 2013; Panos et al., 2013). The strongest relationships were observed in older ( $\geq 50$  years old) ApoE  $\epsilon 4+$  HIV+ individuals with older HIV+ APOE4+ individuals demonstrating the worst cognition (Valcour et al., 2004; Panos et al., 2013). The association between ApoE  $\epsilon 4$  genotype in HIV+ individuals using neuroimaging

methods is less well-studied. A limited number of previous studies suggest that presence of the ApoE  $\epsilon 4$  allele in HIV+ individuals is associated with smaller brain volumes in younger (<50 years) adults (Chang et al., 2011), lower fractional anisotropy in young adults (Hoare et al., 2013), and decreased neuronal integrity and increased inflammation (Chang et al., 2014). Jahanshad et al. (2012) reported greater brain network dysfunction among older (60-80 years) HIV+ ApoE  $\epsilon 4+$  individuals compared to HIV+ APOE- individuals. The magnitude of disruption to brain connectivity correlated with disease duration and was evident even among individuals on stable HAART. Collectively the studies completed to date suggest a negative impact of the ApoE  $\epsilon 4$  allele on brain integrity among HIV+ individuals. It remains less clear whether the  $\epsilon 4$  is similarly relevant across adulthood.

This study examined the association of ApoE  $\epsilon 4$  allele status with a combination of neuroimaging outcomes including brain volumes and metabolite concentrations in a relatively large, diverse, and well-characterized sample of HIV+ individuals ( $n=237$ ). The relationship between ApoE  $\epsilon 4$  allele status and cognitive performance has previously been examined in the same CHARTER cohort, with results revealing no significant relationship (Morgan et al. 2013). However, neuroimaging may reveal changes in brain integrity that are not detected by cognitive performance (Smith et al., 2007; Masters & Ances, 2014). We tested the hypothesis of decreased brain integrity in ApoE  $\epsilon 4+$  individuals compared to ApoE  $\epsilon 4-$  individuals by examining nine brain volumes of interest and four magnetic resonance spectroscopy (MRS) concentrations including: 1) creatine (Cr), 2) choline (CHO), 3) myo-inositol (MI), and 4) N-acetyl-aspartate (NAA) in frontal gray matter (FGM), frontal white matter (FWM) and basal ganglia (BG). In a secondary analysis we compared the relationship between ApoE  $\epsilon 4$  status and neuroimaging outcomes between HIV+ individuals 50 years and older compared to individuals under 50 years of age.

## Methods

### Participants

Participants from the CHARTER study who had genetic testing (ApoE  $\epsilon 4$  genotyping) and neuroimaging (volumetric and MRS) were included in the current analyses ( $n=237$ ). The CHARTER study involves six performance sites in the United States and is an ongoing investigation of the neurological complications due to HIV in the HAART era. All participants in this study were HIV+ and were free of major comorbid medical, psychiatric, or neurological disorders unrelated to the direct effects of HIV (e.g., opportunistic infections, etc.). The majority of participants were on HAART regimens (181 of 237). The full neuroimaging sample has previously been described without inclusion of genotype status (Jernigan et al. 2011). Of 237 HIV+ participants, 69 individuals were ApoE  $\epsilon 4+$  (ApoE  $\epsilon 3/\epsilon 4$   $n=62$  or ApoE  $\epsilon 4/\epsilon 4$   $n=7$ ) and 168 were ApoE  $\epsilon 4-$  (ApoE  $\epsilon 2/\epsilon 3$   $n=32$  or ApoE  $\epsilon 3/\epsilon 3$   $n=136$ ); individuals with ApoE 2/2 ( $n=8$ ) and 2/4 ( $n=18$ ) genotypes were excluded from the current study due to the small number of participants with each genotype. Demographic and clinical characteristics of the participants are listed in Table 1. All procedures were approved by the Institutional Review Boards of each CHARTER site and all participants provided written informed consent.

## Neuromedical Evaluation

Neuromedical assessments included structured medical examinations, interviews, and laboratory measurements: medical history, physical evaluations, current and past medications, neurological examinations, current CD4 cell count, self-reported CD4 nadir cell count, plasma and CSF HIV viral load (Roche Amplicor, v. 1.5, lower limit of quantitation 50 copies/mL), and hepatitis C virus serostatus (positive versus negative serology).

## Genetic Characterization

Genomic DNA was isolated according to manufacturer protocols (Paxgene, Valencia, CA). Genotypes of participants at rs7412 and rs429358, which define APOE  $\epsilon$ 2,  $\epsilon$ 3, and  $\epsilon$ 4 isoforms, were determined using standard TaqMan predesigned SNP genotyping assays (C\_904973\_10 and C\_30846793\_20; Applied Biosystems; Foster City, California).

Genetic ancestry data were also examined. Population stratification was evaluated by adjustment for four principal components variables representing ancestry-related genetic information, which were generated from genome-wide genotype data in CHARTER (African, European, Hispanic, and other), consistent with previous published studies (Kallianpur et al., 2014; Hulgan et al., 2015). Genetic ancestry has been advocated to use in genetics studies instead of race/ethnicity, since the latter is a socio-cultural category that does not fully capture the genetic variation and its influence on biological outcomes such as those considered in this study (Fujimura & Rajagopalan, 2011; Brummel et al., 2015; Mersha & Abebe, 2015).

## Neuroimaging

All imaging was performed on GE 1.5T scanners (8 scanners across 5 CHARTER sites) and included four structural imaging series used for morphometric analyses and three single voxel MRS acquisitions. Structural acquisition series 1 and 2 were coronal with 2.0 mm section thickness, field of view (FOV) 24 cm, matrix size 256 × 256 2D T2 – weighted fast spin echo (FSE) sequence with repetition time (TR) = 5700 ms, echo time (TE) = 90 ms, echo train length (ETL) = 16; and 2D proton density weighted FSE sequence with TR = 3700 ms, TE = 17 ms, ETL = 4. Series 3 and 4 were sagittal acquisitions with section thickness = 1.3 mm, FOV = 24 cm, matrix size 256 × 256 × 124 3D T1 – weighted spoiled gradient echo (SPGR) sequence with TR = 20 ms, TE = 6 ms, flip angle = 30; and 3D proton density weighted SPGR sequence with TR = 20 ms, TE = 6 ms, flip angle = 5. Scanners were annually assessed for quality. The standard CHARTER morphometric analyses are described in detail elsewhere (Jernigan et al., 2011), including image inspection, bias correction, co-registration of MRI volumes, skull-stripping, tissue segmentation, designation of abnormal white matter, and anatomical segmentation. Volumes of interest for this study included cortical and subcortical gray matter, total white matter, abnormal white matter, lateral ventricles, sulcal cerebrospinal fluid (CSF), cerebellar gray and white matter, and cerebellar CSF; total cerebral and cerebellar vaults were also measured. Abnormalities within some of these regions have previously been associated with HIV disease factors within the CHARTER sample (Jernigan et al., 2011; Fennema-Notestine et al., 2013).

MRS was performed using a standardized protocol of point-resolved spectroscopy (Lin et al., 2011; Anderson et al., 2015). Echo time (TE) was 35 milliseconds and relaxation time (TR) was 3000 milliseconds. Three regional voxels were acquired: frontal grey matter (FGM) at 20mm<sup>3</sup> and 64 acquisitions, frontal white matter (FWM) at 20mm<sup>3</sup> and 64 acquisitions, and basal ganglia (BG) at 15mm<sup>3</sup> and 96 acquisitions. MRS concentrations of NAA, CHO, MI, and Cr were quantified using LC Model with water suppression (Provencher, 2001). Water suppression allows for the examination of absolute metabolites, the primary outcome in this study. Ratios to Cr were not used since we have previously found significant associations between Cr and both HIV RNA and nadir CD4 in this sample (Anderson et al., 2015), indicating that Cr is impacted by the disease and therefore not a stable reference marker. Metabolite estimates were included from appropriately placed voxels with adequate spectra (standard deviation <21). Therefore, sample size varied by MRS region or metabolite. Structural volumes and MRS voxels were aligned to estimate the proportion of gray and white matter within each voxel that impacted metabolite estimations (e.g., if the FGM voxel contains more gray matter, the estimate of NAA will be higher regardless of tissue integrity).

### Statistical Analysis

Demographic and HIV disease characteristics were compared between genotype groups using Fisher's exact test for binary and categorical variables, and independent samples *t*-test for continuous variables. Separate multivariable linear regressions were conducted to analyze potential differences according to genotype for the nine brain volumes of interest. Brain volumes and metabolite estimates were log-transformed to ensure normality. Volumetric analyses included scanner and log-transformed intracranial volume as covariates in the regression analyses to adjust for individual differences in head size. MRS analyses included scanner and the log-proportion of a given voxel consisting of the relevant tissue type as covariates: white matter for FWM or gray matter for FGM and BG. Additionally, presence of a neurocognitive comorbidity (incidental vs. contributing conditions where the effect of the condition on cognitive impairment is separable from the effect of HIV), current and nadir CD4 count  $\geq 200$  cp/ $\mu$ L, detectable plasma and CSF viral load, hepatitis C co-infection, genetically-determined ancestry, and age were added as covariates in all analyses. Holm-Bonferroni corrections of *p*-values and confidence intervals were used to correct for multiple comparisons within each age group and type of outcome (volumetrics or spectroscopy). Cohen's *d* values were included as a measure of effect size.

Secondary analyses included linear regressions conducted separately for individuals  $\geq 50$  years and individuals  $<50$  years of age to explore differences between genotype groups across the lifespan. This approach is consistent with previous studies examining the effect of the ApoE  $\epsilon 4$  genotype in HIV (Valcour et al., 2004; Chang et al., 2011; Chang et al., 2014). Analyses were adjusted for all covariates previously listed except for age.

### Results

ApoE  $\epsilon 4$  groups (ApoE  $\epsilon 2/\epsilon 3$  & ApoE  $\epsilon 3/\epsilon 3$  versus ApoE  $\epsilon 3/\epsilon 4$  & ApoE  $\epsilon 4/\epsilon 4$ ) differed significantly on self-reported race/ethnicity ( $p = .015$ ) and on genetically-determined

ancestry ( $p < .008$ ). ApoE  $\epsilon 4+$  individuals were more likely to be African-American (54%) while ApoE  $\epsilon 4-$  individuals were more often Caucasian (49%). When divided by age, these ethnic and ancestry disparities continued to be present within the older adults ( $> 50$  years). Within the younger adult group ( $< 50$  years), ApoE  $\epsilon 4+$  individuals ( $M = 42.0$ ,  $SD = 5.4$ ) were older than ApoE  $\epsilon 4-$  individuals ( $M = 39.9$ ,  $SD = 5.7$ ;  $p < .028$ ). There were no other significant differences between the groups on demographic or clinical characteristics (see Table 1).

Volumetric analyses indicated no significant differences between individuals with regard to  $\epsilon 4$  allele status. ApoE  $\epsilon 4+$  and ApoE  $\epsilon 4-$  individuals had similar volumes for all regions analyzed (total grey and white matter, subcortical gray matter, abnormal white matter, ventricles, sulcal CSF, cerebellar gray and white matter, and cerebellar CSF; all  $p$ 's  $> 0.05$ ). Results did not differ when participants were stratified by age ( $< 50$  and  $> 50$  years old).

MRS analyses indicated no significant differences for any metabolite within the three regions of interest (BG, FGM and FWM;  $p$ 's  $> 0.05$ ). Secondary analyses also revealed no significant differences in metabolite concentrations between genotype groups when participants were further divided by age ( $> 50$  years and  $< 50$  years old). The percent difference between groups with 95% confidence intervals and Cohen's  $d$  values are presented in Table 2. Effect sizes were primarily negligible to small.

## Discussion

This study examined the relationship between ApoE  $\epsilon 4$  genotype status and neuroimaging measures (volumetrics and MRS) in a large, diverse sample of HIV+ individuals while controlling for a number of disease factors, including nadir and current CD4, and detectable plasma HIV RNA. Neither volumetrics nor MRS indices differed between ApoE  $\epsilon 4+$  and ApoE  $\epsilon 4-$  individuals. Secondary analyses identified no significant differences on neuroimaging outcomes between genotype groups when participants were divided by age ( $> 50$  and  $< 50$  years old).

Few studies to date have examined the potential impact of the ApoE  $\epsilon 4$  genotype on neuroimaging outcomes. Some studies suggest that having at least one ApoE  $\epsilon 4$  allele negatively influences select brain imaging measures in HIV+ individuals. Specifically, smaller brain volumes (Chang et al., 2011), lower Cr levels in the BG, and disrupted brain networks (Jahanshad et al., 2012) were linked to ApoE  $\epsilon 4$  status (Chang et al., 2014). Differences in the ethnicity of populations may contribute to the disparity between the current results and previous studies. Two previous studies primarily included Caucasians (Chang et al., 2011; Chang et al., 2014). The ApoE  $\epsilon 4$  allele is more common in African American populations (Logue et al., 2011), and a larger proportion of our cohort was African American, with 54% of African American individuals possessing at least one ApoE  $\epsilon 4$  allele. Additionally, the proportion of individuals possessing at least one allele was higher in our sample (30%) compared to the general population (Eichner et al., 2001; Kuhlmann et al., 2010). This large ApoE  $\epsilon 4+$  sample may reflect the higher proportion of African American individuals included in the present study.



Hoare et al. (2013) also reported worse neuroimaging outcomes in HIV+ individuals with an ApoE  $\epsilon 4$  allele. One important distinction between the work by Hoare and colleagues and the present study is the treatment status of participants. A majority of participants enrolled in the current study were on HAART (76%), whereas the participants studied by Hoare and colleagues were treatment-naïve (2013). Participants in the latter study also exhibited a lower average current CD4 count ( $\epsilon 4+$  group = 195,  $\epsilon 4-$  group = 233; versus  $\epsilon 4+$  = 477,  $\epsilon 4-$  group = 464 in our study), a marker of disease severity. Lower current CD4 counts have previously been associated with reduced brain volumes (Cohen et al., 2010; Pfefferbaum et al., 2014). Both higher CD4 count and current antiretroviral treatment has been associated with white matter integrity (Gongvatana et al., 2011). It is possible that the effect of ApoE  $\epsilon 4$  is greater in immunocompromised individuals. However, additional studies are needed to clarify the relationship between treatment status and ApoE  $\epsilon 4$  genotype.

Our study has several limitations. First, although we had a sizeable group ( $n = 63$ ) of individuals  $\geq 50$  years of age, our sample was relatively young ( $M = 44.5$  years). It is possible that the detrimental effects of the ApoE  $\epsilon 4$  allele may not be present until later in life. For example, Jahanshad and colleagues identified significant disruptions in networks among HIV+ ApoE  $\epsilon 4+$  individuals who were over 60 years old (Jahanshad et al., 2012). Second, we removed two groups from the analyses (ApoE  $\epsilon 2/\epsilon 2$  and  $\epsilon 2/\epsilon 4$ ) due to low cell sizes. Because the ApoE  $\epsilon 2$  allele may be protective against AD in African Americans (Murrell et al., 2006) and a dose effect of the  $\epsilon 4$  allele may increase the risk of AD in homozygotes (Corder et al., 1993), future studies are needed that incorporate larger samples of individuals possessing ApoE  $\epsilon 2$  alleles. Finally, this study did not include a seronegative group.

Future studies are still needed to define variables that could negatively affect brain integrity in HIV. Specifically, cardiovascular and cerebrovascular disease, and genetic factors including tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) and macrophage chemo-attractant protein-1 (MCP-1) are among the numerous neuropathogenic factors that associate with brain integrity in HIV+ individuals (Wright et al., 2010; Kallianpur & Levine, 2014). These alternative host variables may emerge as more salient predictors of neuroimaging outcomes.

In summary, our results suggest that the ApoE  $\epsilon 4$  allele is not associated with abnormal brain volumes or MRS outcomes in a large sample of HIV+ patients across a varied age range. Future studies including large samples across all ApoE  $\epsilon 4$  genotypes ( $\epsilon 2/\epsilon 2$ ,  $\epsilon 2/\epsilon 4$  and  $\epsilon 4/\epsilon 4$ ) are needed to fully capture the effect of ApoE  $\epsilon 4$  status on brain integrity in HIV. Additionally, longitudinal cohort studies that include older HIV+ and HIV-participants ( $>60$  years) are needed to assess brain changes over time related to ApoE  $\epsilon 4$  status.

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Table 1

## Participant Characteristics

	All participants (N = 237)			Age < 50 yr (N = 173)			Age 50 yr (N = 63)		
	ApoE e4- n = 168	ApoE e4+ n = 69	p-value	ApoE e4- n = 126	ApoE e4+ n = 48	p-value	ApoE e4- n = 42	ApoE e4+ n = 21	p-value
Sample size (n)									
Age, mean (SD)	43.4 (8.1)	45.7 (7.3)	0.050	39.9 (5.7)	42.0 (5.4)	.028	54.0 (4.1)	54.0 (3.0)	.98
Male Gender, N (%)	141 (84)	51 (74)	0.100	108 (86)	35 (73)	.074	33 (79)	16 (76)	.99
Ethnicity, No. (%)			0.015			.31			.003
Black	66 (39)	37 (54)		51 (40)	21 (44)		15 (36)	16 (76)	
White	82 (49)	21 (30)		59 (47)	18 (38)		23 (55)	3 (14)	
Hispanic	15 (9)	11 (16)		13 (10)	9 (19)		2 (5)	2 (10)	
Other	5 (3)	0 (0)		3 (2)	0 (0)		2 (5)	0 (0)	
Genetic Ancestry, No. (%)			0.008			.38			.001
Africa	62 (37)	36 (55)		48 (38)	22 (46)		14 (33)	16 (76)	
Europe	101 (60)	26 (39)		73 (58)	23 (48)		28 (67)	4 (19)	
Other	4 (2)	4 (6)		4 (3)	3 (7)		0 (0)	1 (5)	
HIV Treatment, No. (%)			0.24			.33			.49
On HAART	126 (75)	55 (80)		94 (75)	36 (75)		32 (76)	19 (90)	
ARV Naïve	15 (9)	9 (13)		13 (10)	8 (17)		2 (5)	1 (5)	
No ARVs	26 (15)	5 (7)		19 (15)	4 (8)		7 (17)	1 (5)	
Non-HAART	1 (1)	0 (0)		0 (0)	0 (0)		1 (2)	0 (0)	
HIV duration (months), M(SD)	68 (55)	70 (53)	0.73	58 (51)	67 (54)	.33	96 (56)	79 (49)	.22
Nadir CD4, M(IQR)	177(32 - 273)	218(25 - 300)	0.13	183(27 - 292)	223(24 - 300)	.24	160(55- 230)	207(54 - 267)	.28
Current CD4, M(IQR)	464(302 - 621)	477(287 - 586)	0.73	463(306 - 620)	459(305 - 595)	.93	466(273 - 618)	514(283 - 566)	.52
Log10 Plasma VL, M(SD)	2.72 (1.29)	2.57 (1.23)	0.40	2.79 (1.32)	2.55 (1.25)	.29	2.53 (1.18)	2.60 (1.21)	.82
Detectable Plasma VL, N (%)	89 (53)	28 (41)	0.11	69 (55)	19 (40)	.09	20 (48)	9 (43)	.79
Log10 CSF VL, M(SD)	2.15 (0.83)	2.07(0.74)	0.56	2.15(0.82)	2.06(0.75)	.54	2.14 (0.88)	2.10 (0.74)	.88
Detectable CSF VL, N (%)	48 (31)	16 (27)	0.62	38 (33)	10 (25)	.43	10 (27)	6 (30)	.99

M = mean

ARV = Antiretroviral

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VL = Viral load  
HAART = Highly active retroviral therapy  
CSF = Cerebrospinal fluid  
Non-HAART = Indicates use of antiretrovirals, but no HAART regimen  
IQR = Interquartile range

Table 2

Effect of Apolipoprotein  $\epsilon 4$  genotype on neuroimaging variables. Mean differences between groups with and without the  $\epsilon 4$  genotype expressed in terms of percentage difference.

Neuroimaging Variables	All Participants				Age < 50 years				Age 50 years			
	Percent difference between ApoE $\epsilon 4$ - and ApoE $\epsilon 4$ + groups (95% CI)	Cohen's <i>d</i>	Percent difference between ApoE $\epsilon 4$ - and ApoE $\epsilon 4$ + groups	Cohen's <i>d</i>	Percent difference between ApoE $\epsilon 4$ - and ApoE $\epsilon 4$ + groups	Cohen's <i>d</i>	Percent difference between ApoE $\epsilon 4$ - and ApoE $\epsilon 4$ + groups	Cohen's <i>d</i>	Percent difference between ApoE $\epsilon 4$ - and ApoE $\epsilon 4$ + groups	Cohen's <i>d</i>	Percent difference between ApoE $\epsilon 4$ - and ApoE $\epsilon 4$ + groups	
<i>Volumetric Regions</i>												
Cortical GM	-0.4	0.07	1.1	-0.18	-2.2	-0.18	-2.2	-0.18	-2.2	-0.18	-2.2	0.32
Subcortical GM	-1.4	0.16	-0.6	0.07	-3.7	0.07	-3.7	0.07	-3.7	0.07	-3.7	0.49
Abnormal WM	4.4	-0.14	3.3	-0.12	7.5	-0.12	7.5	-0.12	7.5	-0.12	7.5	-0.18
Total WM	-2.4	0.27	-2.3	0.26	-3.9	0.26	-3.9	0.26	-3.9	0.26	-3.9	0.39
Ventricles	8.7	-0.17	5.1	-0.10	9.6	-0.10	9.6	-0.10	9.6	-0.10	9.6	-0.17
Sulcal CSF	16.5	-0.30	1.9	-0.03	54.2	-0.03	54.2	-0.03	54.2	-0.03	54.2	-0.95
Cerebellar GM	-0.7	0.11	-0.3	0.04	-1.3	0.04	-1.3	0.04	-1.3	0.04	-1.3	0.20
Cerebellar WM	1.7	-0.10	3.6	-0.22	-2.7	-0.22	-2.7	-0.22	-2.7	-0.22	-2.7	0.15
Cerebellar CSF	5.1	-0.13	-2	0.05	25.3	0.05	25.3	0.05	25.3	0.05	25.3	-0.66
<i>Spectrum</i>												
FWM-NAA	-1.5	0.14	-0.3	0.03	-1.8	0.03	-1.8	0.03	-1.8	0.03	-1.8	0.21
FWM-CHO	2	-0.11	1.2	-0.06	0.3	-0.06	0.3	-0.06	0.3	-0.06	0.3	-0.02
FWM-CR	0	0.00	1.2	-0.07	-7.8	-0.07	-7.8	-0.07	-7.8	-0.07	-7.8	0.63
FWM-MI	4.7	-0.21	7.2	-0.33	-3.5	-0.33	-3.5	-0.33	-3.5	-0.33	-3.5	0.14
FGM-NAA	0.3	-0.03	0.5	-0.04	-0.2	-0.04	-0.2	-0.04	-0.2	-0.04	-0.2	0.02
FGM-CHO	-0.3	0.02	-1.1	0.08	0	0.08	0	0.08	0	0.08	0	0.00
FGM-CR	-0.8	0.06	-1	0.08	-2.4	0.08	-2.4	0.08	-2.4	0.08	-2.4	0.17
FGM-MI	-2.8	0.17	-4.4	0.28	-1.4	0.28	-1.4	0.28	-1.4	0.28	-1.4	0.08
BG-NAA	2.3	-0.18	2.8	-0.25	2	-0.25	2	-0.25	2	-0.25	2	-0.14
BG-CHO	0.3	-0.02	-1	0.06	2.4	0.06	2.4	0.06	2.4	0.06	2.4	-0.16
BG-CR	2.1	-0.14	3.4	-0.26	-5.9	-0.26	-5.9	-0.26	-5.9	-0.26	-5.9	0.35
BG-MI	2.9	-0.13	1.2	-0.07	12.9	-0.07	12.9	-0.07	12.9	-0.07	12.9	-0.51

Note: All comparisons non-significant



WM = White matter; GM = Gray matter; FWM = Frontal white matter; FGM = Frontal gray matter; BG = basal ganglia

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