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Cognitive and functional resilience despite molecular evidence of Alzheimer's disease pathology

Selam Negash, PhD¹, Sharon Xie, PhD², Christos Davatzikos, PhD³, Christopher M. Clark, MD⁴, John Q. Trojanowski, MD, PhD^{5,6}, Leslie M. Shaw, PhD⁵, David A. Wolk, MD^{4,*}, and Steven E. Arnold, M.D.^{1,4,*}

¹Department of Psychiatry, University of Pennsylvania, Philadelphia, PA

²Department of Biostatistics and Epidemiology, University of Pennsylvania, Philadelphia, PA

³Department of Radiology, University of Pennsylvania, Philadelphia, PA

⁴Department of Neurology, University of Pennsylvania, Philadelphia, PA

⁵Department of Pathology and Laboratory Medicine, University of Pennsylvania, Philadelphia, PA

⁶Center for Neurodegenerative Disease Research, University of Pennsylvania, Philadelphia, PA

Abstract

Background—The correlation between neuropathological lesions and cognition is modest. Some individuals remain cognitively intact despite the presence of significant Alzheimer's disease (AD) pathology, while others manifest cognitive symptoms and dementia in the same context. The aim of the present study was to examine cognitive and cerebral reserve factors associated with resilient functioning in the setting of AD pathology.

Methods—University of Pennsylvania Alzheimer's Disease Center research participants with biochemical biomarker evidence of AD pathology (cerebrospinal fluid Aβ₁₋₄₂ < 192 pg/ml) and comparable medial temporal lobe atrophy were categorized by Clinical Dementia Rating Scale Sum of Boxes (CDR-SOB) score as AD Dementia (CDR-SOB > 1) or AD Resilient (CDR-SOB

Corresponding author: Steven E. Arnold, M.D., Alzheimer's Disease Core Center, University of Pennsylvania, Philadelphia, PA 19104, USA, Steven.Arnold@uphs.upenn.edu.

*Drs. Wolk and Arnold contributed equally for senior authorship.

Conflict of Interest Disclosures: Dr. Clark is full time employee of Avid Radiopharmaceuticals, a wholly owned subsidiary of Eli Lilly and Company. Dr. Trojanowski has received funding for travel and honoraria from Takeda Pharmaceutical Company Ltd.; has received speaker honoraria from Pfizer Inc.; serves as an Associate Editor of *Alzheimer's & Dementia*; may accrue revenue on patents re: Modified avidin-biotin technique, Method of stabilizing microtubules to treat Alzheimer's disease, Method of detecting abnormally phosphorylated tau, Method of screening for Alzheimer's disease or disease associated with the accumulation of paired helical filaments, Compositions and methods for producing and using homogeneous neuronal cell transplants, Rat comprising straight filaments in its brain, Compositions and methods for producing and using homogeneous neuronal cell transplants to treat neurodegenerative disorders and brain and spinal cord injuries, Diagnostic methods for Alzheimer's disease by detection of multiple MRNAs, Methods and compositions for determining lipid peroxidation levels in oxidant stress syndromes and diseases, Compositions and methods for producing and using homogenous neuronal cell transplants, Method of identifying, diagnosing and treating alpha-synuclein positive neurodegenerative disorders, Mutation-specific functional impairments in distinct tau isoforms of hereditary frontotemporal dementia and parkinsonism linked to chromosome-17: genotype predicts phenotype, Microtubule stabilizing therapies for neurodegenerative disorders, and Treatment of Alzheimer's and related diseases with an antibody. Dr. Shaw serves on a scientific advisory board for Innogenetics; serves on the editorial board of *Therapeutic Drug Monitoring*; may potentially receive revenue for patent pending re: O-methylated rapamycin derivatives for alleviation and inhibition of lymphoproliferative disorders, licensed by the University of Pennsylvania to Novartis; receives royalties from publication of *Applied Pharmacokinetics and Pharmacodynamics: Principles of Therapeutic Drug Monitoring* (Wolters Kluwer/Lippincott Williams & Wilkins, 2005). Dr. Wolk has served as a consultant for GE Healthcare and on the advisory board for Neuronetrix. Dr. Steven Arnold serves on the Editorial Boards of *Neuropsychiatry*, *Schizophrenia Bulletin*, and *Translational Neuroscience*. He has served on advisory boards for Bristol Myers Squibb, Eli Lilly, and the Cowen Group. Drs. Negash, Xie, and Davatzikos have no conflicts of interest to disclose. All the authors meet the criteria for authorship, and have provided a statement on financial disclosure.

0.5). Groups were compared for a variety of demographic, clinical, and neuroimaging variables to identify factors that are associated with resilience to AD pathology.

Results—A univariate model identified education and intracranial volume (ICV) as significant covariates. In a multivariate model with backward selection procedure, ICV was retained as a factor most significantly associated with resilience. The interaction term between ICV and education was not significant, suggesting that larger cranial vault size is associated with resilience even in the absence of more education.

Conclusions—Premorbid brain volume, as measured through ICV, provided protection against clinical manifestations of dementia despite evidence of significant accumulations of AD pathology. This finding provides support for the brain reserve hypothesis of resilience to AD.

Keywords

Cognitive Reserve; CSF Biomarkers; Neural Reserve; Education; Intracranial Volume

INTRODUCTION

The relationship between pathology and cognition is increasingly recognized to be complex. While clinicopathological correlation studies show significant associations of plaques, tangles, infarctions and other lesions with cognitive impairment, the relationships are imperfect; there are in fact some individuals who remain unimpaired amidst significant brain pathology[1-3]. The concept of “reserve” or “resilience” has emerged to explain individuals’ ability to tolerate disease-related pathology in the brain without developing clinical symptoms or signs[4]. A number of factors are thought to contribute to this reserve, including education (as a proxy for cognitive reserve) and brain size (proxy for brain reserve) [4-6]. A majority of this evidence, however, comes from postmortem studies, which until recently, was the only way to document AD pathology in the brain. While such postmortem studies have been invaluable, there are inherent limitations, including significant delay between clinical evaluation and autopsy and selection bias[7]. Another important concern is that of variability in the severity of the downstream effects of this pathology with regard to synaptic and neuronal loss, or neurodegeneration, which is often not accounted for in these studies. Given models in which molecular pathologic changes, particularly related to β -amyloid deposition, may precede significant neurodegeneration by an extended period[8], assessment of only these molecular markers adds uncertainty to conclusions of resilience. For example, the extent to which a person is truly resilient or simply earlier in the course of the disease is not clear.

Recent advances in AD research have led to development of biomarkers that are in vivo indicators of a specific aspect of AD pathology. These biomarkers can be dichotomized as indicators of AD molecular pathology (e.g. $A\beta$ plaque deposition) and neuronal degeneration, where decreased CSF- $A\beta_{1-42}$ and amyloid PET imaging indicate the former. The use of low CSF- $A\beta_{1-42}$ levels as marker for AD pathologic processes has been validated in several studies, although variability exists in the threshold values used [9, 10]. Using receiver operating characteristic cutpoints and logistic regression models derived from the autopsy-confirmed CSF biomarker data, Shaw et al. have showed that CSF- $A\beta_{1-42}$ was the most sensitive biomarker for AD detection in CSF from non-ADNI autopsy- confirmed subjects with a receiver operating characteristic area under the curve of 0.913 and sensitivity for AD detection of 96.4% [11]. These findings were also recently validated using a mixture modeling approach on two additional data sets [12]. While there is yet no consensus in this area, recent work suggests that there may be a CSF- $A\beta_{1-42}$ cutoff value that is indicative of the presence of AD pathology [11,12].

Alternatively, biomarkers of neuronal degeneration include volumetric MRI measures of cerebral atrophy reflecting neuronal and neuropil loss and fluorodeoxyglucose (FDG) PET measures of brain metabolism associated with synaptic integrity[11, 3, 14].

As alluded to above, recent work has provided a theoretical model for the cascade of events leading to clinical impairment in AD, in which biomarkers of A β deposition become abnormal first, before neurodegenerative changes and cognitive symptoms. Neurodegenerative biomarkers (e.g. volumetric MRI) become abnormal later and correlate with clinical symptom severity[8]. As such, biomarkers of A β deposition can be considered as indicators of more upstream events that occur early in the disease compared to more distal, downstream events that are associated with neuronal injury and cognitive decline. This emphasizes the need to account for biomarkers of both A β deposition and neuronal degeneration when examining clinical correlations with AD pathology.

In the current study, we utilized *in vivo* biomarkers of AD to examine resilient cognition in the setting of significant AD pathology; cases were matched for AD pathology using biomarkers of both CSF-A β ₁₋₄₂ levels (proxy for A β plaque deposition) and medial temporal lobe atrophy (for neuronal degeneration). The main goal was to test two putative proxies of cognitive and brain reserve (specifically, education and brain size) to determine their relative association with resilience, where resilience was defined as intact cognitive function in a setting of AD pathology (based on CSF markers). An important advance beyond prior work was to also match for a surrogate of the degree of neurodegeneration (medial temporal lobe) associated with this pathology to mitigate against the potential confound that even in the setting of presumed AD pathology, the resilient group may have simply been earlier in the disease process, or have less severe disease.

METHODS

Participants

Participants were identified from the ongoing cohort in the University of Pennsylvania Alzheimer's Disease Center (ADC). ADC research participants are evaluated with a standardized clinical protocol that includes a medical history, physical and neurologic examinations by physicians experienced in dementia evaluations, and neuropsychological testing[15-17]. The Dementia Severity Rating Scale (DSRS) [18, 19], Geriatric Depression Scale (GDS)[21], and Clinical Dementia Rating (CDR)[20] are also performed.

The DSRS includes questions on memory, speech and language, recognition of family members, orientation to time and space, ability to make decisions, social and community activities, home activities, personal care, eating, incontinence (related to AD) and ability to get from place to place. The patient's score is determined by adding the numeric value assigned to each response chosen. Scores range from 0 to 54, with higher scores indicating more severe impairments.

The CDR assesses function in six domains: memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care. Impairment in each domain is rated on a five-point scale as CDR0 (healthy), CDR0.5 (Questionable Dementia), CDR 1 (Mild Dementia), CDR 2 (Moderate Dementia) and CDR 3 (Severe Dementia). The CDR-SOB is obtained by summing each of the domain box scores, with scores ranging from 0 to 18.

Standard protocol approvals and patient consents

Informed consent was obtained from all subjects participating in the study, which was approved by the University of Pennsylvania Institutional Review Board.

MRI Acquisition

T1-weighted images according to the protocol of the Alzheimer's Disease Neuroimaging Initiative (ADNI) were acquired, using the MPRAGE protocol (sagittal acquisition, TR = 3000ms, TE = 3.55ms, TI=1,000ms, flip angle = 8°, voxel dimensions of .94 × .94 × 1.2 mm).

Collection of CSF

CSF samples were obtained by lumbar puncture following an overnight fast. Spinal fluid was withdrawn through an atraumatic 25-gauge sprotte needle and immediately transferred to bar code-labeled polypropylene vials and placed in a -80°C freezer in accordance with standard operating procedures (SOPs) utilized in the ADNI protocol (details also available at <http://www.adni-info.org/index>).

Biomarker analysis using multiplex xMAP (Luminex) technology

The CSF biomarkers included t-tau, p-tau_{181p} and Aβ₄₂ using the multiplex xMAP Luminex™ platform (Luminex Corp, Austin, TX) with the Innogenetics immunoassay kit-based reagents (INNO-BIA AlzBio3, Ghent, Belgium); the full details of this multiplex immunoassay have been previously published[22, 23]. Previous studies validated a day-to-day reproducibility for the 3 biomarkers of <10% variation for CSF samples and <7% for aqueous quality controls (r = 0.98 and 0.90, for t-tau and Aβ₁₋₄₂, respectively for 29 randomly selected samples analyzed twice over a 14-day period (complete details on the validation studies of this CSF immunoassay platform, are at <http://www.adni-info.org/index>)).

Image analysis

Images were processed using previously validated and published techniques [24]. The pre-processing steps included 1) alignment to the AC-PC plane; 2) removal of extra-cranial material (skull-stripping); 3) Tissue segmentation into grey matter (GM), white matter (WM), and CSF, [25]; 4) High-dimensional image warping [26] to a standardized coordinate system, a brain atlas (template) that was aligned with the Montreal Neurologic Institute coordinate space [27]; and 5) formation of regional tissue density RAVENS maps [28], and which allowed us to measure volumes of 93 regions of interest covering all major cortical gyri and subcortical structures, as well as white matter lobar volumes.

Participant Classification

Participants were categorized into two groups along dimensions of cognition and pathology (see also[29]). For cognition, CDR-SOB ≤ 0.5 was considered normal, while CDR-SOB > 1 was abnormal. Subjects with CDR-SOB = 1 were excluded from the analysis to increase separation between the cognitive status of the two groups. For measures of pathology, we applied the threshold value for CSF-Aβ₁₋₄₂ of less than 192 pg/ml, established by Shaw et al. [11], where individuals with CSF levels below this value were considered abnormal. These cutoff values have also been replicated in a recent study that used a mixture modeling approach that was totally independent of clinical AD diagnosis [12].

Thus, individuals with CSF-Aβ₁₋₄₂ < 192 pg/ml and CDR-SOB > 1 were classified as the *Dementia* group, whereas those with CSF-Aβ₁₋₄₂ < 192 pg/ml but having a CDR-SOB ≤ 0.5 were classified as *Resilient*.

Further, and importantly, as shown in Table 1, the two groups were matched on medial temporal lobe (MTL) volume, as a proxy for degree of neurodegeneration, to attenuate the

possibility that the Resilient group was merely in an earlier or prodromal phase of neurodegeneration.

Sample Selection

There were 243 subjects with a clinical diagnosis of normal, MCI or AD for whom both CDR and CSF-A β_{1-42} data were available. Of these, 16 individuals with CDR-SOB = 1 were excluded. Restricting the criteria to those with CSF-A β_{1-42} < 192 pg/ml and MRI data available yielded 75 subjects. Using 2:1 matching procedure, 54 subjects were selected from this sample (18 Resilient and 36 Dementia) who were matched on mean MTL volume in order to ensure that the groups sustained equivalent levels of neuronal degeneration.

Statistical Analysis

Group differences were analyzed using two sample t-tests for continuous variables and Chi-square tests for categorical variables. Regression analysis was conducted in two steps. First, univariate analysis identified potential covariates with $P < 0.10$. Next, multiple logistic regression with backward selection was conducted, where all relevant variables were fit first and then variables with the highest Wald test p values were removed one by one to identify the most significant covariate in the model. Analyses were performed using SAS (SAS Institute, Cary, NC).

RESULTS

The characteristics of participants are shown in Table 1. First, confirmatory analysis of the above classification verified that the two groups had similar CSF-A β_{1-42} levels and did not differ in medial temporal lobe atrophy measures, as shown by the equivalent MTL volume. The CDR sum of boxes, on the other hand, showed significant differences between the Dementia and Resilient groups, consistent with the applied classifications and the cognitive integrity of the resilient group relative to those classified as Dementia. Consistent with this, the AD Dementia group also showed significant impairments on other measures of cognition and dementia, including the Mini-Mental Status Examination (MMSE) and the Dementia Severity Rating Scale (DSRS), where higher values on this scale represent greater impairment (range: 0-54). The groups did not differ on psychiatric symptoms as measured by Geriatric Depression Scale (GDS). In addition, the Dementia group showed significant impairments on a variety of cognitive tests, as shown in Table 1, providing further evidence that the Resilient group exhibited relatively intact cognitive function despite significant AD pathology.

The candidate variables for the study are shown in Table 2. As the table indicates, education and ICV were identified as significant covariates, whereas other variables, such as age, gender, and APOE status did not significantly differ. Thus, the multivariate model included education and ICV as covariates. The backward selection retained ICV in the model, suggesting that this covariate was most significantly associated with resilience (odds ratio = 1.01, 95% CI = 1.003-1.015, $p = 0.0018$, with a 1 ml increase in ICV being associated with 1% increase in the odds of being resilient). The interaction term between ICV and education was not significant, suggesting that larger cranial vault size is associated with resilience even in the absence of more education.

One important limitation to note here, which was also pointed out to us by a Reviewer, is that while the matching procedure was useful in equating the groups on levels of neuronal degeneration, it nevertheless has several drawbacks, including its susceptibility to selection bias. In order to address this concern, we conducted additional multivariate analysis on the larger sample that was not matched on MTL ($n = 75$). Rather, we controlled for this variable

in the whole model that included age, education, gender, APOE status, and ICV. Results remained substantially unchanged in that, even in a model that controlled for MTL, ICV remained a significant covariate (odds ratio = 1.01, 95% CI = 1.006-1.021, $p < 0.0001$). In a separate analysis, we also controlled for two other AD-relevant brain regions (hippocampus and posterior cingulate); these regions were also corrected for ICV. Results retained ICV as the only covariate significantly associated with resilience, (odds ratio = 1.01, 95% CI = 1.005-1.021, $p = 0.0012$).

DISCUSSION

The purpose of the present study was to examine factors associated with resilience in the setting of AD pathology. An important aspect of the study was that it utilized *in vivo* molecular and topographical biomarkers of AD, with a main design to match groups for two of the most established biomarkers of AD – A β deposition and medial temporal lobe atrophy. This approach attempted to address a confound of simply using a measure of A β pathology to define a cognitively normal ‘resilient’ group. Without accounting for neurodegenerative change, it is possible that those classified as resilient are just earlier in the course of the disease compared to those who manifest dementia. By matching on medial temporal lobe atrophy, in addition to CSF A β 42 levels, we were more likely to ensure that the resilient and dementia groups sustained similar levels of A β deposition as well as neurodegeneration. In this context, we could better determine the mediators of resilience to the downstream consequences of AD pathology.

Results identified education and ICV as significant covariates, where the resilient group had more years of education and larger developmental brain size (measured through ICV) compared to the dementia group. A backward selection procedure retained ICV in the final model, suggesting that developmental brain size is the most highly associated with resilience.

The finding that larger brain size could protect against dementia has been reported in earlier studies; clinicopathological as well as epidemiological studies have shown that individuals with larger brain volume, associated with more neurons and synaptic connections, can tolerate more pathological damage before manifesting clinical symptoms of AD[30, 31]. The present study adds to the existing literature in two important ways. First, it utilized *in vivo* molecular and topographical biomarkers of A β deposition and neurodegeneration respectively, and second, resilient and dementia groups were matched for the degree of AD pathology using both these biomarkers. Thus, the current finding supports the notion that individuals with larger ICV likely had a reserve that allowed them to tolerate disease-related pathology in the brain without developing clinical symptoms or signs.

The concept of reserve has emerged to explain the disjunction between the degree of brain pathology and its clinical manifestations[32, 33]. Although inter-related, there have been two distinctive themes to the reserve hypothesis, where *brain* reserve is proposed as a passive model that arises from developmentally greater premorbid volume which is presumed to encompass more neurons, synapses and connectivity[34, 35], while cognitive reserve is hypothesized as an active model that posits individual differences in the ability to cope with or compensate for brain pathology [36]. Support for brain reserve hypothesis dates back to early studies showing larger brain volume and more neurons in patients with AD who were cognitively normal before death[38]. Epidemiological and cross-sectional studies have also shown that individuals with larger brain size, measured by head circumference or ICV, are less likely to develop AD or cognitive decline [36-38]. Recently, Perneczky and colleagues assessed whether premorbid brain size, measured using simple head circumference, modified the relationship between brain atrophy and cognitive decline

in AD and found that for a given degree of atrophy, cognitive performance was better in patients with a larger head circumference[39]. Some studies, however, have not found evidence supporting the brain reserve view[40, 41].

The cognitive reserve hypothesis posits that individuals with greater cognitive reserve are better able to cope with brain damage, although this construct is also still contentious. One important proxy for cognitive reserve is education[42]. Several studies have now documented individuals with higher education have greater cognitive reserve such that increased pathological burden is required to bring about clinical dementia compared to those with less education[7, 43, 44]. The mechanisms underlying this reserve, however, are less understood. A recent report by EClipSE Collaborative Members combined data from three prospective population-based autopsy studies to determine the potential role of education in neuroprotection or compensation[45]. It found that more education did not protect individuals from developing neuropathology, but mitigated the impact of pathology on clinical expression of dementia before death. The relationship between education (as a proxy for cognitive reserve) and brain size (as a proxy for brain reserve) is also unknown and likely difficult to disentangle.

The present study examined the two main proxies of reserve, and found that brain size was more highly associated with brain pathology and cognition, although education was also identified as a significant covariate in a univariate model. The interaction term between ICV and education did not reach significance, suggesting that the association between brain size and resilience was not dependent on education level. More studies are needed that delineate the relationship between education, brain reserve, and neuropathology, as these have important implications for the understanding of resilience and successful aging.

It is important to recognize the limitations of this study. While education was identified as a significant covariate in the univariate model, it did not reach significance in the multivariate analysis, which could be due to lack of power. Our sample of research participants at an academic medical center was also not randomly assigned from the population. Thus, larger and prospective samples, followed longitudinally over time, would better establish the validity and generalizability of the present findings. Finally, we investigated a relatively limited number of potential mediators of resilience and further work will need to include other promising lifestyle, personality, and genetic factors. There are also likely pathophysiological events that are “upstream” of A β deposition, and variability in these events needs to be accounted for.

Nonetheless, the present study identified a group of individuals who remained cognitively intact, despite sustaining equivalent amount of AD pathology as those with dementia. This finding supports the concept of reserve, repair or resilience factors, such as premorbid brain volume (and perhaps also education), which can protect against the deleterious effects of brain pathology.

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Table 1
Cognitive, psychiatric, and genetic characteristics

	Resilient (SD)	Dementia (SD)	Statistic t or χ^2	p
<i>N</i>	18	36		
Variables				
<i>CSF-Aβ_{1-42} (pg/ml)</i>	131.2 (33.3)	133.6 (24.9)	0.27	0.7856
$\dagger$ <i>MTL (cc)</i>	0.0036 (0.0005)	0.0036 (0.0003)	0.11	0.9128
<i>ICV (cc)</i>	1204 (1095)	1098 (1136)	-3.26	0.0020*
<i>Years of Education</i>	16.3 (4.2)	13.4 (4.7)	-2.27	0.0287*
<i>Age at Initial Evaluation</i>	72.5 (8.2)	72.7 (8.3)	0.11	0.9085
<i>Gender (% Female)</i>	44%	64%	1.85	0.1731
<i>APOE $\epsilon 4$ %</i>	82%	62%	2.23	0.1352
<i>GDS</i>	2.6 (2.3)	2.9 (2.6)	0.44	0.6644
<i>CDR-SOB</i>	0.28 (0.3)	4.31 (2.5)	9.43	<.0001*
<i>MMSE</i>	28.1 (1.2)	22.9 (5.6)	-5.31	<.0001*
<i>DSRS</i>	4.3 (4.4)	9.9 (4.8)	4.32	0.0001*
<i>WL Immediate Recall</i>	6.67 (1.99)	4.90 (2.45)	-2.35	0.025*
<i>WL Delayed Recall</i>	4.60 (2.9)	1.65 (1.66)	-3.44	0.003*
<i>Clock Draw</i>	2.47 (1.55)	4.25 (2.83)	2.38	0.024
<i>Clock Copy</i>	1.67 (1.23)	3.05 (2.28)	2.29	0.029
<i>Category Fluency</i>	15.73 (5.09)	10.60 (4.99)	-2.98	0.006
<i>Boston Naming</i>	23.80 (7.85)	20.75 (8.05)	-1.13	0.269
<i>Praxis Construction</i>	5.80 (3.14)	3.37 (2.48)	-2.45	0.021
<i>Digit Symbol</i>	37.33 (14.16)	23.53 (13.47)	-2.88	0.007
<i>LM Immediate Recall</i>	9.80 (4.35)	5.25 (3.29)	-3.39	0.002
<i>LM Delayed Recall</i>	7.60 (5.9)	2.95 (3.7)	-2.65	0.015

CSF = cerebrospinal fluid; *MTL* = medial temporal lobe; *ICV* = intracranial volume; *CDR-SOB* = Clinical Dementia Rating sum of boxes; *MMSE* = Mini-Mental Status Examination; *DSRS* = Dementia Severity Rating Scale; *GDS* = Geriatric Depression Scale; *WL* = Word List; *LM* = Logical Memory; *APOE* = Apolipoprotein E.

$\dagger$ *MTL* is corrected for *ICV*.

Table 2
Odds Ratio Estimates for Covariates in an Univariate Model

	Odds Ratio	95% CI	p-value
<i>Age</i>	0.99	0.93 – 1.07	0.9063
<i>Gender</i>	2.21	–0.9 – 0.18	0.1740
<i>Education</i>	1.19	1.02 – 1.43	0.0215
<i>ICV</i>	1.01	1.003 – 1.015	0.0018
<i>APOE Status</i>	2.88	–1.33 – 0.14	0.1236

ICV = intracranial volume; APOE = Apolipoprotein E.