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A Pilot Study of Neuropsychological Functions, *APOE* and Amyloid Imaging in Patients with Gliomas

D.D. Correa, PhD^{1,2}, M. Kryza-Lacombe, MA³, X. Zhou, MD⁴, R.E. Baser, MS⁵, B.J. Beattie, MS⁶, Z. Beiene⁴, J. Humm, PhD⁴, L.M. DeAngelis, MD^{1,2}, I. Orlow, PhD⁵, W. Weber, MD^{4,6}, and J. Osborne, MD^{4,6}

¹Departments of Neurology Memorial Sloan-Kettering Cancer Center, New York NY

²Departments of Neurology Weill Cornell Medical College, New York, NY

³San Diego State University/University of California, San Diego Joint Doctoral Program in Clinical Psychology, San Diego, CA

⁴Departments of Radiology Memorial Sloan-Kettering Cancer Center, New York NY

⁵Departments of Epidemiology and Biostatistics Memorial Sloan-Kettering Cancer Center, New York NY

⁶Departments of Medical Physics Memorial Sloan-Kettering Cancer Center, New York NY; Departments of Radiology Weill Cornell Medical College, New York, NY

Abstract

Brain tumor patients treated with radiotherapy (RT) often develop cognitive dysfunction, and recent studies suggest that the *APOE* ϵ -4 allele may influence cognitive outcome. The ϵ -4 allele is known to promote beta (β) amyloid deposition in the cortex, and preliminary evidence suggests that RT may be associated with this process. However, it is unknown whether β -amyloid accumulation contributes to treatment neurotoxicity. In this pilot study, we assessed neuropsychological functions and β -amyloid retention using ¹⁸F-florbetaben (FBB) PET in a subset of brain tumor patients who participated in our study of *APOE* polymorphisms and cognitive functions. Twenty glioma patients treated with conformal RT $\pm$ chemotherapy participated in the study: 6 were *APOE* ϵ -4 carriers and 14 were non- ϵ -4 carriers. Patients completed a neuropsychological re-evaluation (mean time interval = 5 years, SD=0.83) and brain

Corresponding Author: Denise D. Correa, PhD, ABPP-CN, Department of Neurology, Memorial Sloan-Kettering Cancer Center, 1275 York Avenue, New York, NY 10021, Telephone number: 212-610-0487; FAX number: 646-888-3175, corread@mskcc.org.

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MRI and FBB PET scans. Wilcoxon signed-rank test comparisons between prior and current neuropsychological assessments showed a significant decline in attention (Brief Test of Attention, $p=0.018$), and a near significant decline in verbal learning (Hopkins Verbal learning Test-Learning, $p=0.07$). Comparisons by *APOE* status showed significant differences over time in attention/working memory (WAIS-III digits forward, $p=0.028$ & digits backward, $p=0.032$), with a decline among *APOE* ϵ -4 carriers. There were no significant differences in any of the FBB PET analyses between *APOE* ϵ -4 carriers and non- ϵ -4 carriers. The findings suggest that glioma patients may experience worsening in attention and executive functions several years after treatment, and that the *APOE* ϵ -4 allele may modulate cognitive decline, but independent of increased β -amyloid deposition.

Keywords

Cognitive; *APOE*; Amyloid; Brain Tumors; Word count = 2; 977

Introduction

Patients with brain tumors treated with radiotherapy (RT) $\pm$ chemotherapy (CHT) often develop cognitive dysfunction that interferes with their quality of life. It is considered the most frequent complication among long-term survivors [1], with deficits in attention, executive functions, learning and retrieval being the most prevalent [2]. The delayed effects of RT may occur years after treatment, and are thought to produce progressive damage through vascular injury, disruption of oligodendrocytes and normal myelin turnover, and neurodegeneration [3-6]. The combination of RT and CHT may have an additive neurotoxic effect [7]. Preliminary evidence from an autopsy study of brain tumor patients suggested that RT was associated with an increase in beta (β) amyloid deposition, especially in the form of amyloid angiopathy [8], a pathologic finding in Alzheimer's disease (AD). A more recent study of mice exposed to particle irradiation furthered this hypothesis as an increase in β -amyloid plaque pathology was noted [9].

The Apolipoprotein E (*APOE*) ϵ -4 allele is common in the population with 25% carrying at least one ϵ -4 allele, and is a known genetic risk factor for AD [10]. The ϵ -4 allele is associated with decreased neuronal growth and repair [11] and promotes β -amyloid deposition in brain tissue [12, 13]. Studies using amyloid imaging with positron emission tomography (PET) showed increased β -amyloid retention in the frontal, temporal, parietal and cingulate cortices in AD patients compared to age-matched controls [14], particularly in *APOE* ϵ -4 carriers [15, 16]. Increased amyloid deposition was also reported in patients with head trauma, epilepsy, cerebrovascular disease carrying the *APOE* ϵ -4 allele, suggesting that it may have an important role in neuronal repair and plasticity after a variety of brain injuries [17-19].

We reported that brain tumor survivors treated with RT $\pm$ CHT or CHT alone who were carriers of at least one *APOE* ϵ -4 allele ($n=50$) had significantly lower scores in learning and delayed recall, and a trend toward worse performance in executive functions, relative to non- ϵ -4 carriers ($n=161$) [20]. However, it is unknown whether brain tumors patients treated with

RT $\pm$ CHT who are *APOE* ϵ -4 carriers are at increased risk for progressive cognitive decline or β -amyloid retention. In this pilot study, we assessed neuropsychological functions and β -amyloid retention using ^{18}F -florbetaben (FBB) PET in a subset of *APOE* ϵ -4 allele carriers and non-carriers [20].

Materials and Methods

Subjects

Twenty brain tumor patients were recruited from a cohort of patients who participated in our study of *APOE* polymorphisms and cognitive functions [20]. The plan was to recruit equal numbers of *APOE* ϵ -4 allele carriers and non- ϵ -4 carriers, and the sample size was determined partly based on patient availability, considering that 19 *APOE* ϵ -4 allele carriers and 60 non- ϵ -4 carriers treated with RT $\pm$ CHT remained on active follow-up. Study eligibility included: participation in the prior study (protocol #09-151) and provision of consent to have DNA stored and genotyping results used in future studies; completion of treatment with RT $\pm$ CHT; in stable disease remission on magnetic resonance imaging (MRI) scans prior to accrual. All patients provided written informed consent. Patients underwent a neuropsychological re-evaluation and brain MRI and FBB PET scans.

Measures

Neuropsychological Assessment—Patients completed a neuropsychological re-evaluation including tests used previously [20]. The test battery was re-administered by a neuropsychologist (DDC) or a trained research assistant. Cognitive raw test scores were compared with published normative values according to age, and converted into z-scores.

Neuropsychological Tests

- Digit Span subtest of the WMS-III (Longest Digit Span Forward-LDSF; Longest Digit Span Backward-LDSB)[21]
- Brief Test of Attention (BTA) [22]
- Trail Making Test Parts A & B (TMT-A, TMT-B) [23]
- Phonemic Verbal Fluency (VF) [24]
- Hopkins Verbal Learning Test-Revised [25] (Learning [HVLTL], Delayed Recall [HVLTD], Discrimination Index [HVLTDI]).

Genetics—*APOE* epsilon allelic data were available for all patients as previously described [20].

Imaging Acquisition and Reconstruction—Patients underwent a brain MRI on a 3 Tesla scanner (GE, Milwaukee, WI), and three-dimensional high-resolution T1-weighted magnetization prepared rapid gradient echo acquisition (MPRAGE) and fluid attenuation inversion recovery (FLAIR) sequences were acquired. PET images were acquired using a PET/CT scanner (DSTE; GE Healthcare) operating in three-dimensional mode. Patients were injected with a single dose of 300 MBq of FBB in a slow intravenous bolus injection,

and allowed to rest for approximately 90 minutes. Patients were immobilized in a PET head holder and had a low-dose CT scan for the purpose of MRI image registration and attenuation correction, and a 20-minute static PET acquisition scan of the brain starting at 90–110 min after injection. The resulting PET-MRI data sets were exported to HERMES software (Hermes Medical Solutions Inc. Greenville N.C.) for analysis. Each dose of FBB was delivered by Piramal Imaging on the same day as the scheduled PET study for each patient, in accordance with the applicable regulatory guidelines. The MRI and PET scans were performed on the same day. The 3D co-registration of PET-CT to MRI was performed using an algorithm available in the HERMES software which adjusted the relative alignment of the scans seeking to maximize the mutual information between the anatomical CT and T1 and FLAIR MRI data sets. The PET emission data was re-sampled using the same transformation matrix as was applied to the CT to yield registered PET-MRI scans.

Image Analysis – FBB PET—Visual assessment (VA) of the PET scans was performed by a clinically certified reader (J.O.) using a standard regional cortical tracer uptake (RCTU) scoring system [26] (1=no tracer uptake, 2=moderate tracer uptake, 3=pronounced tracer uptake) in 4 brain areas (lateral temporal cortex, frontal cortex, parietal cortex, posterior cingulate). To make this VA semiquantitative, standardized uptake values (SUVs), defined as the decay corrected brain radioactivity concentration, normalized for injected dose and body weight, were calculated for the following brain regions of interest (ROIs) for all patients, on both hemispheres where appropriate: frontal cortex, lateral and medial temporal cortices, parietal cortex, occipital cortex, posterior and anterior cingulate cortex, cerebellar cortex, thalamus, putamen, periventricular white matter (centrum semiovale), and pons. These ROIs were selected based on studies of β -amyloid retention in AD patients [27] and manually defined by a radiologist blinded to the patients' clinical history and *APOE* ϵ -4 status using the co-registered FLAIR MRI-PET images (Figure 1). The tumor and resection cavity were manually traced and excluded from the ROIs based on the MRI images, if applicable.

For each ROI, we recorded average, median, minimum, maximum and standard deviation of the SUV voxel intensities (SUV_{av} , SUV_{med} , SUV_{min} , SUV_{max} , SUV_{σ}) of the individual voxel intensities. These data describe the uniformity and dispersion of FBB within each ROI, and allow the measurement of the region-to-region variability within a given patient. Regional SUV ratios (SUVRs) were computed by dividing the regional SUV_{av} of a given region by the SUV_{av} from the cerebellar cortex. The cerebellar cortex was chosen as a reference region as it has been reported to be without β -amyloid deposition in AD patients [26], and this region was not included in the RT field for any of the patients. A composite SUVR-neocortex score was derived for each patient as described by Bullich et al. [28], by averaging the mean value of the SUVRs from six cortical regions (frontal, parietal, lateral temporal, anterior and posterior cingulate and occipital cortices).

Wilcoxon rank-sum tests were used to compare SUVRs in each ROI and the neocortex composite score between the *APOE* ϵ -4-carrier and ϵ -4-non-carrier patient groups. Spearman's rank correlations were used to assess the association between regional SUVRs and cognitive test z-scores.

Demographic and Neuropsychological Tests Analyses—Descriptive statistics for demographic variables were generated with frequencies for categorical variables and with means and standard deviations, or median and ranges as appropriate for continuous variables. Demographics were compared between APOE ε-4-carriers and non-carriers using Wilcoxon rank-sum tests for continuous variables and Fisher's exact tests for categorical variables. Wilcoxon signed-rank tests were used for comparisons of cognitive test z-scores between the prior and current evaluations for all patients, and Wilcoxon rank-sum tests were used for comparing z-scores between APOE ε-4-carrier and ε-4-non-carrier patient groups.

Results

Patient Characteristics

Twenty patients participated in this study, including six carriers and fourteen non-carriers of the *APOE* ε-4 allele. The target accrual of equal numbers of *APOE* ε-4 carriers and non-carriers was not reached as only six of the nineteen ε-4 carriers who were on active follow up agreed to participate. Among the 20 patients enrolled, 14 (70%) had high-grade gliomas (anaplastic astrocytoma, glioblastoma, and 6 (30%) had low-grade gliomas (astrocytoma, oligodendroglioma). Seventeen patients (85%) had conformal fractionated RT and CHT, and 3 (15%) had conformal RT-only; RT dose ranged from 54 to 60 Gy. CHT regimens included temozolomide (70%), and carmustine or other agents (30%). Only one patient had disease relapse between the time of participation in the initial and the current study, and had completed treatment with temozolomide approximately one year prior to the current enrollment. There were no significant differences in demographic, disease or treatment history for the 20 patients according to *APOE* ε-4 status (Table 1).

Neuropsychological Functions

All 20 patients had an initial neuropsychological assessment [20], and had completed treatment at a mean of 4 years (SD=3.4) at the time of our prior study (Time 1). These patients were re-evaluated in this pilot study approximately five years later (mean=5.21 years, SD=0.83) (Time 2). The results of Wilcoxon signed-rank tests comparing neuropsychological test performance between prior (Time 1) and current (Time 2) assessments showed a significant decline in the BTA ($p=0.018$), and a trend toward a significant decline in the HVLT-Learning ($p=0.07$) for all patients (Table 2). Comparisons of neuropsychological test score changes between Time 1 & Time 2 by *APOE* status showed significant differences for the LDSF ($p=0.028$) and LDSB ($p=0.032$), with a decline in performance for *APOE* ε-4 carriers but not for non-ε-4-carriers (Table 3).

FBB PET Image Analyses

VA of the PET scans performed by a certified reader demonstrated a characteristic FBB uptake pattern in the white matter, and no increased uptake in any cortical gray matter area. All patients received a RCTU score of 1 (no tracer uptake), which is considered a normal finding. Wilcoxon signed-rank test results showed no significant differences between the left and right hemispheres on any of the regional SUVRs. Therefore, all subsequent analyses combined left and right SUVRs for each ROI. There were no significant differences in any of the SUVRs between patients who were *APOE* ε-4 carriers and non-ε-4 carriers (Table 4).

Figure 2 shows brain FBB PET images and co-registered PET MRI images for an *APOE* ϵ -4 carrier and for a non- ϵ -4 carrier patient.

There were no significant correlations between cognitive test z-scores and regional SUVRs after adjusting for multiple comparisons. Patients had no difficulties completing the MRI and PET studies and reported no adverse effects.

Discussion

The results of this pilot study showed that a subset of patients with gliomas treated with conformal RT $\pm$ CHT had continued decline in attention and verbal learning abilities over an approximately nine-year period, and that the *APOE* ϵ -4 allele may have influenced cognitive decline. The findings suggest that progressive worsening in aspects of attention and executive functions may occur over several years following RT $\pm$ CHT despite adequate disease control. Cognitive studies of long term survivors of brain tumors have included primarily patients with low-grade gliomas, considering their longer survival rates relative to those with high-grade gliomas [29]. However, a recent study [30] reported cognitive impairment across several domains in a small group of glioblastoma patients who survived more than three years. Taphoorn et al. [31] studied cognitive outcome in a large cohort of low-grade glioma patients (most 1-22 years post RT), in patients with hematologic cancers, and healthy controls. Glioma patients obtained lower scores than the cancer control group on graphomotor speed, visual memory, and executive functions, and some of the test scores declined over time only among those treated with RT. A follow-up study [32] included a subset of these glioma patients who underwent a re-evaluation at a mean of 12 years (range = 6-28 years) after the initial assessment. Patients who received RT showed a further decline in attention, executive function, and processing speed, suggesting that both partial and whole brain RT was associated with cognitive dysfunction several years after treatment. Surma-aho et al. [33] assessed cognitive functions in low-grade glioma patients approximately seven years post-RT $\pm$ CHT or surgical resection alone. Patients treated with RT had significantly lower scores in percent visual retention and estimated Performance IQ in comparison those who did not receive RT. Our group [34] studied cognitive functions in 40 patients with low-grade gliomas; 16 had RT $\pm$ CHT 6 months to 9 years prior to enrollment. Patients treated with RT $\pm$ CHT had lower scores in attention and executive functions, graphomotor speed, and memory than untreated patients. In the context of these studies, our results provide additional evidence that long term glioma survivors may continue to experience cognitive decline, possibly related to the combined effects of disease and treatment delayed effects.

We also examined longitudinal changes in neuropsychological functions according to *APOE* ϵ -4 status. The preliminary findings showed significantly worse performance over time in attention and working memory in carriers of at least one ϵ -4 allele relative to non- ϵ -4 carriers over an approximately five-year period, suggesting that the ϵ -4 allele may increase susceptibility to continued cognitive impairment in long term survivors. Several studies described an association between the *APOE* ϵ -4 allele and diminished memory and executive functions in healthy middle-aged [35] and a faster rate of cognitive decline in older ϵ -4 carriers [36]. Abnormal modulation of cholinergic function described in association with the *APOE* ϵ -4 has been reported to influence attention in healthy older individuals [37-39].

Treatment with donepezil, an acetylcholinesterase inhibitor, has been shown to improve attention, motor speed and memory in brain tumor patients [40, 41] possibly through activation of the forebrain cholinergic system [42]. In our prior cross-sectional study of *APOE* polymorphisms and cognitive functions [20], we described that the *APOE* ϵ -4 allele and additional SNPs in the *APOE* gene may increase the vulnerability of brain tumor patients to cognitive dysfunction. Studies in patients with breast cancer also described the role of the *APOE* ϵ -4 allele in moderating cognitive outcome [43]. Taken together, these reports suggest that the *APOE* ϵ -4 allele may influence cognitive outcome and contribute to the rate of decline in patients with cancer, and with brain tumors specifically.

It has been reported that in addition to reducing cholinergic integrity and function, the *APOE* ϵ -4 allele may increase β -amyloid deposition, disrupt neuronal repair, and influence the regulation of phospholipid and cholesterol following brain injury [44]. It may also accelerate age-related changes in the breakdown of myelin [45]. Studies using amyloid imaging with FBB PET showed increased β -amyloid retention in the frontal, temporal, parietal and cingulate cortices in AD patients compared to age-matched controls [14, 46], particularly in *APOE* ϵ -4 carriers [15, 16]. In the context of these studies and preliminary evidence that RT may be associated with an increase in β -amyloid deposition [8], we used FBB PET [27, 28, 46] to examine amyloid retention in glioma survivors according to *APOE* ϵ -4 status. The results showed no significant differences in regional SUVRs between *APOE* ϵ -4 carriers and non- ϵ -4-carriers. VA of PET scans showed FBB uptake in the white matter for all patients, which is consistent with tracer binding to the lipid-containing myelin sheath [47] and considered a normal finding. There was no increased tracer uptake in the grey matter for any of the patients. VA is used by clinically certified FBB PET readers to categorize scans as positive (moderate/pronounced RCTU) or negative (no RCTU) for beta amyloid deposition using a robust visual assessment method which was autopsy validated [48]. The addition of SUVR analysis made this assessment semiquantitative, but did not change the findings. The levels observed in our patients were not suggestive of RT effect altering the binding as the β -amyloid retention levels appeared unaffected by known patterns of focal therapy. These preliminary findings suggest that RT $\pm$ CHT and the *APOE* ϵ -4 allele may not be strongly associated with increased β -amyloid cortical retention in these glioma survivors, despite evidence of cognitive decline. Disruption of other pathways associated with the *APOE* ϵ -4 allele, such as reduction in cholinergic function and disruption of neuronal repair and myelin integrity may have influenced cognitive outcome in these patients. In addition to the small number of patients, some of the characteristics of our sample may have contributed to the negative FBB PET findings including: (1) treatment with conformal RT instead of whole-brain RT, resulting in more limited tissue exposure to radiation; (2) relatively young age of the sample considering that amyloid deposition increases with older age [49, 50].

The findings of this study are interpreted with caution considering the small sample size and the unequal numbers of *APOE* ϵ -4 carriers and non- ϵ -4-carriers. The sample size may have limited the power to detect small to moderate size effects, and to study possible interactions with disease-related factors. For instance, we cannot exclude the possibility that the decline in working memory and verbal learning among all patients, and in attention and working memory in *APOE* ϵ -4 carriers was related to an interaction with other factors such as disease

duration, tumor location as most patients had frontal lobe tumors, and treatment delayed effects. Despite these limitations, this is the first study to describe longitudinal changes in cognition according to *APOE* ϵ -4 status and to examine β -amyloid retention in long-term glioma survivors. Large scale studies including disease and healthy control comparison groups could assist in further clarifying the possible association among the *APOE* ϵ -4 allele, β -amyloid retention and neuropsychological function in this clinical population. The findings in the context of recent reports also highlight the importance of expanding these lines of research to include additional genetic polymorphisms that may influence cognition and treatment neurotoxicity [41], which may ultimately lead to the identification of patients that may be at increased risk.

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References Cited

- Behin, A., DeLattre, JY. Neurologic sequelae of radiotherapy on the nervous system. In: Schiff, D., Wen, PY., editors. *Cancer Neurology in Clinical Practice*. Humana Press; Totowa, New Jersey: 2003. p. 173-191.
- Wefel JS, Kayl AE, Meyers CA. Neuropsychological dysfunction associated with cancer and cancer therapies: a conceptual review of an emerging target. *Br J Cancer*. 2004; 90:1691–1696. DOI: 10.1038/sj.bjc.6601772 [PubMed: 15150608]
- Fishel ML, Vasko MR, Kelley MR. DNA repair in neurons: so if they don't divide what's to repair? *Mutat Res*. 2007; 614:24–36. DOI: 10.1016/j.mrfmmm.2006.06.007 [PubMed: 16879837]
- Nordal RA, Wong CS. Molecular targets in radiation-induced blood-brain barrier disruption. *Int J Radiat Oncol Biol Phys*. 2005; 62:279–287. DOI: 10.1016/j.ijrobp.2005.01.039 [PubMed: 15850934]
- Warrington JP, Ashpole N, Csiszar A, Lee YW, Ungvari Z, Sonntag WE. Whole brain radiation-induced vascular cognitive impairment: mechanisms and implications. *J Vasc Res*. 2013; 50:445–457. DOI: 10.1159/000354227 [PubMed: 24107797]
- Greene-Schloesser D, Robbins ME, Peiffer AM, Shaw EG, Wheeler KT, Chan MD. Radiation-induced brain injury: A review. *Front Oncol*. 2012; 2:1–18. DOI: 10.3389/fonc.2012.00073
- DeAngelis, LM., Posner, JB. Side effects of radiation therapy. In: DeAngelis, LM., Posner, JB., editors. *Neurologic Complications of Cancer*. 2nd. Oxford University Press; New York: 2009. p. 551-555.
- Sugihara S, Ogawa A, Nakazato Y, Yamaguchi H. Cerebral beta amyloid deposition in patients with malignant neoplasms: its prevalence with aging and effects of radiation therapy on vascular amyloid. *Acta neuropathologica*. 1995; 90:135–141. [PubMed: 7484088]
- Cherry JD, Liu B, Frost JL, Lemere CA, Williams JP, Olschowka JA, O'Banion MK. Galactic cosmic radiation leads to cognitive impairment and increased abeta plaque accumulation in a mouse model of Alzheimer's disease. *PloS one*. 2012; 7:e53275.doi: 10.1371/journal.pone.0053275 [PubMed: 23300905]
- Corder EH, Saunders AM, Strittmatter WJ, Schmechel DE, Gaskell PC, Small GW, Roses AD, Haines JL, Pericak-Vance MA. Gene dose of apolipoprotein E type 4 allele and the risk of Alzheimer's disease in late onset families. *Science*. 1993; 261:921–923. [PubMed: 8346443]
- Utermann G. Alzheimer's disease. The apolipoprotein E connection. *Curr Biol*. 1994; 4:362–365. [PubMed: 7922348]
- Quigley H, Colloby SJ, O'Brien JT. PET imaging of brain amyloid in dementia: a review. *Int J Geriatr Psychiatry*. 2011; 26:991–999. DOI: 10.1002/gps.2640 [PubMed: 21905095]

13. Bennett DA, Schneider JA, Wilson RS, Bienias JL, Berry-Kravis E, Arnold SE. Amyloid mediates the association of apolipoprotein E ϵ 4 allele to cognitive function in older people. *J Neurol Neurosurg Psychiatry*. 2005; 76:1194–1199. DOI: 10.1136/jnnp.2004.054445 [PubMed: 16107349]
14. Villemagne VL, Burnham S, Bourgeat P, Brown B, Ellis KA, Salvado O, Szeoke C, Macaulay SL, Martins R, Maruff P, Ames D, Rowe CC, Masters CL, Australian Imaging B, Lifestyle Research G. Amyloid beta deposition, neurodegeneration, and cognitive decline in sporadic Alzheimer's disease: a prospective cohort study. *Lancet Neuro*. 2013; 12:357–367. DOI: 10.1016/S1474-4422(13)70044-9
15. Morris JC, Roe CM, Grant EA, Head D, Storandt M, Goate AM, Fagan AM, Holtzman DM, Mintun MA. Pittsburgh compound B imaging and prediction of progression from cognitive normality to symptomatic Alzheimer disease. *Arch Neurol*. 2009; 66:1469–1475. DOI: 10.1001/archneurol.2009.269 [PubMed: 20008650]
16. Morris JC, Roe CM, Xiong C, Fagan AM, Goate AM, Holtzman DM, Mintun MA. APOE predicts amyloid-beta but not tau Alzheimer pathology in cognitively normal aging. *Ann Neurol*. 2010; 67:122–131. DOI: 10.1002/ana.21843 [PubMed: 20186853]
17. Mielke MM, Savica R, Wiste HJ, Weigand SD, Vemuri P, Knopman DS, Lowe VJ, Roberts RO, Machulda MM, Geda YE, Petersen RC, Jack CR Jr. Head trauma and in vivo measures of amyloid and neurodegeneration in a population-based study. *Neurology*. 2014; 82:70–76. DOI: 10.1212/01.wnl.0000438229.56094.54 [PubMed: 24371306]
18. Chetelat G, La Joie R, Villain N, Perrotin A, de La Sayette V, Eustache F, Vandenberghe R. Amyloid imaging in cognitively normal individuals, at-risk populations and preclinical Alzheimer's disease. *NeuroImage Clinical*. 2013; 2:356–365. DOI: 10.1016/j.nicl.2013.02.006 [PubMed: 24179789]
19. Kim HJ, Ye BS, Yoon CW, Cho H, Noh Y, Kim GH, Choi YS, Kim JH, Jeon S, Lee JM, Kim JS, Choe YS, Lee KH, Kim ST, Kim C, Kang DR, Ki CS, Lee JH, Werring DJ, Weiner MW, Na DL, Seo SW. Effects of APOE ϵ 4 on brain amyloid, lacunar infarcts, and white matter lesions: a study among patients with subcortical vascular cognitive impairment. *Neurobiol Aging*. 2013; 34:2482–2487. DOI: 10.1016/j.neurobiolaging.2013.05.009 [PubMed: 23769398]
20. Correa DD, Satagopan J, Baser RE, Cheung K, Richards E, Lin M, Karimi S, Lyo J, DeAngelis LM, Orlov I. APOE polymorphisms and cognitive functions in patients with brain tumors. *Neurology*. 2014; 83:320–327. DOI: 10.1212/wnl.0000000000000617 [PubMed: 24944262]
21. Wechsler, D. Wechsler Adult Intelligence Scale-Third Edition. The Psychological Corporation; New York: 1997.
22. Schretlen D, Bobholz JH, Brandt J. Development and psychometric properties of the brief test of attention. *The Clinical Neuropsychologist*. 1996; 10:80–89.
23. Robert, K., Heaton, S., Miller, Walden, Taylor, Michael J., Grant, Igor. Revised comprehensive norms for an expanded Halstead-Reitan battery: Demographically adjusted neuropsychological norms for african american and caucasian adults. Psychological Assessment Resources Inc.; Florida: 2004.
24. Benton L, Hamsher K, Sivan A. Controlled oral word association test. Multilingual aphasia examination. 1994
25. Benedict RHB, Schretlen D, Groninger L, Brandt J. Hopkins Verbal Learning Test-Revised: Normative data and analysis of inter-form and test-retest reliability. *The Clinical Neuropsychologist*. 1998; 12:43–55.
26. Catafau AM, Bullich S, Seibyl JP, Barthel H, Ghatti B, Leverenz J, Ironside JW, Schulz-Schaeffer WJ, Hoffmann A, Sabri O. Cerebellar Amyloid-beta Plaques: How Frequent Are They, and Do They Influence 18F-Florbetaben SUV Ratios? *J Nucl Med*. 2016; 57:1740–1745. DOI: 10.2967/jnumed.115.171652 [PubMed: 27363836]
27. Barthel H, Gertz HJ, Dresel S, Peters O, Bartenstein P, Buerger K, Hiemeyer F, Wittemer-Rump SM, Seibyl J, Reininger C, Sabri O, Florbetaben Study G. Cerebral amyloid-beta PET with florbetaben (18F) in patients with Alzheimer's disease and healthy controls: a multicentre phase 2 diagnostic study. *Lancet Neuro*. 2011; 10:424–435. DOI: 10.1016/S1474-4422(11)70077-1
28. Bullich S, Seibyl J, Catafau AM, Jovalekic A, Koglin N, Barthel H, Sabri O, De Santi S. Optimized classification of 18F-Florbetaben PET scans as positive and negative using an SUVR quantitative

- approach and comparison to visual assessment. *NeuroImage Clinical*. 2017; 15:325–332. DOI: 10.1016/j.nicl.2017.04.025 [PubMed: 28560157]
29. Stupp R, Mason WP, van den Bent MJ, Weller M, Fisher B, Taphoorn MJ, Belanger K, Brandes AA, Marosi C, Bogdahn U, Curschmann J, Janzer RC, Ludwin SK, Gorlia T, Allgeier A, Lacombe D, Cairncross JG, Eisenhauer E, Mirmanoff RO. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. *N Engl J Med*. 2005; 352:987–996. DOI: 10.1056/NEJMoa043330 [PubMed: 15758009]
 30. Solanki C, Sadana D, Arimappamagan A, Rao K, Rajeswaran J, Subbakrishna DK, Santosh V, Pandey P. Impairments in Quality of Life and Cognitive Functions in Long-term Survivors of Glioblastoma. *J Neurosci Rural Pract*. 2017; 8:228–235. DOI: 10.4103/0976-3147.203829 [PubMed: 28479798]
 31. Taphoorn MJ, Schiphorst AK, Snoek FJ, Lindeboom J, Wolbers JG, Karim AB, Huijgens PC, Heimans JJ. Cognitive functions and quality of life in patients with low-grade gliomas: the impact of radiotherapy. *Ann Neurol*. 1994; 36:48–54. DOI: 10.1002/ana.410360111 [PubMed: 8024261]
 32. Douw L, Klein M, Fagel SS, van den Heuvel J, Taphoorn MJ, Aaronson NK, Postma TJ, Vandertop WP, Mooij JJ, Boerman RH, Beute GN, Sluimer JD, Slotman BJ, Reijneveld JC, Heimans JJ. Cognitive and radiological effects of radiotherapy in patients with low-grade glioma: long-term follow-up. *Lancet Neuro*. 2009; 8:810–818. DOI: 10.1016/S1474-4422(09)70204-2
 33. Surma-aho O, Niemela M, Vilkkilä J, Kouri M, Brander A, Salonen O, Paetau A, Kallio M, Pyykkonen J, Jaaskelainen J. Adverse long-term effects of brain radiotherapy in adult low-grade glioma patients. *Neurology*. 2001; 56:1285–1290. [PubMed: 11376174]
 34. Correa DD, Kryza-Lacombe M, Baser RE, Beal K, DeAngelis LM. Cognitive effects of donepezil therapy in patients with brain tumors: a pilot study. *J Neurooncol*. 2016; 127:313–319. DOI: 10.1007/s11060-015-2035-3 [PubMed: 26738844]
 35. Flory JD, Manuck SB, Ferrell RE, Ryan CM, Muldoon MF. Memory performance and the apolipoprotein E polymorphism in a community sample of middle-aged adults. *Am J Med Genet*. 2000; 96:707–711. [PubMed: 11121165]
 36. Caselli RJ, Locke DE, Dueck AC, Knopman DS, Woodruff BK, Hoffman-Snyder C, Rademakers R, Fleisher AS, Reiman EM. The neuropsychology of normal aging and preclinical Alzheimer's disease. *Alzheimer's & dementia : the journal of the Alzheimer's Association*. 2013; 12:1–9. DOI: 10.1016/j.jalz.2013.01.004
 37. Parasuraman R, Greenwood PM, Kumar R, Fossella J. Beyond heritability: neurotransmitter genes differentially modulate visuospatial attention and working memory. *Psychol Sci*. 2005; 16:200–207. DOI: 10.1111/j.0956-7976.2005.00804.x [PubMed: 15733200]
 38. Greenwood PM, Lambert C, Sunderland T, Parasuraman R. Effects of apolipoprotein E genotype on spatial attention, working memory, and their interaction in healthy, middle-aged adults: results From the National Institute of Mental Health's BIOCARD study. *Neuropsychology*. 2005; 19:199–211. DOI: 10.1037/0894-4105.19.2.199 [PubMed: 15769204]
 39. Bellgrove MA, Mattingley JB. Molecular genetics of attention. *Annals of the New York Academy of Sciences*. 2008; 1129:200–212. DOI: 10.1196/annals.1417.013 [PubMed: 18591481]
 40. Shaw EG, Rosdhal R, D'Agostino RB Jr, Lovato J, Naughton MJ, Robbins ME, Rapp SR. Phase II study of donepezil in irradiated brain tumor patients: effect on cognitive function, mood, and quality of life. *J Clin Oncol*. 2006; 24:1415–1420. DOI: 10.1200/JCO.2005.03.3001 [PubMed: 16549835]
 41. Correa DD, Satagopan J, Cheung K, Arora AK, Kryza-Lacombe M, Xu Y, Karimi S, Lyo J, DeAngelis LM, Orlow I. COMT, BDNF, and DTNBP1 polymorphisms and cognitive functions in patients with brain tumors. *Neuro Oncol*. 2016; 18:1425–1433. DOI: 10.1093/neuonc/now057 [PubMed: 27091610]
 42. Pepeu G, Giovannini MG, Bracco L. Effect of cholinesterase inhibitors on attention. *Chemico-biological interactions*. 2013; 203:361–364. DOI: 10.1016/j.cbi.2012.09.016 [PubMed: 23047023]
 43. Ahles TA, Li Y, McDonald BC, Schwartz GN, Kaufman PA, Tsongalis GJ, Moore JH, Saykin AJ. Longitudinal assessment of cognitive changes associated with adjuvant treatment for breast cancer: the impact of APOE and smoking. *Psychooncology*. 2014; 23:1382–1390. DOI: 10.1002/pon.3545 [PubMed: 24789331]

44. Relkin NR, Kwon YJ, Tsai J, Gandy S. The National Institute on Aging/Alzheimer's Association recommendations on the application of apolipoprotein E genotyping to Alzheimer's disease. *Annals of the New York Academy of Sciences*. 1996; 802:149–176. [PubMed: 8993494]
45. Ryan L, Walther K, Bendlin BB, Lue LF, Walker DG, Glisky EL. Age-related differences in white matter integrity and cognitive function are related to APOE status. *Neuroimage*. 2011; 54:1565–1577. DOI: 10.1016/j.neuroimage.2010.08.052 [PubMed: 20804847]
46. Villemagne VL, Ong K, Mulligan RS, Holl G, Pejoska S, Jones G, O'Keefe G, Ackerman U, Tochon-Danguy H, Chan JG, Reiningner CB, Fels L, Putz B, Rohde B, Masters CL, Rowe CC. Amyloid imaging with (18)F-florbetaben in Alzheimer disease and other dementias. *J Nucl Med*. 2011; 52:1210–1217. DOI: 10.2967/jnumed.111.089730 [PubMed: 21764791]
47. Stankoff B, Freeman L, Aigrot MS, Chardain A, Dolle F, Williams A, Galanaud D, Armand L, Lehericy S, Lubetzki C, Zalc B, Bottlaender M. Imaging central nervous system myelin by positron emission tomography in multiple sclerosis using [methyl-(1)(1)C]-2-(4'-methylaminophenyl)-6-hydroxybenzothiazole. *Ann Neurol*. 2011; 69:673–680. DOI: 10.1002/ana.22320 [PubMed: 21337603]
48. Seibyl J, Catafau AM, Barthel H, Ishii K, Rowe CC, Leverenz JB, Ghetti B, Ironside JW, Takao M, Akatsu H, Murayama S, Bullich S, Mueller A, Koglin N, Schulz-Schaeffer WJ, Hoffmann A, Sabbagh MN, Stephens AW, Sabri O. Impact of Training Method on the Robustness of the Visual Assessment of 18F-Florbetaben PET Scans: Results from a Phase-3 Study. *J Nucl Med*. 2016; 57:900–906. DOI: 10.2967/jnumed.115.161927 [PubMed: 26823561]
49. Ellis KA, Lim YY, Harrington K, Ames D, Bush AI, Darby D, Martins RN, Masters CL, Rowe CC, Savage G, Szoek C, Villemagne VL, Maruff P, Group AR. Decline in cognitive function over 18 months in healthy older adults with high amyloid-beta. *Journal of Alzheimer's disease : JAD*. 2013; 34:861–871. DOI: 10.3233/JAD-122170
50. Lim YY, Ellis KA, Ames D, Darby D, Harrington K, Martins RN, Masters CL, Rowe C, Savage G, Szoek C, Villemagne VL, Maruff P, Group AR. Abeta amyloid, cognition, and APOE genotype in healthy older adults. *Alzheimer's & dementia : the journal of the Alzheimer's Association*. 2013; 9:538–545. DOI: 10.1016/j.jalz.2012.07.004

Figure 1.

Regions of Interest (ROIs) drawn on axial FLAIR MRI scans and used to analyze the ^{18}F -florbetaben PET images. ROIs were defined for each patient for the: a) cerebellar cortex; b) medial and lateral temporal cortex; c) occipital cortex; d) frontal cortex, caudate head, putamen, thalamus; e) parietal cortex and right frontal lesion; f) anterior and posterior cingulate cortex, white matter, and left frontal lesion.

Figure 2.

^{18}F -florbetaben PET images (*top row*) and PET images co-registered to the FLAIR images (*bottom row*) of: a) an *APOE* ϵ -4 carrier patient with a right frontal lesion; b) an *APOE* non- ϵ -4-carrier patient with a left frontal lesion. Radiotracer uptake was restricted to the white matter for both patients.

Table 1
Demographic, Disease and Treatment History

Demographic/Disease/Treatment History ^I	<i>APOE</i> ε-4 Positive (N=6)	<i>APOE</i> ε-4 Negative (N=14)
Male (%)	50	50
Right-Handed (%)	67	100
Current Age (years)		
Mean (SD)	51 (9.1)	50 (9.9)
Median (range)	53 (34-60)	47 (35-66)
Education (years), Mean (SD)	15 (1.9)	16 (1.9)
Estimated VIQ, Mean (SD)	114 (6.6)	115 (6.0)
Tumor Type		
Low Grade Glioma (%)	17	36
High Grade Glioma (%)	83	64
Tumor Location		
Frontal (%)	100	64
Temporal (%)	0	21
Frontal-Temporal/Parietal (%)	0	14
Predominant Tumor Side		
Left (%)	33	43
Right (%)	50	57
Bilateral (%)	17	0
Treatment Type		
RT ± Chemotherapy (%)	100	79
RT only (%)	0	21
Time since Treatment Completion, months		
Mean (SD)	130 (24.5)	106 (40.5)
Median (range)	132 (100-157)	96 (58-191)

SD= Standard Deviation. VIQ= Verbal IQ (North American Adult Reading Test or Barona Index); RT=Radiotherapy;

^I Treatment history reflects all therapy received including treatment at relapse, if applicable.

Table 2
Neuropsychological Z-Scores at Initial and Follow-up Assessments

Cognitive Test	Time 1 Median [Q1-Q2]	Time 2 Median [Q1-Q2]	Change Score (T2-T1) Median [Q1-Q2]	p-value
LDSF	-0.70 [-1.14;0.28]	-0.41 [-0.98;0.46]	0.00 [-0.62;0.83]	0.847
LSB	-0.35 [-0.62;0.29]	-0.34 [-0.56;0.32]	0.01 [-0.63;0.68]	0.603
TMT-A	-0.30 [-0.72;0.45]	-0.20 [-0.43;0.35]	0.20 [-0.30;0.60]	0.755
TMT-B	-0.35 [-1.40;-0.05]	-0.65 [-1.42;0.12]	0.00 [-1.05;0.53]	0.281
BTA	-0.20 [-1.32;0.16]	-0.93 [-1.46;-0.35]	-0.50 [-1.17;0.32]	0.018
VF	-0.64 [-1.60;0.77]	-0.48 [-1.06;0.56]	0.16 [-0.43;0.40]	0.570
HVLT-L	-0.21 [-0.80;0.38]	-0.52 [-1.52;-0.08]	-0.24 [-1.20;0.26]	0.071
HVLT-D	-0.76 [-1.94;0.41]	-0.47 [-1.35;0.41]	0.00 [0.00;0.58]	0.748
HVLT-DI	0.42 [-0.18;0.73]	-0.02 [-0.18;0.73]	0.00 [-0.77;0.77]	0.676

Q1= Quartile 1; Q2= Quartile 2; LDSF = Longest Digit Span Forward; LDSB = Longest Digit Span Backward; DSYM = Digit Symbol; TMT-A = Trail Making Test, Part A; ; TMT-B = Trail Making Test, Part B; BTA = Brief Test of Attention; VF= Verbal Fluency; HVLT- L = Hopkins Verbal Learning Test- Learning; HVLT-D = Hopkins Verbal Learning Test- Delayed Recall; HVLT-DI = Hopkins Verbal Learning Test- Discrimination Index. The p-values represent one-sided Wilcoxon signed-rank tests of the hypothesis of decline in performance from Time 1 to Time 2. Significant (p<0.05) and near significant (p<0.10) p-values are shown in bold.

Table 3
Neuropsychological Z-Scores at Initial and Follow-up Assessments per APOE ε-4 Status

Cognitive Test	APOE e-4 Positive N=6					APOE e-4 Negative N=14					p-value
	Time 1		Time 2		Change (T2-T1) [Q1-Q2]	Time 1		Time 2		Change (T2-T1) [Q1-Q2]	
	Median	[Q1-Q2]	Median	[Q1-Q2]		Median	[Q1-Q2]	Median	[Q1-Q2]		
LDSF	-0.32 [-1.09;0.85]		-1.03 [-1.14;-0.41]		0.00 [-0.96;0.00]	-0.70 [-1.09;-0.42]		-0.41 [-0.46;0.50]		0.77 [-0.44;0.83]	0.028
LDSB	0.44 [0.11;0.82]		-0.46 [-1.08;-0.35]		-1.24 [-1.36;0.18]	-0.58 [-0.62;-0.05]		0.05 [-0.51;0.68]		0.04 [0.00;0.69]	0.032
TMT-A	0.20 [-0.60;0.92]		-0.15 [-0.35;0.13]		0.15 [-0.65;0.50]	-0.30 [-0.68;0.13]		-0.20 [-0.55;0.45]		0.20 [-0.25;0.60]	0.386
TMT-B	-0.75 [-1.48;-0.18]		-0.90 [-1.60;-0.35]		0.15 [-0.73;0.73]	-0.25 [-1.22;0.03]		-0.65 [-1.40;0.18]		0.00 [-1.15;0.32]	0.675
BTA	-0.46 [-1.14;-0.04]		-1.19 [-1.55;-0.98]		-0.70 [-0.94;0.13]	-0.14 [-1.34;0.35]		-0.74 [-1.28;-0.15]		-0.37 [-1.21;-0.31]	0.500
VF	0.10 [-1.59;2.37]		-0.31 [-1.42;0.62]		-0.08 [-0.49;0.03]	-0.66 [-1.52;0.59]		-0.48 [-1.04;0.46]		0.20 [-0.28;0.46]	0.177
HVLT-L	-0.21 [-0.61;-0.01]		-0.88 [-1.80;0.12]		-0.02 [-1.05;0.26]	-0.21 [-0.87;0.51]		-0.52 [-1.38;-0.28]		-0.30 [-1.07;0.26]	0.533
HVLT-D	-1.06 [-1.79;-0.32]		-0.88 [-1.26;0.12]		0.19 [0.00;0.93]	-0.57 [-1.85;0.41]		-0.18 [-1.35;0.34]		0.00 [-0.44;0.58]	0.857
HVLT-DI	-0.18 [-1.54;0.06]		0.73 [0.29;0.73]		0.91 [0.77;1.83]	0.73 [-0.18;0.73]		-0.18 [-0.47;0.58]		0.00 [-0.91;0.00]	0.998

Q1= Quartile 1; Q2= Quartile 2; LDSF = Longest Digit Span Forward; LDSB = Longest Digit Span Backward; DSYM = Digit Symbol; TMT-A = Trail Making Test, Part A; ; TMT-B = Trail Making Test, Part B; BTA = Brief Test of Attention; VF= Verbal Fluency; HVLT- L = Hopkins Verbal Learning Test- Learning; HVLT-D = Hopkins Verbal Learning Test- Delayed Recall; HVLT-DI = Hopkins Verbal Learning Test- Discrimination Index. The p-values represent one-sided Wilcoxon rank-sum tests of the hypothesis that APOE ε-4 carriers (positive) experienced greater decline than APOE non-ε-4-carriers (negative); significant p values (p<0.05) are shown in bold.

Table 4
Regional Standardized Uptake Value Ratios (SUVRs) per APOE Status (Medians and Quartiles)

ROIs (L + R)	N	<i>APOE</i> ε-4 Positive N=6 SUVR Median [Q1;Q2]	<i>APOE</i> ε-4 Negative N=14 SUVR Median [Q1;Q2]	p-value
Frontal Cortex	20	1.08 [0.93;1.26]	1.03 [0.92;1.15]	0.467
Lateral Temporal Cortex	20	1.08 [1.03;1.16]	0.99 [0.89;1.04]	0.124
Medial Temporal Cortex	20	1.17 [1.14;1.22]	1.35 [1.22;1.52]	0.931
Parietal Cortex	20	1.22 [1.11;1.37]	1.16 [1.06;1.42]	0.50
Occipital Cortex	20	1.13 [1.04;1.36]	1.17 [1.07;1.39]	0.598
Anterior Cingulate	19	1.18 [1.13;1.23]	1.18 [1.07;1.27]	0.356
Posterior Cingulate	20	1.30 [1.26;1.40]	1.27 [1.14;1.40]	0.282
Caudate Head	20	0.94 [0.67;1.01]	0.89 [0.79;1.12]	0.50
Putamen	20	1.35 [1.32;1.42]	1.58 [1.34;1.78]	0.931
Thalamus	20	1.55 [1.53;1.76]	1.53 [1.42;1.96]	0.282
Pons	20	1.76 [1.49;2.04]	1.60 [1.06;1.80]	0.142
White Matter	20	2.12 [1.72;2.24]	2.15 [1.95;2.38]	0.745
Neocortex	20	1.20 [1.12;1.28]	1.13 [1.06;1.20]	0.310

Q1= Quartile 1; Q2= Quartile 2; ROI=region of interest;

I region of interest (ROI) delineated in patient and healthy control PET images. The p-values represent one-sided Wilcoxon rank-sum tests of the hypothesis that *APOE* ε-4 carriers (positive) would have higher SUVrs than *APOE* non-ε-4-carriers (negative).