THE RELATIONSHIP BETWEEN FASTING SERUM GLUCOSE, BRAIN METABOLISM AND NEUROPSYCHOLOGICAL FUNCTIONING IN OLDER AND YOUNGER ADULTS

by

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Abstract

Objective: To characterize the association between longitudinal changes in fasting serum glucose and changes in flourodeoxyglucose Positron Emission Tomography (FDG PET) measurements of regional cerebral metabolic rate for glucose (rCMRgl) in brain regions preferentially affected by Alzheimer's disease (AD). A secondary objective was to investigate whether higher fasting serum glucose levels are associated with lower rCMRgl in younger adults within these same AD relevant brain areas.

Methods: For the primary study, baseline, interim, and 4.4 ± 1.0-year follow-up fasting serum glucose and PET CMRgl were analyzed in 80 cognitively unimpaired, non-diabetic, 61.5 ± 5 year-old persons with a first-degree family history of AD, including 38 carriers and 42 non-carriers of the apolipoprotein E (APOE) ε 4 allele. An automated brain-mapping algorithm was used to characterize associations between changes in fasting serum glucose levels and changes in rCMRgl. Longitudinal changes in fasting serum glucose levels and their correlation with changes in six pre-selected neuropsychological test measures of memory, attention and processing speed were also assessed with linear regression. The secondary study included a cross sectional sample of 31 cognitively unimpaired, non-diabetic participants, 31.2 ±5.4 years of age. General linear model-based voxel-wise analyses were performed to examine the correlation between fasting serum glucose and rCMRgl.

Results: In the primary study of older adults, average fasting serum glucose levels increased over longitudinal measurement, and changes in these levels were inversely associated with longitudinal CMRgl changes in the vicinity of brain regions preferentially affected by AD ($p < 0.05$, corrected for multiple comparisons). Fasting serum glucose was also inversely associated with performance on a measure of visuospatial memory ($p < 0.05$, corrected for multiple

comparisons). In the younger sample, fasting serum glucose levels were inversely associated with rCMRgl in left frontal pole and right primary visual cortex regions ($p < .05$, corrected for multiple comparisons).

Conclusions: In older adults, fasting serum glucose increases across time and is inversely related to rCMRgl in AD relevant regions and to visual memory test scores. This relationship between serum glucose and regional brain metabolism may begin in metabolically sensitive areas at a younger age.

Introduction

Available studies support an association between Type II Diabetes Mellitus (DM) and cognitive decline in later adulthood (Biessels, 2008; Knopman, Mosley, Catellier, & Coker, 2009; Yaffe et al., 2012), or the development of some type of dementia, including AD (Luchsinger, 2012). Subsequent research has investigated whether factors associated with the development of DM additionally contribute to risk for cognitive changes. Many of these studies focus on "cardiometabolic" risk factors (such as elevated serum glucose and/or insulin levels, high cholesterol, and abdominal obesity), which are health indicators that incur a higher risk for the development of cardiovascular disease or DM (Eckel, Kahn, Robertson, & Rizza, 2006). For example, a recent study determined that higher serum glucose levels within the previous five years was associated with an increased risk of developing dementia, even in individuals without DM (Crane et al., 2013).

Tests of memory, particularly those of delayed recall, are important in the study of AD risk as delayed recall deficits are evident very early in the course of the disease and are predictive of those who are shown to meet criteria for diagnosis several years later (for review, see Bondi, Salmon & Kaszniak, 2010). Most notably, higher fasting serum glucose is associated with lower delayed recall scores in studies of middle aged to older adults. Significant inverse correlations have been shown in cognitively normal non-diabetic (Kerti, et al., 2013; Dahle et al., 2009; Dik et al., 2007; Yaffe et al., 2004; Young et al., 2006), and cognitively normal diabetic samples (Dik et al., 2007; Yaffe et al., 2007), and in cross sectional (Dahle et al., 2009; Dik et al., 2007; Yaffe et al., 2004; Yaffe et al., 2007) and longitudinal analyses (Yaffe et al., 2004; Young et al., 2006).

Executive function, the term used to describe the interrelated set of cognitive processes that permit self directed behavior (i.e. planning, organizing, strategizing and volitional attention control) becomes seriously impaired later in the course of AD than the appearance of clear memory problems (Duke & Kaszniak, 2000). However, there is recent data to suggest that some aspects of executive functioning are mildly affected during its preclinical phase (Bondi, Salmon & Kaszniak, 2010). Furthermore, measurable aspects of executive function are sensitive to factors that regulate glucose control. Higher levels of cardiometabolic risk indicators, including elevated serum glucose, have been associated with lower scores on tasks of simple and complex attention (Bruehl, Sweat, Hassenstab, Polyakov, & Convit, 2010; Mortimer, 2010 ; Yaffe et al., 2004), working memory (Dahle et al., 2009; Messier 2010), and phonemic fluency (Bruehl et al., 2010; Young et al., 2006).

In order to address challenges associated with efficiently identifying risk factors or a preclinical stage of AD, researchers have proposed the use of brain imaging measurements, like FDG PET, in the ongoing evaluation of changes that precede the behavioral manifestations of the disease (Reiman et al., 2011; Sperling et al., 2011). Two FDG PET studies have demonstrated that indicators of cardiometabolic risk are associated with glucose hypometabolism in brain areas that are preferentially affected by AD in cognitively unimpaired older adults, in both insulin resistant (Baker, et al., 2010) and non-diabetic samples (Burns, et al., 2013). Both studies indicated that these associations were statistically significant irrespective of possession of the *apolipoprotein* E (APOE) ε4 allele, an established genetic risk factor for late onset AD. Structural Magnetic Resonance Imaging (MRI) studies of cognitively healthy non-diabetic adults have demonstrated that higher levels of fasting serum glucose are associated with greater atrophy of the

hippocampus, a critical brain region involved with memory formation and affected by aging and later life disease processes (Wu, et al., 2008), in both cross sectional (Kerti, et al., 2013; Rasgon et al., 2011) and longitudinal (Cherbuin, Sachdev, & Anstey, 2012) samples. Findings in the longitudinal MRI study (Cherubin, et al., 2012) were similar to those of PET studies (Burns et al., 2013; Baker et al., 2010), in that results were not limited to those participants with the APOE ε4 genetic risk for AD.

Functional neuroimaging studies of cardiometabolic risk for AD (Baker et al., 2010; Burns, et al., 2013; Langbaum, et al., 2011; Reiman, et al., 2010) have been largely cross sectional, thereby limiting conclusions that can be drawn regarding the relationship between fasting serum glucose and brain changes over time. Furthermore, when assessing brain function and cognition in older adults, it is important to recognize that cerebral vascular changes occur with age and may interact with glucoregulatory processes (Awad, Gagnon, Desrochers, Tsiakas, & Messier, 2002). Therefore, the study of possible association between fasting serum glucose and rCMRgl in a younger sample would provide evidence regarding an association between the two in the absence of age-related cerebral vascular changes.

In our older sample, we hypothesized that changes in fasting serum glucose across time would be inversely associated with changes in cerebral metabolic glucose rate in areas of the brain that have been preferentially affected by AD. These areas include those identified in previous FDG PET studies of AD risk and involve precuneus/posterior cingulate, parietal, prefrontal, and occipital brain regions (Alexander, et al., 2002). As in our cross sectional study (Burns, et al., 2013), these longitudinal relationships were hypothesized in both carriers and non-carriers of the

APOE e4 allele. Additional analyses were conducted to determine whether or not these associations were greater in APOE ε4 carriers than non-carriers. Although it was expected that neuropsychological findings would remain within normal limits in this cognitively healthy cohort, it was hypothesized that there would be a significant decline associated with elevated baseline fasting serum glucose, particularly in tasks that assess memory (specifically delayed recall) and executive functioning. In the younger sample, we predicted that while there would be a significant inverse correlations between fasting serum glucose and CMRgl in AD-related regions, they would be less extensive than in our studies of older adults. These areas include those identified in our previous FDG PET studies of AD risk and involve precuneus/posterior cingulate, parietal, prefrontal, and occipital brain regions (Burns, et al., 2013; Reiman, et al., 1996; Reiman, et al., 2001; Reiman et al., 2004).

Longitudinal Study of Older Adults

Methods

Participants. The present study is based on existing data sets (National Institute on Mental Health RO1 MH57899 to EMR; National Institute on Aging 9R01AG031581-10 and P30 AG19610 to EMR), from studies designed to investigate APOE-ε4 and the preclinical course of AD as measured by FDG-PET and neuropsychological test scores (Reiman et al., 1996; Reiman et al., 2001). Recruitment materials for these studies included newspaper and magazine ads, direct mail advertising, newspaper articles, and community presentations. In order to be eligible for the study, volunteers needed to be 47-68 years of age, cognitively healthy, and without any self-reported history of stroke, neurologic conditions, head injury, DM or use of glucose lowering medications. Hachinski ischemic scores (Hachinski et al., 2006) were calculated for all participants. A family history of AD in a first-degree family member was required for

participation. All study volunteers participated in initial APOE-ε4 testing, a medical exam, clinical ratings, neuropsychological tests, volumetric MRI and FDG PET. The participants returned for neuropsychological and imaging visits once every two years (Reiman et al., 2001).

All participants understood that they would not be informed of their APOE-ε4 genotype. All participants denied memory or other cognitive impairment, had a minimum score of 27 on the Mini Mental State Examination (MMSE; Folstein, Folstein, & McHugh, 1975), and were classified as normal following a neurological exam. Based on a structured psychiatric interview, study participants did not satisfy criteria for a current psychiatric disorder and had a score of less than 10 on the Hamilton Depression Rating Scale (HAM-D; Hamilton, 1960). All volunteers provided informed consent and participated under guidelines provided by the Human Subjects Committees at Banner Good Samaritan Medical Center and Mayo Clinic (Reiman et al., 1996; Reiman et al., 2001). For the purpose of the present project, participants selected for the longitudinal/older participant study were eligible for analyses if they had three consecutive FDG PET scans acquired per the parent study protocol from the same HR+ scanner (Siemens, Knoxville, TN). Review of records ensured that participants were not subsequently withdrawn from the study due to medical reasons outlined in exclusion criteria.

This longitudinal study compares baseline, interim, and 4.4 ± 1.0 year neuropsychological test scores, FDG PET measurements, and fasting serum glucose levels for 80 cognitively normal, non-diabetic, 61.5 ± 4.8 year-old persons with a first-degree family history of AD, including 38 carriers and 42 non-carriers of the APOE ε4 allele. Baseline fasting serum glucose levels ranged from 75 to 115 mg/dl (normal range) with an average fasting serum glucose value of 91.0 ± 8.0.

Brain imaging. Automated algorithms (SPM8, Welcome Department of Cognitive Neurology, London, U.K.) were utilized to align the sequential PET images from each subject, deform the images into the coordinates of a standard brain atlas (Talairach & Tournoux, 1998) and normalize PET data for the variation in absolute measurements by proportionate scaling. General Linear Model (GLM) based voxel-wide analyses were performed using SPM to generate the statistical parametric maps of: significant rCMRgl changes over time in the entire sample, significant rCMRgl changes over time in the APOE ε4 non-carriers, significant rCMRgl changes over time in the APOE ε4 carriers, significantly greater rCMRgl changes in carriers than non-carriers, and significantly greater rCMRgl changes in non-carriers than carriers.

Voxel-based analyses of this type, which involve a large number of comparisons, are subject to Type-1 error rate inflation. Previous research has indicated that an uncorrected $p < 0.005$ provides an optimal trade-off between Type 1 and Type 2 errors (Reiman et al., 1997). The present study has retained this threshold for all imaging-related analyses. Additionally, in order to correct for multiple comparisons, the small volume correction (SVC) procedure in SPM was utilized, as indicated, to adjust significance levels for the number of resolution elements in a priori areas of interest including the precuneus, posterior cingulate, parietal, temporal, prefrontal, and occipital brain regions. The SVC procedure utilized a $p < 0.05$ threshold. Voxel-wise, random effect modeling based on GLM multiple regression analyses was used to examine linear relationships between changes in fasting serum glucose and longitudinal rCMRgl changes within the entire sample, and within each of the APOE ε4 sub groups. Changes in fasting serum

glucose and longitudinal rCMRgl change is defined as the respective slope of changes for these variables across the three time points.

Fasting serum glucose levels. Acquisition of fasting serum glucose levels occurred consistently throughout every PET procedure to permit the quantification of cerebral glucose utilization, as per convention in this field. At each visit, the Lifescan StureStepFlexx hand-held glucometer acquired and analyzed five venous blood samples over the course of the sixty-minute scan (at 7, 12, 20, 25, and 45 minutes post-FDG injection). As in a previously published report (Burns, et al., 2013), the glucose level acquired at the 7-minute time mark was the fasting serum glucose value used in analyses. Fasting was defined as a minimum of four hours, consistent with guidelines provided by the Society of Nuclear Medicine for FDG PET brain imaging (Waxman et al., 2009).

Neuropsychological test scores. Tests selected to assess verbal and visuospatial delayed recall include the Auditory Verbal Learning Test Long Term Memory score (AVLT- LTM; Rey, 1958), and the Complex Figure Test Recall (CFT-R; Rey, 1968), respectively. Tests of executive functioning that were selected from those available in the parent data set include the Arithmetic, Digit Span and Digit Symbol Coding subtests of the Wechsler Adult Intelligence Scale-Revised (WAIS-R; Wechsler, 1981) to assess working memory, attention, and processing speed; and the Controlled Oral Word Association Test (COWAT; Benton & Hamsher, 1976) to assess phonemic fluency. As indicated in Table 1 only age-corrected scaled scores were available, with the exception of the AVLT-LTM, CFT-R and COWAT, for which raw scores were recorded in the data set. The relationship between changes in fasting serum glucose and

changes in each of the neuropsychological tests was analyzed with linear regression. Changes in fasting serum glucose and in neuropsychological test scores were defined as the slope of these respective variables across the three time points. Age, education, and APOE ε4 were then entered, in that order, into a hierarchical regression analysis to address these variables' association with cognitive performance.

Results

A description of the participant sample can be found in Table 1. There were no statistically significant differences between APOE ε4 subgroups in age, gender, education, neuropsychological test scores or fasting serum glucose levels. There was a significant difference between APOE ε4 carriers and non-carriers on their HAM-D scores (p =0.03) with non-carriers scoring higher than carriers. However, although the difference in scores were statistically significant, the scores themselves are low for both groups, and do not reflect clinically significant depression (Hamilton, 1960). Hachinski scores ranged from 0-1 with 20% of the sample receiving a score of 1. Every score of 1 was attributed to history of hypertension.

Increases in average fasting serum glucose were observed across the assessment intervals (Figure 1). Longitudinal changes in fasting serum glucose were inversely associated with changes in rCMRgl in left prefrontal and left parietotemporal regions, and bilaterally in precuneus and posterior cingulate brain regions that have previously been implicated in AD (Figure 2 and Figure 3a). Left prefrontal, left parietotemporal and bilateral precuneus regions survived statistical correction for multiple comparisons (Figure 2). Table 2 lists the brain atlas coordinates and magnitude of the brain regions in with the strongest correlations between fasting serum glucose and rCMRgl in AD-related locations.

In APOE ε4 non-carriers, there was an inverse association between changes in fasting serum glucose across time and changes in rCMRgl in left prefrontal and left parietal, and bilaterally in precuneus AD related brain regions. Findings in each of these brain regions survived correction for multiple comparisons (Figure 3b). In carriers of the APOE ε4 allele, there was an inverse association between fasting serum glucose changes and changes in rCMRgl across time in left prefrontal, left parietotemporal, left precuneus and bilateral posterior cingulate AD related brain regions. None of these findings survived correction for multiple comparisons (Figure 3c). We compared the slopes of the regression lines of the relationship between changes in serum glucose and changes in rCMRgl in carriers and non-carriers of the APOE-e4 allele. The slopes of these lines were not significantly greater in carriers than non-carriers, nor were they greater in non-carriers than carriers in AD affected brain regions. This indicates that APOE-e4 status did not interact with changes in serum glucose on rCMRgl changes in AD relevant brain regions (Results not pictured). This suggests that the differences between the carrier and non-carrier groups in regions of inverse relationship between fasting serum glucose and rCMRgl that survived correction for multiple comparison are due to the smaller sample sizes of these subgroups, in comparison to the parent sample, with consequent reduction in power.

In terms of neuropsychological outcomes, there was a significant inverse correlation between changes in fasting serum glucose levels across time and changes in the CFT-R, (r = -0.3, p = .002). This relationship remained significant when age, education, and APOE ε4 status were first entered into a hierarchical regression analysis to address their association with this measure of visuospatial memory. There were no additional significant findings in tests of verbal memory

(AVLT-LTM) or executive function (COWAT, WAIS –R subtests of Arithmetic, Digit Span, or Digit Symbol Coding).

Therefore, in summary, changes in fasting serum glucose levels across time were inversely associated with changes in rCMRgl across time in AD-related areas. A similar pattern of results was seen in the two APOE ε4 genetic subgroups, and these associations did not significantly interact with ε4 carrier/ non-carrier status in these specific brain regions. There was also an inverse association between changes in fasting serum glucose and changes in a measure of visuospatial memory.

Cross Sectional Study of Younger Adults

Methods

Participants. Similar to the longitudinal sample, this study was based on an existing dataset (Alzheimer's Association II RG-98-088 to EMR). It utilized the same recruitment strategies, and inclusion/exclusion criteria with the exception of required age range and family history of AD. In this study, younger adults between the ages of 18-40 were recruited irrespective of family history (Reiman et al., 2004). This cross sectional study compares FDG PET measurements and fasting serum glucose levels for 31 cognitively normal, non-diabetic, 31.1 ± 5.4 year-old persons, including 18 non-carriers and 13 carriers of the APOE ε 4 allele. Baseline fasting serum glucose levels ranged from 69 to 100 mg/dl (normal range) with an average fasting serum glucose value of 81.6 ± 8.3 mg/dl.

Brain Imaging and fasting serum glucose levels. The acquisition and preprocessing of PET and the sampling of serum glucose levels were conducted in the same manner as in the longitudinal

study of the older adult sample. However, participants were scanned only once on the ECAT 951/31 scanner. General linear model based voxel-wise analyses examined whether: a) higher levels of fasting serum glucose were associated with lower rCMRgl in the entire sample; b) higher levels of fasting serum glucose were associated with lower rCMRgl in each of the APOE ε4 non-carrier and carrier groups. As in the primary study, the $p < .005$ threshold was initially used to identify areas of significant association between fasting serum glucose and rCMRgl, followed by SVC with a $p < .05$ threshold. The statistical maps were superimposed onto a map of rCMRgl reductions previously generated for probable AD patients (Alexander et al., 2002) and a spatially standardized, volume rendered MRI in SPM.

Neuropsychological test scores. The set of neuropsychological test scores utilized for this laboratory's AD studies are listed in Table 3. Unlike the study of older adults, no a priori analyses were planned for this study. However, since significant findings were found in a measure of delayed recall in the study of older adults, post hoc analyses of the correlation between fasting serum glucose and AVLT-LTM and CFT-R was conducted, with alpha criterion set at the $p < 0.05$ level.

Results

A description of the participants can be found in Table 3. There were no statistically significant differences between APOE ε4 non-carriers or carriers subgroups in age, gender, education, clinical ratings, neuropsychological test scores or fasting serum glucose levels.

Fasting serum glucose levels were significantly inversely correlated with rCMRgl bilaterally in parietotemporal brain regions that have previously been implicated in AD (Figure 4 and 5a); and bilaterally in aging-related frontal regions (Bergenfield et al., 2010), as well as the right primary visual cortex (V1). Left frontal pole and right V1 regions survived statistical correction for multiple comparisons. Table 4 lists the brain atlas coordinates and magnitude of the strongest correlation between fasting serum glucose and rCMRgl in AD-related locations, and the regions that survived SVC.

In APOE ε4 non-carriers, fasting serum glucose was significantly inversely associated with reduced rCMRgl bilaterally in AD-related parietotemporal and precuneus brain regions, along with other non-AD related prefrontal, temporal, and V1 regions (Figure 5b). In carriers of the APOE ε4 allele, fasting serum glucose was significantly inversely correlated with reduced rCMRgl in AD-related left temporal and right parietotemporal areas, as well as prefrontal areas not typically associated with AD specific changes (Figure 5c). None of these findings (in AD related or other regions) survived SVC.

Post hoc analyses of two neuropsychological measures of delayed recall were performed. Although there was not a statistically significant correlation between fasting serum glucose and CFT-R ($p = 0.4$), there was a significant correlation between fasting serum glucose and AVLT-LTM ($r = -0.4$, $p = .01$). As in results from the study of the older sample, this relationship remained significant when age, education, and APOE ε4 status were first entered into a hierarchical regression analysis to address their association with cognitive performance.

To summarize, in younger adults, levels of fasting serum glucose were inversely associated with rCMRgl in AD-related areas, with correlations in aging related prefrontal regions and the primary visual cortex surviving correction for multiple comparisons. Furthermore, in this cognitively healthy, non-diabetic sample, there was a significant inverse association between fasting serum glucose levels and scores on a measure of verbal memory.

Discussion

The present study of cognitively unimpaired older adults demonstrated a longitudinal increase in fasting serum glucose and a significant inverse correlation between longitudinal changes in fasting serum glucose levels and concurrent changes in rCMRgl in precuneus/posterior cingulate, prefrontal, and parietal brain regions. In addition to these areas belonging to a distinct group of brain regions demonstrating reduced rCMRgl in AD patients (Alexander et al., 2002), there is also evidence of a similar pattern of hypometabolism in healthy older adults at genetic risk for AD (Reiman, et al., 1996; Reiman et al., 2001). Most importantly, the present study extends our previous cross sectional observations regarding the relationship between fasting serum glucose and rCMRgl (Burns et al., 2013) to a longitudinal sample. This inverse longitudinal relationship was observed in the present sample of older adults with no reported history of DM, thereby supporting and extending previous FDG PET findings in diabetic and pre-diabetic participants (Baker et al., 2010).

As in our original study (Burns et al., 2013) and others investigating the interaction between cardiometabolic and genetic risk on brain imaging measurements of AD risk (Baker et al., 2010; Cherubin et al., 2012; Rasgon et al., 2011), these associations were present in both non-carriers and carriers of the APOE ε4 allele, and were not significantly greater in carriers than non-

carriers. Thus, the present results are consistent with the hypothesis that the AD risk imposed by elevated fasting serum glucose and other cardiometabolic risk factors may be present prior to the diagnosis of frank DM, and that this risk may be independent of the genetic risk associated with possession of the APOE ε4 allele (Burns, et al., 2013).

Consistent with our secondary hypothesis, in the present sample of younger adults there was a significant, but less extensive association between elevated fasting serum glucose and reduced rCMRgl in AD related parietotemporal regions previously implicated in PET AD risk studies of younger (Reiman et al., 2004) and older (Reiman et al., 1996; Reiman et al., 2001) adults. Findings that survived correction for multiple comparisons in this smaller sample were located outside of AD relevant areas, and included frontal pole and V1 regions. These preliminary metabolic findings in the frontal regions of the younger adults overlap with areas of structural changes seen in normal aging (Bergfield et al., 2010), and raise the possibility that peripheral glucose control may play a role in the normal trajectory of age related changes in the brain. Furthermore, these results further inform interpretation of the findings in the older sample in that the lack of an inverse relationship between longitudinal changes in fasting serum glucose and rCMRgl in the older sample in these frontal brain areas may reflect aging-related volumetric changes in that region that have already occurred.

In addition to providing data relevant to the question of whether cardiometabolic risk factors accelerate some of the brain changes associated with normal aging or conspire with other AD risk factors in adults, our study is consistent with findings in even younger participants that implicate prefrontal regions as particularly sensitive to indicators of glucose control. Elevated

levels of glycosylated hemoglobin, in indicator of glucose control over time, have been associated with lower values in measures of prefrontal volume and lower scores on measures of executive function in obese adolescents with DM (Bruehl, 2011). Future studies with larger samples of younger adults are needed to confirm whether the associations observed in the present study replicate, and how the present findings may inform future research on the role of cardiometabolic risk in brain and neuropsychological functioning across the lifespan.

Both of the present studies confirmed that fasting serum glucose levels were inversely associated with neuropsychological measures of delayed recall, which are particularly impacted in the development of AD (Bondi, Kaszniak & Salmon, 2010). In our study of older adults, a longitudinal increase in fasting serum glucose across time was demonstrated, as was an inverse association between changes in fasting serum glucose and changes in a measure of *visuospatial* memory. Despite the majority of studies supporting *verbal* memory as particularly sensitive to changes in glucose control (see Discussion above), there is evidence of elevated fasting serum glucose's impact on CFT-R in studies that specifically assess pre-diabetic (Roriz-Filo, et al., 2009) and diabetic participants (Moran et al., 2013; Tournoy et al., 2010). Further longitudinal studies of our older sample are needed to clarify whether the changes in CFT-R demonstrated here are associated with subsequent diagnoses of DM, cognitive impairment or both.

In contrast to our findings with older adults, we did not, a priori, expect memory scores in our younger sample to suggest impairment. However, our results related to verbal memory in this younger cohort extend previous findings in cognitively normal, non-diabetic, middle aged older adults (Dahle et al., 2009; Dik et al., 2007; Yaffe et al., 2004) to a younger sample. Although the

present study demonstrates a relationship between fasting serum glucose and *visuospatial* memory in *older* adults and *verbal* memory in *younger* adults, findings support the assertion that declarative memory function is sensitive to factors that regulate glucose control (Watson & Craft, 2004).

As in our original study (Burns et al., 2013) the major limitation of this study is that each parent study (of either older or younger adults), was not prospectively designed to assess glucose control in study participants. We acknowledge that reductions in rCMRgl, changes in rCMRgl across time, and our findings related to delayed recall measures could be related to complex processes that involve insulin levels , insulin resistance (Cholerton, Baker, &Craft, 2013) or metabolic syndrome (Yaffe, 2007) . In our younger adult group, the magnitude of the correlations between fasting serum glucose and rCMRgl may have been limited by the small sample size and truncated range of serum glucose levels relative to our original older sample of 124 older adults (Burns, et al., 2013). Hence future studies are necessary to fully address the question of whether or not the relationship between elevated fasting serum glucose and rCMRgl in AD-related regions in older adults is evident in a younger age prior to the onset of age-related vascular changes.

Neuropsychological observations in both samples were limited to the availability of a standard set of measures utilized in the laboratory's aging and AD protocols. It is recommended that future studies consider inclusion of batteries that could more comprehensively evaluate executive functioning, such as provided by measures from the DKEFS battery (i.e. Trail Making Test, Color-Word Interference; Delis, Kaplan & Kramer, 2001), process scores related to Digit Span

(i.e. Digit Backwards; Wechsler, 1981), and subscale scores that may relate to executive functioning within the context of learning and recall of verbal information (i.e., Source Memory Recognition, Repetitions, and Set-Switching Accuracy of The California Verbal Learning Test-2; Delis, Kramer & Kaplan, 2000).

In summation, the present study contributes to accumulating research evidence suggesting that elevated levels of serum glucose and other indicators of cardiometabolic dysfunction are associated with neuroimaging and neuropsychological measures of AD risk. It complements and extends previous studies in in its longitudinal design and in its examination of these relationships in older and younger samples. Lastly, this study continues to support the use of neuroimaging measures, like PET, as an additional approach by which to identify and assess AD risk factors; and to inform the design and timing of prospective trials of preventative interventions (Caselli & Reiman, 2012; Reiman et al., 2011).

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Table 1

Baseline participant characteristics, clinical ratings, fasting serum glucose measurements, and neuropsychological test scores[a] for younger adults

	Total sample		APOE ε4 subgroups	
	Mean	**Non-carriers (n=18)**	**Carriers (n=13)**	***p*-value[b]**
Age (SD)	61.5 (4.8)	61.5 (5.2)	61.4 (4.3)	0.94
Gender (%F)	52 (65%)	27 (64%)	25 (66%)	0.90
Education (SD)	16.1 (2.0)	16.3 (1.9)	15.8 (2.2)	0.23
Fasting serum glucose (mg/dl)	91.0 (8.0)	91.5 (8.6)	90.4 (7.4)	0.55
History of hypertension[c]	16 (20%)	5 (11.9%)	11 (28.9%)	0.06
BMI	26.7 (4.5)	26.5 (4.8)	27.0 (4.2)	0.63
Years between V_1 and V_3[d]	4.4 (1.0)	4.6 (1.2)	4.2 (0.8)	0.13
MMSE	29.7 (0.7)	29.6 (0.8)	29.8 (0.6)	0.36
HAM-D	1.5 (2.3)	2.1 (2.8)	1.0 (1.2)	0.03
AVLT				
Long term memory	9.4 (3.0)	9.1 (2.9)	9.6 (3.2)	0.43
Complex Figure Test				
Recall	19.0 (7.5)	18.8 (7.8)	19.2 (7.2)	0.80
COWAT	46.9 (10.4)	44.8 (9.3)	47.9 (11.4)	0.19
WAIS-R				
Digit span	11.5 (2.7)	11.0 (3.0)	12.1 (2.3)	0.05
Arithmetic	12.7 (2.4)	12.7 (2.2)	12.6 (2.6)	0.77
Digit Symbol	12.6 (2.0)	12.5 (2.2)	12.8 (1.7)	0.48

[a] Raw scores are reported, with the exception of WMS-R and WAIS-R subtests, which are age-corrected scaled scores.

[b] Unless otherwise indicated, values are mean ± SD. *p*-values were calculated with analysis of variance (ANOVA) or chi square test, uncorrected for multiple comparisons ($p < 0.05$), as appropriate.

[c] Reported as number (and percentage) of participants with a history of hypertension.

[d] V_1 and V_3 are Visits 1 and 3 respectively.

Table 2

Location and magnitude of the most significant correlations between fasting serum glucose levels and rCMRgl in older adults

AD-related brain region		Atlas coordinates (mm)[a]			Brodmann area	*r*	*p*-value[b]
		X	**Y**	**Z**			
Parietotemporal	Left	-57	-57	29	40	-0.5	$3.3 \times 10^{-7*}$
Precuneus/Posterior Cingulate	Left	-20	-71	55	7	-0.4	$8.5 \times 10^{-4*}$
	Right	12	-55	32	31	-0.4	$7.7 \times 10^{-4*}$
Prefrontal	Left	-36	5	59	6	-0.5	$2.4 \times 10^{-6*}$

The data were extracted from voxels associated with the most significant correlations in regions previously found to be associated with abnormally low rCMRgl in patients with AD.[6]

[a] The coordinates were obtained from Talairach and Tournoux.[16] X is the distance to the right (+) or left (-) of the midline, Y is the distance anterior (+) or posterior (-) to the anterior commissure, and Z is the distance superior (+) or inferior (-) to a horizontal plane through the anterior and posterior commissures.

[b] The reported significance levels are one-tailed and uncorrected for multiple comparisons ($p < .005$). Correlations that remained significant ($p < 0.05$) after correcting for multiple comparisons are marked with an asterisk.

Table 3

Participant characteristics, clinical ratings, fasting serum glucose measurements , and neuropsychological test scores[a] for younger adults

	APOE ε4		
	Non-carriers (n=18)	**Carriers (n=13)**	***p*-value[b]**
Age (SD)	30.6 (5.6)	31.8 (5.3)	0.57
Gender (%F)	12 (66.7)	10(76.9)	0.83
Education (SD)	15.8 (1.6)	16.2 (1.7)	0.59
Fasting serum glucose (mg/dl)	80.9 (7.8)	82.5 (9.2)	0.60
Reported family history[c] (% yes)	6 (33.3)	8 (61.5)	0.12
MMSE	29.8 (0.4)	29.9 (.3)	0.48
HAM-D	1.3 (2.3)	0.9 (1.8)	0.59
AVLT			
Total learning	54.6 (8.6)	51.3 (7.0)	0.27
Short term memory	12.1 (2.1)	11.2 (3.0)	0.35
Long term memory	11.6 (2.6)	10.6 (3.4)	0.36
Complex Figure Test			
Copy	35.3 (1.0)	35.3 (1.0)	0.94
Recall	21.4 (5.5)	21.2 (7.6)	0.91
Boston Naming Test	55.8 (3.3)	54.3 (3.0)	0.20
COWAT	43.9 (9.7)	43.2 (8.0)	0.81
WMS-R Orientation	13.9 (0.2)	13.9 (0.3)	0.82
WAIS-R			
Information	11.1 (2.2)	10.5 (2.0)	0.46
Digit span	11.9 (3.1)	10.8 (1.7)	0.24
Block design	11.9 (2.4)	10.8 (3.1)	0.27
Arithmetic	10.8 (2.9)	10.5(1.9)	0.75
Similarities	12.1 (1.8)	11.3(2.1)	0.27

[a] Raw scores are reported, with the exception of WMS-R and WAIS-R, which are age-corrected scaled scores.

[b] Unless otherwise indicated, values are mean ± SD. *p*-values were calculated with analysis of variance (ANOVA) or chi square test, uncorrected for multiple comparisons ($p < 0.05$).

[c] Due to the younger age of this sample, family history was defined as first or second degree family history of AD.

Table 4

Location and magnitude of the most significant correlations between fasting serum glucose levels and rCMRgl in younger adults

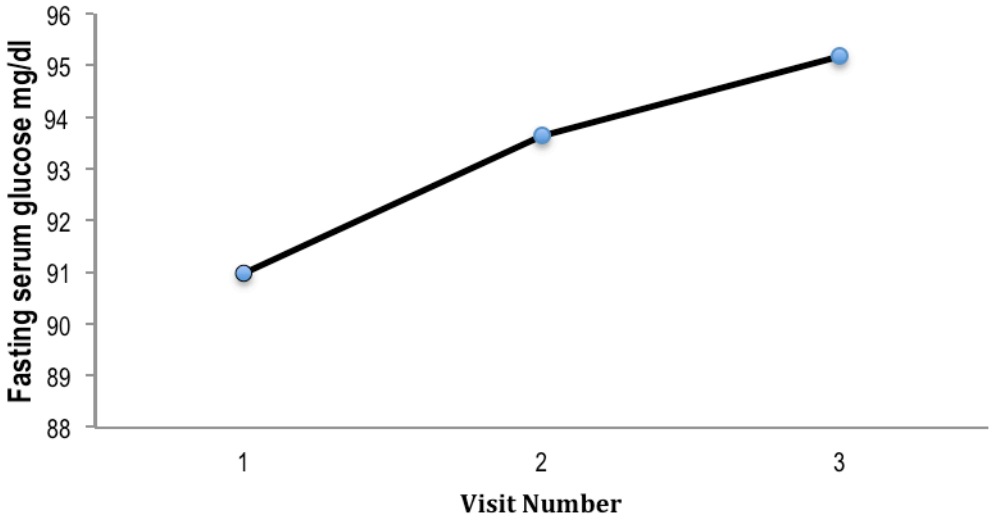
AD-related brain region		Atlas coordinates (mm)[a]			Brodmann area	*r*	*p*-value[b]
		X	**Y**	**Z**			
Parietal	**Left**	-61	-47	28	40	-0.5	1.6×10^{-3}
	Right	53	-49	28	40	-0.6	7.0×10^{-4}
Temporal	**Left**	-59	-29	-5	21	-0.5	1.7×10^{-3}
	Right	59	-56	14	22	-0.6	7.7×10^{-4}
Other brain regions							
Prefrontal	**Left**	-22	63	-13	11	-0.7	$8.0 \times 10^{-6*}$
	Right	28	32	24	9	-0.6	$1.2 \times 10^{-4*}$
Occipital	**Right**	22	-77	11	17	-0.6	$1.4 \times 10^{-4*}$

The data were extracted from voxels associated with the most significant correlations in regions previously found to be associated with abnormally low rCMRgl in patients with AD.[6]

[a] The coordinates were obtained from Talairach and Tournoux.[16] X is the distance to the right (+) or left (-) of the midline, Y is the distance anterior (+) or posterior (-) to the anterior commissure, and Z is the distance superior (+) or inferior (-) to a horizontal plane through the anterior and posterior commissures.

[b] The reported significance levels are one-tailed and uncorrected for multiple comparisons ($p < .005$). Correlations that remained significant ($p < 0.05$) after correcting for multiple comparisons are marked with an asterisk.

Figure 1. Increase in average (mean) fasting serum glucose levels across time in the older adult sample.



Mean (SD) fasting serum glucose levels at Visits 1, 2, and 3 were: 91.0 (8.0), 93.7 (9.1), and 95.2 (8.6). The overall mean length of time between Visit 1 and Visit 2 and Visit 2 and Visit 3 was 1.9 (0.5) years, and 2.5 (0.9) years, respectively.

Figure 2. In the older adult sample, longitudinal increases in fasting serum glucose are associated with decreases in rCMRgl in AD related brain regions

Statistical maps generated from this study were projected onto the lateral and medial surfaces of the left and right cerebral hemispheres. Purple areas are those that have demonstrated reduced rCMRgl in AD patients. (a) Dark blue areas reflect initial findings in regions that have previously been determined to demonstrate reduced rCMRgl in AD patients, while light blue areas represent initial findings outside of these AD-related regions ($p < 0.005$, uncorrected for multiple comparisons; (b) Labeled areas survived the SVC procedure, which was utilized to correct for multiple comparisons in AD-related search regions ($p < 0.05$).

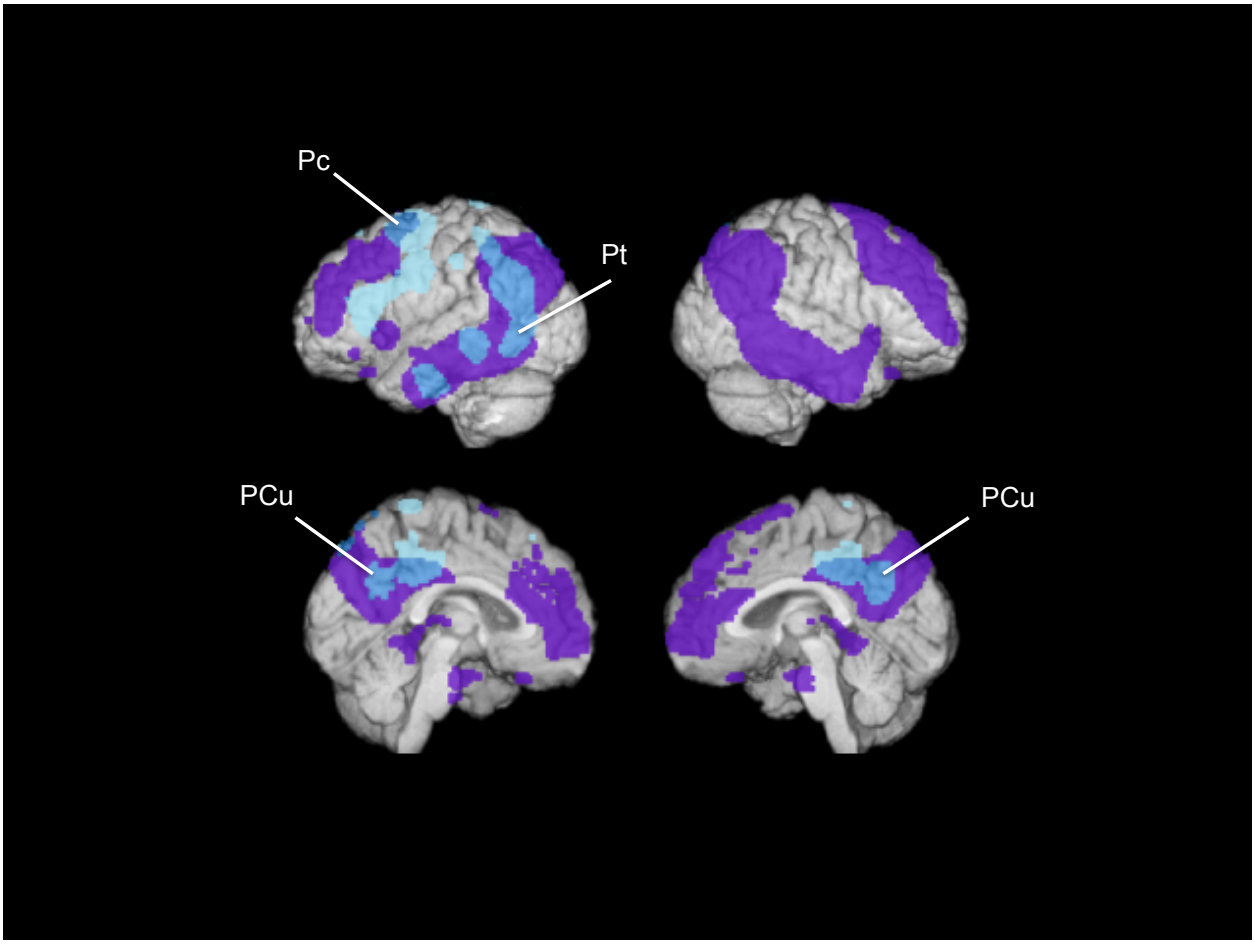


Figure 3. Findings in older adults by APOE ε4 carrier group
Statistical maps generated from this study were projected onto the lateral and medial surfaces of the left and right cerebral hemispheres, and feature brain regions in which increases in fasting serum glucose levels over time are associated with decreases in rCMRgl in the entire sample (a), non-carriers (b), and carriers (c) of the APOE ε4 allele. Purple areas are those that have demonstrated reduced rCMRgl in AD patients. Dark blue areas reflect initial findings in regions that have previously been determined to demonstrate reduced rCMRgl in AD patients, while light blue areas represent initial findings outside of these AD-related regions ($p < 0.005$, uncorrected for multiple comparisons).

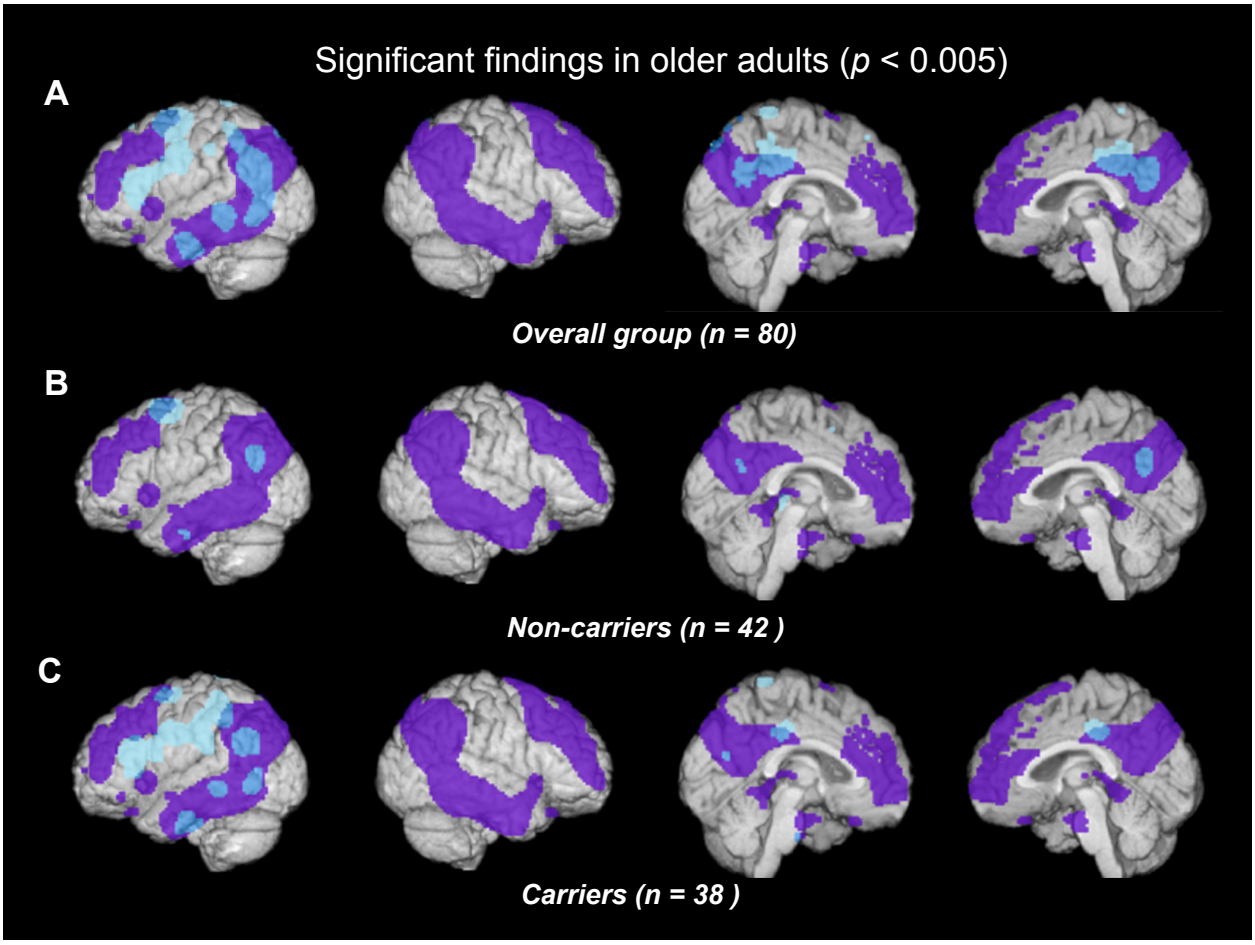


Figure 4. The association between higher fasting serum glucose levels and reduced rCMRgl in younger adults

Statistical maps generated from this study were projected onto the lateral and medial surfaces of the left and right cerebral hemispheres. Purple areas are those that have demonstrated reduced rCMRgl in AD patients. (a) Dark blue areas reflect initial findings in regions that have previously been determined to demonstrate reduced rCMRgl in AD patients, while light blue areas represent initial findings outside of these AD-related regions ($p < 0.005$, uncorrected for multiple comparisons; (b) Labeled areas survived the SVC procedure, which was utilized to correct for multiple comparisons ($p < 0.05$).

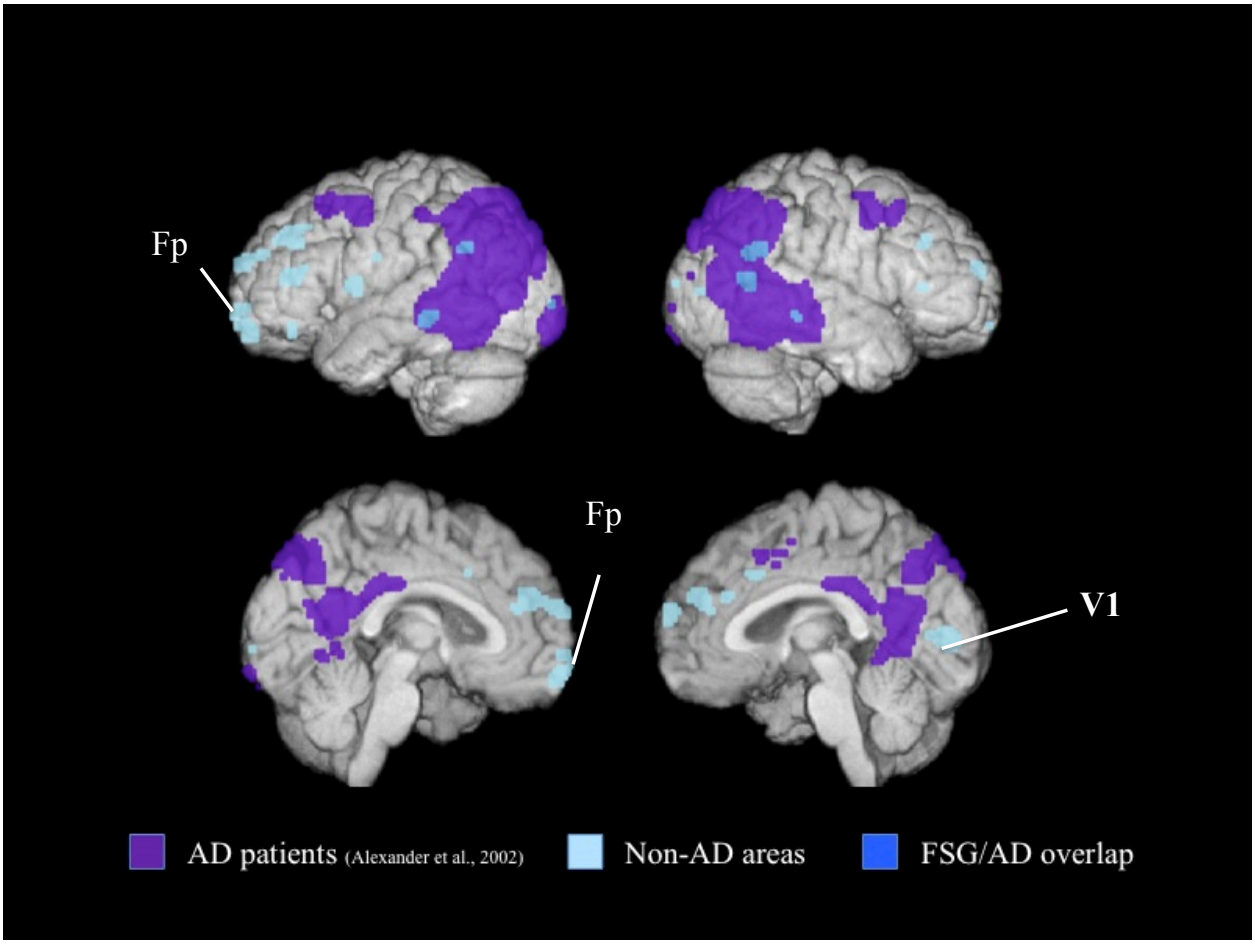


Figure 5. Findings in the young adults by APOE ε4 carrier group
Statistical maps generated from this study were projected onto the lateral and medial surfaces of the left and right cerebral hemispheres, and feature brain regions in which elevated fasting serum glucose was associated with reduced rCMRgl in the entire sample (a), non-carriers (b), and carriers (c) of the APOE ε4 allele. Purple areas are those that have demonstrated reduced rCMRgl in AD patients. Dark blue areas reflect initial findings in regions that have previously been determined to demonstrate reduced rCMRgl in AD patients, while light blue areas represent initial findings outside of these AD-related regions ($p < 0.005$, uncorrected for multiple comparisons).