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Association of insulin resistance with cerebral glucose uptake in late middle-aged adults at risk for Alzheimer's disease

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Abstract

Importance—Converging evidence suggests that Alzheimer's disease (AD) involves insulin signaling impairment. AD patients and people at risk for AD show reduced glucose metabolism, as indexed by F18-fluorodeoxyglucose positron emission tomography ([F18]FDG-PET).

Objective—To determine if insulin resistance (IR) predicts AD-like global and regional glucose metabolism deficits in late middle-aged participants at risk for AD. A secondary objective was to examine if IR-predicted variation in regional glucose metabolism was associated with worse cognitive performance.

Setting—A general community sample enriched for AD family history.

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Participants—Population-based, cross-sectional study of 150 cognitively normal, late middle-aged (mean=60.67 years) adults from the Wisconsin Registry for Alzheimer's Prevention.

Design—Participants underwent cognitive testing, fasting blood draw, and an [F18]FDG-PET scan at baseline. The Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) was used to assess peripheral insulin resistance. Regression analysis tested the statistical effect of HOMA-IR on global glucose metabolism. A voxel-wise analysis was used to determine if HOMA-IR predicted regional glucose metabolism. Finally, predicted variation in regional glucose metabolism was regressed against cognitive factors. Covariates included age, sex, body mass index, Apolipoprotein E genotype, AD family history status, and a reference region used to normalize regional uptake.

Main Outcome Measures—Regional glucose uptake determined using [F18]FDG-PET, and neuropsychological factors.

Results—Higher HOMA-IR was associated with lower global glucose metabolism ($\beta=-0.29$, $p<.01$) and lower regional glucose metabolism across large portions of frontal, lateral parietal, lateral temporal, and medial temporal lobe (MTL; $p<.05$, family-wise error corrected). The association was especially robust in left MTL ($R^2=0.178$). Lower left MTL glucose metabolism predicted by HOMA-IR was significantly related to worse immediate memory ($\beta=0.317$, $p<.001$) and delayed memory ($\beta=0.305$, $p<.001$) performance.

Conclusions—Our results show that IR, a prevalent and increasingly common condition in developed countries, is associated with significantly lower regional cerebral glucose metabolism, which in turn may predict worse memory performance. Midlife may be a critical period for initiating treatments to lower peripheral IR in order to maintain neural metabolism and cognitive function.

Keywords

Insulin resistance; fluorodeoxyglucose; memory

Introduction

Glucoregulatory impairment has reached epidemic proportions in the United States. According to the American Diabetes Association, 29.1 million Americans have diabetes, and more than half of adults over 64 years of age have "pre-diabetes"[1]. Type 2 diabetes increases the risk of Alzheimer's disease (AD) and both clinical and pre-clinical hypergylcemia are characterized by insulin resistance. Insulin resistance is broadly defined as reduced tissue responsiveness to the action of insulin[2]. Insulin, a key hormone involved in carbohydrate metabolism, facilitates microvascular blood flow, glucose uptake, and glucose oxidation for adenosine-5′-triphosphate generation[3].

In addition to its function in the periphery of the body, insulin has increasingly been recognized as playing an important role in the brain. Insulin resistance is related to higher AD risk,[4] and several animal studies link central insulin resistance with the pathological features of AD, including atrophy, mitochondrial dysfunction, neuroinflammation, and progressive memory deficits [see de La Monte[5] for review]. In humans, brain insulin

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resistance has been found in postmortem hippocampal tissue in patients with AD, and the degree of insulin signaling inhibition corresponds to the severity of antemortem cognitive dysfunction[6]. Several recent studies have shown a deleterious effect of insulin resistance on regional brain volume, both cross-sectionally[7–9] and longitudinally[10]. Our group has also recently shown that participants with metabolic syndrome, a condition linked with insulin resistance, have markedly lower cerebral blood flow[11], a presumed index of neural function. Finally, we have found that higher insulin resistance predicts temporal and frontal amyloid deposition in late-middle aged participants at risk for AD[12].

Peripheral insulin resistance has also been linked with impaired cerebral metabolic rate of glucose in the brain[13]. Glucose metabolism is commonly assessed using [F18] Fluorodeoxyglucose Positron Emission Tomography ([F18]FDG-PET) uptake. Baker and colleagues showed that higher insulin resistance is associated with lower basal and task-based FDG uptake in older cognitively intact adults (mean age 74.4 years) with dysglycemia[13]. Willette et al.[14] showed similar associations in AD patients. Patterns of lower glucose utilization included hypometabolism in posterior cingulate cortex and precuneus, as well as frontal and temporal cortices. Peripheral insulin resistance strongly corresponds to brain insulin resistance, either due to reduced insulin transport into brain or potentially similar changes in receptor sensitivity and activation[6,15]. The findings are intriguing given that lower glucose metabolism in these brain regions is also a feature characteristic of AD[16–19]. Lower glucose metabolism has also been observed in mild cognitive impairment (MCI)[20] and in cognitively healthy carriers of the Apolipoprotein E ε4 allele (*APOE-ε4*), a genetic risk factor for AD[21,22]. However, the relationship between insulin resistance and brain glucose utilization in middle-age is unknown. Understanding the neural effects of midlife insulin resistance is important, given that the onset of type 2 diabetes is most common in middle age and increases risk for AD[23].

In this study, we assessed the effect of insulin resistance on glucose utilization as indexed by [F18]FDG-PET uptake in a cognitively healthy, late middle-aged cohort of adults enriched for parental family history of AD. We hypothesized that participants with higher insulin resistance would show lower glucose utilization in brain regions that exhibit hypometabolism in early AD. Given that glucose utilization is tied to functional status, we also tested the extent to which variation in medial temporal lobe (MTL) glucose metabolism predicted by insulin resistance was associated with cognitive performance. Finally, based on prior work in this area[21,24], we tested the main effects of both *APOE-ε4* and parental family history of AD on glucose metabolism.

Research Design and Methods

Participants

Demographics are listed in Table 1. One hundred and fifty cognitively normal, older middle-aged adults (M = 60.67 ± 5.82 years) were recruited from the Wisconsin Registry for Alzheimer's Prevention (WRAP) study[25]. This on-going study examines genetic, biological, and lifestyle factors that contribute to the development of dementia-related cognitive decline and neural dysfunction. Participants were originally recruited between the ages of 40 to 65 years of age and were classified as either having a positive or negative family history of

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AD[25]. Positive parental family history of AD classification was defined as having one or both parents with AD as determined by autopsy (13 cases), or by validated interview[26], reviewed by a multidisciplinary diagnostic consensus panel, and as outlined by research criteria[27,28]. Detailed medical history and phone interviews were conducted to confirm AD negative participants. The inclusion criteria for this study consisted of: no clinical diagnosis of a memory disorder, no contraindication for brain imaging, a subsequent normal magnetic resonance imaging (MRI) scan, no current diagnosis of major psychiatric disease or other major medical conditions (e.g., myocardial infarction, or recent history of cancer), and no history of head trauma. All participants underwent MRI, FDG-PET, and neuropsychological testing. Participants were categorized as *APOE-ε4* carriers (one or two ε4 alleles) or non-carriers (zero ε4 alleles). *APOE* extraction and isoform classification have been described previously[29].

Neuropsychological Testing

WRAP participants undergo an extensive battery of neuropsychological tests. A previous factor analytic study of the WRAP cognitive battery within the larger cohort found that the tests map onto six cognitive factors[30,31]. The scores used in the current study were derived from tests administered at the participants' most recent WRAP visit and represent cognitive domains known to change with age and AD include Immediate Memory, Verbal Learning & Memory, Working Memory, and Speed & Flexibility.

HOMA-IR, Diabetes Status, and Body Mass Index

Glucose and insulin were collected after a 12-hour fast during the clinical visit nearest in time to the FDG scan. Insulin resistance was indexed by HOMA-IR and calculated by taking the product of basal glucose (mg/dL) and basal insulin (μU/mL) and dividing by 405[32]. Matthews et al., by contrast, derived HOMA-IR using glucose in mmol/L[32]. While HOMA-IR was considered as a continuous variable, we also determined how many participants in our sample had type 2 diabetes using American Diabetes Association criteria, where participants with fasting blood glucose over 125 mg/dL were identified as having type 2 diabetes. No participants were currently or previously taking medication for glycemic control; however five participants had a self-reported history of diabetes. HOMA estimation of percentage beta cell function displayed normal variation (data not shown). Body mass index (BMI) was calculated based on height and weight.

[F18] FDG-PET

Images were acquired supine and head-first on one Siemens HR+ PET scanner in 3D mode after a 4 hour fast (where water was allowed). Blood glucose was closely monitored prior to the injection of [F18]FDG. Following injection with 5.0 ± 0.5 mCi of [F18]FDG, participants remained awake but relaxed in a quiet room. Imaging began 45 minutes post-injection. The scan was acquired as six 5-min. frames. A 5-min. transmission scan was acquired following the emission scan. The dynamic PET data was reconstructed using ECAT v7.2.2 software. A filtered back projection algorithm (DIFT) was used with brain mode sinogram trimming, zoom = 2.8, and a 4mm Gaussian filter to a reconstructed image of 128×128×63 voxel matrix (voxel size = 1.84mmx 1.84mm×2.43mm). The PET data were

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corrected for the attenuation of annihilation radiation (using segmented attenuation maps), scanner normalization, and scatter radiation.

In order to account for between- and within-subject noise, a reference cluster was used as a covariate in statistical analyses[33,34]. The reference cluster consisted of sixty-five 2 × 2 × 2 mm contiguous voxels centered in the right cuneus, a region where no significant relationship between [F18]FDG signal and HOMA-IR was found (controlling for age, sex, *APOE-ε4* genotype, and family history status) ($\beta = -0.09$, $t(148) = -1.1$, $p = 0.27$). The region was derived via a data-driven method that identifies brain regions unaffected by the variable of interest and has previously been shown to improve detection of disease-related hypometabolism[34–36]. The raw values from the reference region were extracted with MarsBaR[37].

Statistics

In order to test for effects of HOMA-IR, *APOE-ε4*, and family history status on global glucose metabolism (adjusted by the reference region), multiple regression analysis was implemented in SPSS (IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp). In addition to testing for main effects, we assessed for interactions between HOMA-IR and *APOE-ε4*, as well as HOMA-IR and family history status. Both analyses of main effects and interactions were conducted using one design matrix model and controlled for age at time of scan, sex, BMI, and reference region. Voxel-wise statistical analysis used Statistical Parametric Mapping (SPM8) software (www.fil.ion.ucl.ac.uk/spm) to test for the regional effect of HOMA-IR on glucose metabolism. We controlled for covariates identical to the global analysis. A voxel-wise analysis was also conducted to test for the regional main effects of family history status and *APOE-ε4* on glucose metabolism, again controlling for age, sex, BMI, and reference region. Models were also run that included either a HOMA-IR and *APOE-ε4* or HOMA-IR and family history interaction term. Type 1 error was minimized by using voxel-level Family Wise Error (FWE) correction of $p < .05$. Multiple regression analysis was also used to regress HOMA-IR predicted variation in glucose metabolism from an a priori defined left MTL region against cognitive factors. These analyses covaried age at time of scan, sex, family history status, *APOE-ε4*, BMI, and reference region. Sample size was insufficient to conduct robust mediation analysis[38]. Logarithmic transformation of HOMA-IR was used in all analyses to optimize normality and reduce heteroscedasticity.

Results

Demographics and Cognition

Demographics, the four cognitive factors, and other summary data across participants are shown in Table 1. Additional metabolic risk factor characterization is provided in eTable 1.

Associations of insulin resistance, *APOE-ε4* genotype, and family history status with global [F18]FDG-PET

A single multiple regression model tested the statistical effects of HOMA-IR, *APOE-ε4*, and family history of AD on global glucose metabolism. Higher HOMA-IR was associated with

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lower global glucose metabolism, $\beta = -0.29$, $t(143) = -3.10$, $p < .01$. Figure 1 shows the degree of this insulin resistance association. The same regression model showed a significant effect of *APOE-ε4*, where carriers with one or two ε4 alleles had lower global glucose metabolism, $\beta = -0.16$, $t(143) = -2.01$, $p < .05$ compared to non-carriers. There was no significant effect of family history status on global glucose metabolism, nor did insulin resistance interact with *APOE-ε4* or family history status to affect FDG-PET uptake.

Associations of insulin resistance, *APOE-ε4* genotype, and family history status with regional [F18]FDG-PET

In a single voxel-wise regression model ($p < .05$ FWE at voxel level), HOMA-IR, *APOE-ε4*, and family history status were used to see if there were regional associations with glucose metabolism. Higher HOMA-IR was robustly associated with lower glucose metabolism in one contiguous cluster throughout the brain (k = 173612 voxels), with a maximum (Z score = 7.21) in left posterior MTL. The cluster spanned large portions of ventral prefrontal, cingulate, temporal, insula, and posteromedial cortices (Figure 2). Additionally, associations were seen in bilateral cerebellum. Coverage was sparse or absent in motor and pre-motor cortices, as well as dorsal prefrontal cortex. Thresholding revealed that associations were strongest in hippocampus and MTL, rostral and posterior cingulate, as well as precuneus and cuneus. The graph in Figure 2 shows the degree of this association between insulin resistance and mean signal in left MTL. There was no significant effect of *APOE-ε4* or family history status on regional glucose metabolism. There was no interaction between *APOE-ε4* and HOMA-IR or family history status and HOMA-IR.

Relationships between insulin resistance, MTL [F18]FDG-PET, and cognitive function

Mean predicted variation in glucose metabolism specific to HOMA-IR was extracted using the Eigenvariate tool in SPM8. The region of interest was left MTL, which was of a priori interest before voxel-wise analyses were conducted. Left medial temporal glucose metabolism was regressed against each of the four cognitive factors. Covariates were identical to the voxel-wise analysis. Adjusted glucose metabolism was associated with the Immediate Memory factor score, $\beta = .317$, $t(148) =$, $p < .001$, the Verbal Learning and Memory factor score, $\beta = .305$, $t(148) = 3.895$, $p < .001$), and weakly with the Speed and flexibility factor score, $\beta = 0.204$, $t(148) = 2.537$, $p < .05$ (Figure 3). There was no significant relationship with the working memory factor score, $\beta = .118$, $t(148) = 1.448$, $p > .05$ (Figure 3).

Discussion

Several studies suggest that insulin resistance is associated with brain changes that may contribute to AD pathology in the preclinical phase. This study assessed the extent to which insulin resistance may affect glucose metabolism as measured by [F18]FDG-PET uptake. We found that middle-aged adults with higher HOMA-IR showed lower glucose metabolism, and further, glucose metabolism was related to memory function.

Our results concur with findings in older adults indicating that insulin resistance[13], hyperglycemia[39] and diabetes[40] are associated with hypometabolism on FDG-PET. Insulin

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resistance and hyperglycemia are related conditions, and hyperglycemia, even in the pre-diabetic range, is associated with significantly increased risk of later development of dementia[41]. However, fasting insulin and fasting glucose are not always correlated[42] and insulin resistance may confer increased risk for AD independent of glycemic status within 3 years of assessment[4]. Our sample was on average 15 years younger than the sample studied in Baker et al.[13], although the affected regions are similar. In particular, both studies show an association between higher HOMA-IR and less glucose metabolism in bilateral prefrontal cortex, temporal, and posteromedial parietal cortices. Willette et al. found[14] similar associations in the same regions among AD patients. Interestingly, we also found bilateral hypometabolism in the cerebellar cortex, a region with appreciable insulin receptor density[43,44]. While not typically considered a region affected by AD, a few reports have found mild cerebellar hypometabolism in AD[45,46]. Post-mortem AD brains also show deficient insulin signaling in cerebellum[6], while intranasal insulin may maintain glucose metabolism[13].

A strong association between higher HOMA-IR and lower glucose metabolism was found in left MTL. It has been well established, at least in rodents, that piriform cortex, and adjoining cornu ammonis fields 1 and 2, have a high density of insulin receptors relative to moderate density in cerebral cortex[44,47]. Interestingly, when we examined mean glucose metabolism in left MTL, we found that lower glucose metabolism was associated with worse immediate and delayed memory performance factors. This result is in line with Wolk and Dickerson[48], who found that entorhinal and perirhinal volumes in mild AD patients predicted later trials of the Rey Auditory Verbal Learning Test, on which the verbal learning and memory factor used in the current study is based. This finding provides a potential link between insulin resistance and cognitive decline.

There are several possible mechanisms that may underlie the association between higher insulin resistance and less glucose metabolism. For example, our group has found that higher peripheral insulin resistance in asymptomatic late middle-aged participants is linked with amyloid deposition measured in vivo[12]. In stable MCI participants enriched for amyloid status, Willette et al. observed that higher HOMA-IR predicted less prefrontal glucose metabolism only in the amyloid-positive group[14]. Loss of neuronal function due to mitochondrial damage is another possible mechanism. Both AD and type 2 diabetes are characterized by mitochondrial dysfunction[49–51], providing a potential common link between the two diseases. Neurons rely heavily on mitochondria for the synthesis of adenosine triphosphate, and are therefore vulnerable to mitochondrial dysfunction. Indeed, lower expression of nuclear genes influencing mitochondrial energy metabolism co-localize with brain regions that show deficits in glucose utilization in AD patients. Insulin resistance may also facilitate several additional mechanisms that result in neurodegeneration including increased oxidative stress, neuroinflammation, and dysregulated lipid metabolism[52].

Akin to our previous report examining HOMA-IR and brain atrophy in asymptomatic adults[10], HOMA-IR associations with regional glucose metabolism in this study were robust, even with FWE correction, with moderate to moderate-strong relationships in most regions. Baker and colleagues[13] found stronger relationships among cognitively normal aged adults with pre-diabetes or type 2 diabetes. Our finding that insulin resistance is

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associated with both increased amyloid burden and decreased glucose uptake in AD-centric brain regions, indicates that IR confers nontrivial risk for AD in midlife. It is also worth noting that HOMA-IR in this cohort appeared to predict glucose metabolism more strongly than *APOE-ε4*, which is an important predictor of glucose uptake deficits[53] and AD in general. However, this study was cross-sectional in nature, and no causal inferences about insulin resistance may be inferred. While we found an effect of *APOE-ε4* on global glucose metabolism, we did not observe any regional effects. Furthermore, HOMA-IR did not interact with *APOE-ε4* status to affect global or regional glucose metabolism. Interactions between *APOE-ε4* and metabolic dysfunction have been observed in previous studies, including effects on CSF biomarkers in preclinical AD[54], post mortem plaque and tangle burden in patients with AD dementia[55], development of amnestic MCI[56], and response to intranasal insulin therapy[57,58]. Burns et al. have also found interactions between hyperglycemia and *APOE-ε4* on FDG-PET[39]. While several studies do point toward a moderating effect of *APOE-ε4* when considering the effects of insulin resistance on neural pathology, findings across the field are still mixed. In an existing report that shares similarities with our study, Roberts et al. examined diabetic individuals and did not find an interaction between diabetes and *APOE-ε4* on FDG-PET [40]. While our sample was enriched for parental family history of AD, HOMA-IR did not interact with family history status, nor did family history alone have an effect on glucose metabolism. Previous studies have found an effect of parental family history of AD on cerebral glucose metabolism, however, the findings are most robust when both parents are affected, or maternal family history is considered.[59–61]

In conclusion, this study provides evidence that insulin resistance is associated with brain glucose utilization in a late middle-age cohort enriched for AD risk factors. Several studies indicate that peripheral insulin resistance and related conditions such as metabolic syndrome and diabetes are risk factors for cognitive decline and AD, and are linked with increased risk of death from dementia[62–65]. The prevalence of AD continues to grow, and midlife may be a critical period for initiating treatments aimed at preventing or delaying the onset of AD. Accumulating evidence suggests that treatments targeting mechanisms involved in insulin signaling may impact central glucose utilization and should be investigated in the context of presymptomatic AD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

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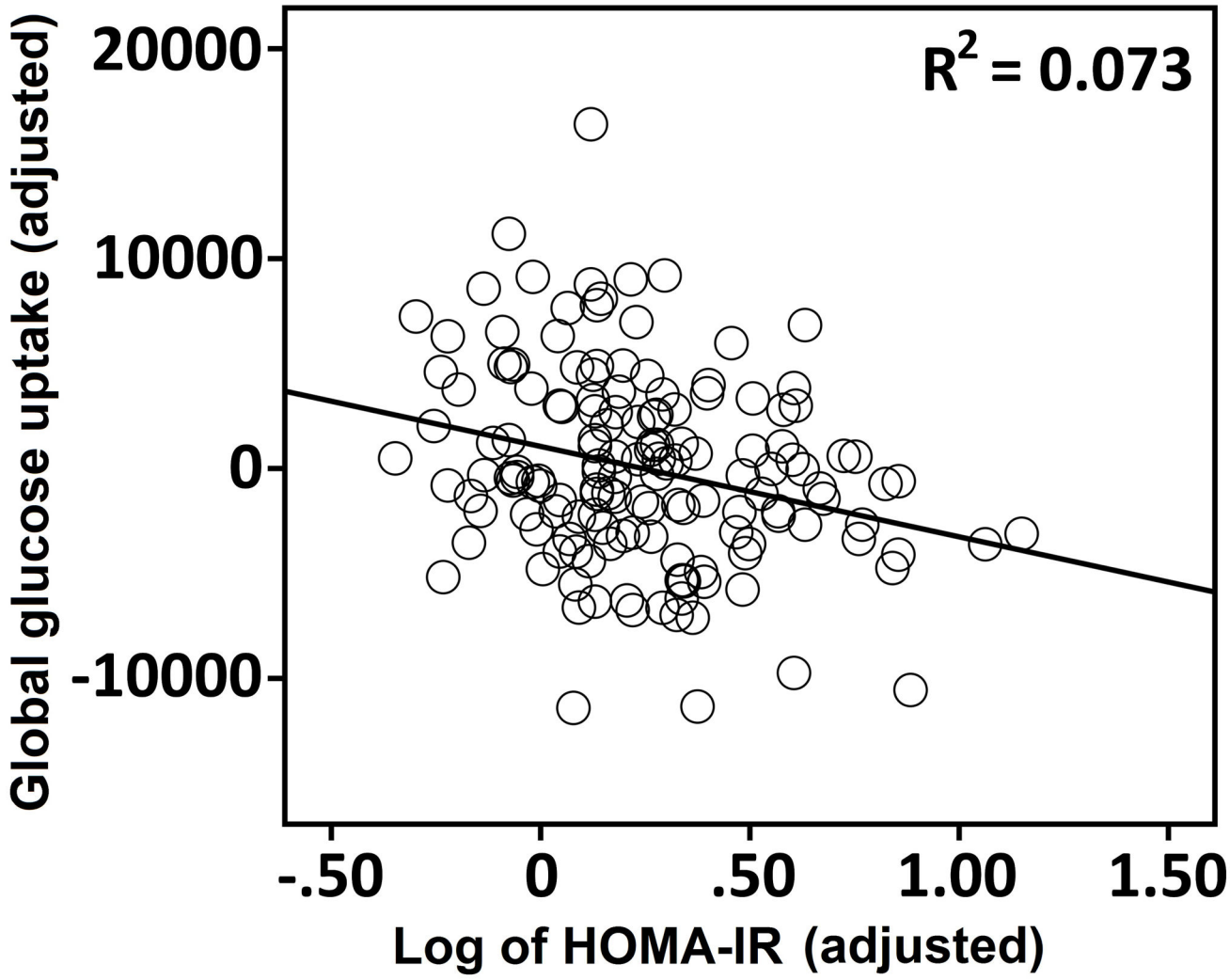

Figure 1.

The association between HOMA-IR and global FDG-PET uptake in 150 late middle-aged adults. Uptake and HOMA-IR values were adjusted by the following covariates: age, sex, family history status, *APOE-ε4* genotype, body mass index, and the FDG-PET reference region. * = $p < .05$.

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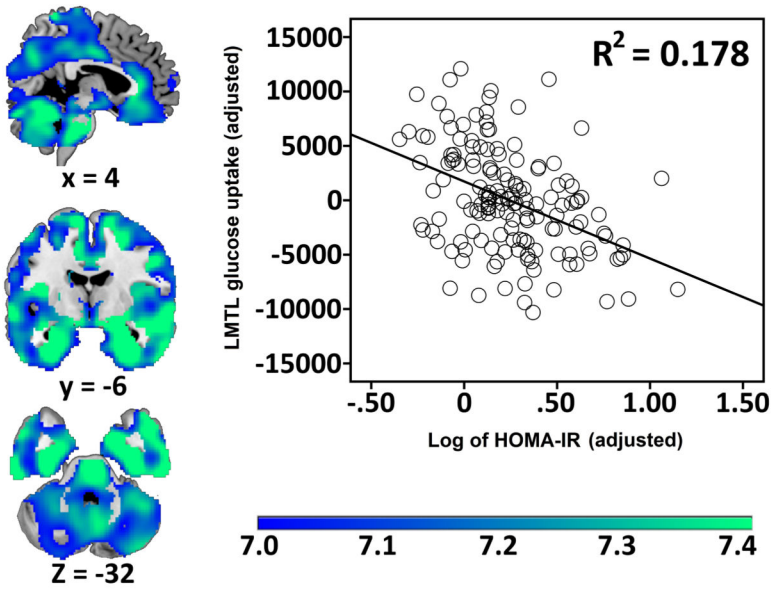

Figure 2.

The association between higher HOMA-IR and lower regional FDG-PET uptake in 150 late middle-aged adults ($p < .05$ FWE). Results are displayed on representative cross-sections for temporal, parietal, and frontal regions. Uptake values were adjusted by the following covariates: age, sex, family history status, *APOE-ε4* genotype, and glucose metabolism in the reference region. The color bar depicts t-values. Brains are oriented in neurological space. FWE = family-wise error corrected.

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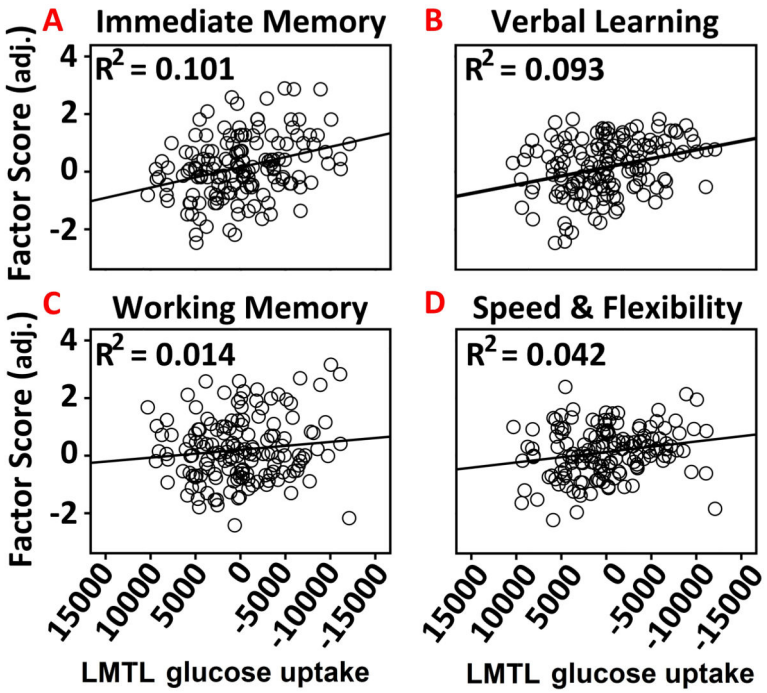

Figure 3.

The association between left medial temporal FDG-PET uptake predicted by the HOMA-IR analysis and cognitive function factors. (**A–B**) Higher FDG-PET in left medial temporal lobe (MTL), as a function of lower HOMA-IR, predicted better performance on the verbal learning and immediate memory factors. (**C–D**) Left MTL was not associated with the working memory factor, but was associated with the speed and flexibility factor. The FDG-PET signal was adjusted by the FDG reference region, age, sex, *APOE-ε4* genotype, family history status, and HOMA-IR. * = p < .05; *** = p < .001. .

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Table 1

Demographics and other participant information

	M* ± *SD	***Range***
Age	60.7 ± 5.8	47.8 – 71.3
Insulin (μU/mL)	2.0 ± 7.0	2 – 48
Glucose (mg/dL)	94.6 ± 10.0	74 – 132
HOMA-IR	2.2 ±1.9	0.5 – 14.1
BMI	28.2 ± 5.3	18.5 – 47.3
Speed & Flexibility	0.1 ± 0.9	−2.2 – 2.4
Working Memory	0.2 ± 1.1	−2.4 – 3.2
Verbal Learning	0.2 ± 1.0	−2.5 – 1.8
Immediate Memory	0.2 ± 1.1	−2.5 – 2.9
	n (%)	
Women	108 (72.0%)	
Family History	103 (68.7%)	
APOE ε4 Genotype	61 (40.7%)	
Type 2 Diabetes	7 (4.7%)	

APOE-ε4 = Apolipoprotein E ε4 genotype; BMI = Body Mass Index; HOMA-IR = Homeostatic Model Assessment of Insulin Resistance. The individual tests which loaded onto the identified factors were as follows: Rey Auditory Verbal Learning Test[66] Trials 1 and 2 loaded onto Immediate Memory; Rey Auditory Verbal Learning Test[66] Trials 3–5 and Delayed Recall Trial loaded onto Verbal Learning & Memory; Wechsler Adult Intelligence Scale – 3rd edition[67], Digit Span forward and backward, and Letter-Numbering Sequencing subtests loaded onto Working Memory; and the interference trial from the Stroop Test[68], and Trail Making Test A and B[69] loaded onto Speed & Flexibility.