

Insulin Sensitivity as a Mediator of the Relationship Between BMI and Working Memory-Related Brain Activation

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Midlife obesity is associated with cognitive deficits and cerebral atrophy in older age. However, little is known about the early signs of these deleterious brain effects or the physiological mechanisms that underlie them. Functional magnetic resonance imaging (fMRI) allows us to detect early changes in brain response to cognitive challenges while behavioral performance is still intact. Accordingly, we examined the impact of obesity on functional activation during a 2-Back task in 32 cognitively normal middle-aged adults, who were classified into normal, overweight, and obese groups according to BMI. Additionally, we examined insulin sensitivity as a potential mediator of the relationship between BMI and brain activation. Insulin sensitivity is of special interest because insulin is strongly associated with both obesity and central nervous system functioning. Group differences in task-related brain activation were examined in *a priori* regions of interest (ROIs) using ANOVA. The obese BMI group displayed significantly lower task-related activation in the right parietal cortex, BA 40/7, ($F(2,29) = 5.26$, $P = 0.011$) than the normal ($P = 0.016$) and overweight ($P = 0.047$) BMI groups. Linear regression and bootstrapping methods for assessing indirect effects indicated that insulin sensitivity fully mediated the relationship between task-related activation in the right parietal cortex and BMI ($F(3,28) = 9.03$, $P = 0.000$), $\beta = 0.611$, $P = 0.001$, 95% confidence interval: -2.548 to -0.468). In conclusion, obesity in middle age was related to alterations in brain activation during a cognitive challenge and this association appeared to be mediated by insulin sensitivity.

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INTRODUCTION

The rising prevalence of obesity has become a major public health concern. In the past 20 years, the number of individuals who are classified as overweight or obese in the United States has doubled, currently encompassing almost two-thirds of the adult population (1). Obesity plays a major role in the development of diabetes, hypertension, cardiovascular disease, and many types of cancer (2). More recently, attention has been drawn to the negative impact of high body mass on cognition. In rodents, diet-induced obesity is associated with impairments in spatial learning (3). Among humans, large epidemiological studies have reported that obesity at midlife is significantly associated with higher incidence of dementia in old age. Individuals who were obese during middle age were five times more likely to receive a diagnosis of vascular dementia and three times more likely to develop Alzheimer's disease (4). Even in the absence of dementia, obesity has been associated with poorer memory and executive function in

older adults (5). Consistent with these findings, higher BMI in middle age is also related to greater cerebral atrophy later in life (6).

Although several studies have examined obesity in relation to brain structure, little is known about how functional brain activation during cognition may differ according to BMI. Functional magnetic resonance imaging (fMRI) has the advantage of being highly sensitive to early changes in the neural substrates supporting cognition, before symptoms of clinically significant cognitive impairment are evident. For example, neuroimaging has demonstrated that individuals at genetic risk for Alzheimer's disease display lower activation in brain areas critical for memory even when their behavioral performance is intact (7). Thus, fMRI may be a useful tool for enhancing early detection of cognitive vulnerability and identifying brain regions particularly susceptible to early disease processes.

A number of different hypotheses have been generated as the potential mechanisms linking obesity and cognitive decline,

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Table 1 Participant characteristics (n = 32)

	Normal (n = 9)	Overweight (n = 11)	Obese (n = 12)	P value
Age, years	51.8 ± 4.3	52.0 ± 5.1	48.5 ± 8.6	0.37
Sex (male/female), n	2:7	6:5	6:6	0.30
Education, years	15.1 ± 1.7	15.1 ± 2.3	15.0 ± 4.3	0.97
BMI, kg/m ²	22.4 ± 2.2	27.4 ± 1.4	34.3 ± 3.5	0.00
Systolic blood pressure, mmHg	119 ± 10	123 ± 11	125 ± 11	0.53
Diastolic blood pressure, mmHg	73 ± 6	76 ± 7	74 ± 9	0.63
LDL-cholesterol, mg/dl	123 ± 26	140 ± 48	143 ± 26	0.43
HDL-cholesterol, mg/dl	64 ± 10	54 ± 15	41 ± 12	0.00
Triglyceride, mg/dl	122 ± 73	141 ± 72	208 ± 106	0.07
Glucose, mg/dl	92.7 ± 10.4	92.3 ± 5.6	99.8 ± 10.6	0.10
Insulin, μU/ml	13.0 ± 9.8	21.1 ± 11.7	38.6 ± 31.1	0.03
Insulin sensitivity (QUICKI)	0.34 ± 0.03	0.31 ± 0.02	0.29 ± 0.02	0.00

HDL, high-density lipoprotein; LDL, low-density lipoprotein; QUICKI, quantitative insulin sensitivity check index.

including vascular damage, inflammation, triglycerides, and circulating levels of glucocorticoids (8). One mechanism that is particularly interesting given its role in the central nervous system is insulin regulation. Insulin receptors are present throughout the brain, particularly in regions that are fundamental for cognition such as the hippocampus and cerebral cortex (9). Insulin alters key processes involved with learning and memory such as cerebral glucose metabolism (10).

In the periphery, insulin regulates glucose homeostasis and carbohydrate, lipid, and protein metabolism through concerted action of multiple intracellular signaling pathways (11). The hormone is secreted by the pancreas in response to elevations in blood glucose, which stimulates the uptake of glucose into peripheral tissues via translocation of the glucose transporter-4 on the plasma membrane (12). The efficiency of this process is referred to as insulin sensitivity and abnormally low insulin sensitivity is referred to as insulin resistance. Insulin resistance is associated with decreased cellular response to insulin and perturbations of the insulin-signaling pathway, resulting in attenuated glucose transporter-4 translocation, reduced glucose uptake, and the secretion of abnormally high levels of insulin from the pancreas (11). Obesity is among the strongest risk factors for the development of insulin resistance (13). Given the susceptibility of insulin regulation to obesity and its multifaceted role in the central nervous system, insulin sensitivity may mediate the association between adiposity and differences in functional brain activation.

In the present study, we employed fMRI to determine whether alterations in brain activity during cognition are detectable in cognitively intact, otherwise healthy middle-aged overweight and obese adults. Based on neuroimaging findings from other cognitively vulnerable populations (7), we hypothesized that obese individuals would display lower activation in task-related areas. Moreover, we hypothesized that insulin sensitivity would mediate the BMI-related alterations in brain activation. In order to test these hypotheses, we recruited healthy, middle-aged adults and classified them according to the World Health

Organization standards as having normal, overweight, or obese BMI (14). Participants underwent blood oxygen level-dependent fMRI during completion of a 2-Back verbal working memory task (15). The 2-Back task engages executive processes known to be vulnerable in adults with higher BMIs (5). On a separate visit, fasting blood glucose and insulin levels were measured in order to determine insulin sensitivity.

METHODS AND PROCEDURES

Participants

Right-handed adults between the ages of 40 and 60 years were recruited through flyers and newspaper advertisements. Individuals with a history of coronary artery disease, angina pectoris, myocardial infarctions, heart failure, and cardiac surgery were excluded. Additional exclusion criteria included history of neurological disease (e.g., stroke, Parkinson's disease, and clinically significant traumatic brain injury), major psychiatric illness (e.g., schizophrenia and bipolar disorder), substance abuse (i.e., diagnosed abuse and/or previous hospitalization for substance abuse), metabolic disorder (i.e., diabetes, thyroid disorder), smoking (within the last 2 years), or MRI contraindications. Thirty-five participants completed the initial screen and were enrolled in the study after providing written consent. Three participants were excluded from analyses because their fasting blood glucose concentrations classified them as diabetic based upon the American Diabetes Association classification criteria (fasting blood glucose >126 mg/dl) (16). The remaining 32 participants were classified into normal weight, overweight, or obese groups based upon the World Health Organization's BMI categorization (normal: 18.5–24.9, overweight: 25.0–29.9, obese ≥30 kg/m²) (14). Participant characteristics by group are presented in [Table 1](#).

Procedures

The study procedures were approved by the local institutional review committee. Participants completed a medical history interview with a research assistant. Participants underwent a neuropsychological evaluation, general health assessment, and brain imaging on separate days, completing the study within 1 month.

Neuropsychological assessment

All participants completed a 2-h assessment battery including standard clinical neuropsychological instruments with established reliability

Table 2 Neuropsychological measures

	Normal (n = 9)	Overweight (n = 11)	Obese (n = 12)	P value
<i>Global cognition</i>				
MMSE	28.4 ± 1.7	28.7 ± 1.0	27.7 ± 1.4	0.17
<i>Full scale IQ</i>				
WASI	117.4 ± 11.5	117.4 ± 8.2	107.6 ± 12.7	0.07
<i>Memory</i>				
CVLT-II delayed recall	12.3 ± 3.1	10.9 ± 3.9	10.3 ± 3.2	0.39
RCF delayed recall	14.7 ± 7.3	14.5 ± 4.5	17.2 ± 5.3	0.48
<i>Attention-executive function</i>				
COWA	44.8 ± 13.4	40.0 ± 8.8	37.7 ± 11.5	0.37
Trails A, sec	28.2 ± 6.4	27.4 ± 6.7	28.8 ± 9.3	0.91
Trails B, sec	64.6 ± 24.8	64.7 ± 12.8	77.0 ± 34.1	0.43
Digit span, total	16.3 ± 3.8	17.4 ± 4.9	17.2 ± 2.3	0.79
<i>Emotional function</i>				
BDI-II	4.7 ± 3.4	5.8 ± 4.6	9.7 ± 2.6	0.17
STAI-T, scaled	49.0 ± 6.4	54.1 ± 15.8	42.8 ± 14.2	0.24

BDI-II, Beck Depression Inventory-II; COWA, Controlled Oral Word Association Test; CVLT-II, California Verbal Learning Test-II; IQ, intelligence quotient; MMSE, Mini Mental State Exam; RCF, Rey Complex Figure Test; STAI-T, Spielberger Trait Anxiety Inventor-T; WASI, Wechsler Abbreviated Scale of Intelligence.

and validity. The battery included measures of global cognitive functioning (Mini Mental State Exam), intelligence quotient (IQ) (Wechsler Abbreviated Scale of Intelligence, WASI Full Scale IQ (FSIQ)), memory (California Verbal Learning Test-II, Rey Complex Figure Test), and attention-executive functioning (Wechsler Adult Intelligence Scale-III, Digit Span Subtest; Controlled Oral Word Association Test; Trail Making Test A&B) (17). Emotional functioning was assessed with self-report measures (Beck Depression Inventory-II (18); Spielberger Trait Anxiety Inventory (19)). All tests were administered and scored by a trained research assistant using standard administration and scoring criteria (17).

General health assessment

Participants abstained from caffeine and fasted for at least 4h before the assessment. Body weight in kg and height in cm were measured on a beam-balance scale for the subsequent calculations of BMI. BMI was calculated by dividing weight in kg by height in m². Following 15 min of rest, participants sat upright while brachial blood pressure was measured using a semiautomated device (Dinamap XL, Johnson & Johnson Medical, Tampa, FL). Approximately 3 ml of fasting blood was collected from the antecubital vein by venipuncture. The concentrations of glucose, triglycerides, high-density lipoprotein-cholesterol, and low-density lipoprotein-cholesterol were measured using standard enzymatic technique (Cholestech LDX System; Cholestech, Hayward, CA). Plasma was separated and stored at -80°C until further analysis. The plasma sample was analyzed for insulin using a radioimmunoassay kit (MP Biomedicals, Orangeburg, NY). Insulin sensitivity was calculated using the quantitative insulin sensitivity check index (QUICKI), a measure that has been well validated in relation to euglycemic-hyperinsulinemic clamps (20). The QUICKI is calculated by computing the inverse of the sum of logarithmically expressed values of fasting glucose and insulin. Higher QUICKI values are indicative of better insulin sensitivity.

Working memory task paradigm

Working memory was assessed using a verbal *n*-Back task, consisting of alternating blocks of 0-Back, 2-Back, and rest conditions (15). During each 0- and 2-Back block, a series of 12 individual consonants were visually presented in random order for 500 ms each with 2,500 ms inter-stimulus interval. Participants responded to target letters (33% in each block) using a two-button MR-compatible response box. In the 0-Back

condition, the target was a prespecified letter (H) and in the 2-Back condition, the target was any letter that was identical to the one presented two stimuli earlier. Task performance was assessed by measuring mean accuracy rates and reaction time for all correct trials. During each rest block, a fixation cross appeared in the middle of the screen for 30 s. The task was programmed and presented using E-Prime Software (Psychology Software Tools, Pittsburgh, PA). During neuroimaging, two consecutive 6-min runs consisting of three blocks of alternating 0-Back, 2-Back, and rest conditions were presented. Before neuroimaging, participants were given an opportunity to practice the task on a laptop computer to ensure adequate performance.

Neuroimaging data acquisition

MRI data for each participant were acquired in a single session on a 3T GE Signa Excite MRI scanner equipped with a standard head coil. T₁-weighted anatomical scans of the entire brain in the sagittal plane were collected using a high-resolution spoiled gradient echo sequence (256 × 256 matrix, field of view = 24 × 24 cm², 1 mm slice thickness, 0 gap). Functional imaging was performed while participants completed the 2-Back task. The task was back-projected from a laptop onto a screen positioned at the participant's head, and viewed through a double-mirror attached to the head coil. Functional imaging was performed using a whole brain echo-planar imaging sequence (repetition time = 3,000 ms, echo time = 30 ms, field of view = 24 × 24 cm², 64 × 64 matrix, 42 axial slices, 3 mm slice thickness, 0.3 mm gap).

Neuroimaging data processing

All echo-planar imaging images were processed using Analysis of NeuroImages software (21). Each time series was spatially registered to the sixth volume of the session to reduce the effects of head movement. Data preprocessing also included adjustment for differences in adjacent slice timing due to interleaved slice acquisition, temporal smoothing, spatial filtering, and transformation to standard stereotaxic space. Task-related brain activation was determined using voxel-wise multiple regression analyses with the following parameters: a 0-Back/2-Back reference waveform convolved with a gamma function, and covariates accounting for instruction screens, and head movement.

A priori regions of interest (ROIs) were created from published coordinates that were empirically derived from a verbal 2-Back task in healthy

Table 3 *A priori* regions of interest

Region	X	Y	Z	F (2,29)	P value
Superior frontal gyrus, BA 8/6	13	8	54	0.229	0.797
Middle frontal gyrus, BA 46/49	-42	23	39	3.864	0.033
	37	37	33	4.645	0.018
Inferior frontal gyrus, BA 44/6	-47	6	15	3.431	0.046
	43	6	31	1.933	0.033
Insula	-32	20	8	0.129	0.879
	-39	-1	29	0.586	0.563
	-47	-2	43	0.585	0.564
Precentral gyrus, BA 6/4	-30	-6	57	0.836	0.444
	-26	-60	45	0.838	0.443
Parietal cortex, BA 40/7	32	-56	43	5.261	0.011
	18	1	23	0.301	0.742

individuals (Table 3) (15). These ROIs were selected because they have been consistently activated by the *n*-back task across a great number of verbal working memory studies (22). All stereotactic coordinates refer to Talairach space (23). The ROIs were applied to individual data to determine mean task-related activation intensity in each region.

Statistical analysis

Descriptive statistics were calculated for selected participant characteristics (Table 1) and neuropsychological measures (Table 2). Differences between the groups were explored using univariate ANOVA.

Differences in mean 2-Back-related activation intensity between the normal, overweight, and obese groups were analyzed within each *a priori* ROI using ANOVA (Table 3). Given a strong trend toward FSIQ differences between the groups, analyses were repeated with a multivariate analysis of variance with IQ as a covariate. A Sidak-corrected α -level of 0.015 was used as the criterion of statistical significance to account for multiple comparisons and preserve the 5% type I error rate. The relationship between 2-Back-related activation and 2-Back performance (reaction time and percent correct) was explored using correlation in the one ROI where group differences were observed.

A mediation effect of insulin sensitivity was assessed for the relationship between BMI group and 2-Back-related activation in the right parietal cortex (BA 40/7), the brain region in which groups differences were found. Multiple regression was used to assess mediation according to Baron and Kenny's mediation model (24). BMI group membership was recoded using two dummy code variables, BMI group 1 and BMI group 2, before inclusion in the linear regression model. According to Baron and Kenny's model, four conditions must be met to determine mediation: (i) significant relationship between the independent variable (BMI group) and the dependent variable (2-Back-related activation), (ii) significant relationship between the independent variable (BMI group) and the potential mediator (insulin sensitivity), (iii) significant relationship between the potential mediator (insulin sensitivity) and the dependent variable (2-Back-related activation), and (iv) nonsignificant relationship between the independent variable (BMI group) and the dependent variable (2-Back-related activation), after controlling for potential mediator (insulin sensitivity). A two-tailed α -level of 0.05 was used as the criterion for significance for the mediation analysis.

An additional assessment on the significance of the mediation model was conducted by calculating confidence intervals. Confidence intervals were obtained using Preacher and Hayes' (25) bootstrapping method for assessing indirect effects. 2-Back-related right superior activation was entered as the dependent variable, BMI group was entered as the independent variable, and insulin sensitivity was added as the proposed

mediator in the SPSS macro created by Preacher and Hayes (25). A 95% confidence interval that does not include 0 was considered as the criterion for significance.

All data were analyzed using SPSS 16.0 computer software (SPSS, Chicago, IL).

RESULTS

Descriptive statistics regarding the participant characteristics are presented in Table 1. There were no significant differences between the three groups in age, years of education, systolic and diastolic blood pressure, fasting blood concentrations of glucose, low-density lipoprotein-cholesterol, and triglycerides (Table 1). As expected, the groups differed in terms of BMI ($F(2,29) = 56.82, P = 0.000$). The groups also differed on fasting blood high-density lipoprotein-cholesterol ($F(2,29) = 9.72, P = 0.001$), insulin concentrations ($F(2,29) = 4.18, P = 0.026$) and insulin sensitivity ($F(2,29) = 9.49, P = 0.001$). There were no significant group differences in any of the neuropsychological measures but there was a trend toward lower FSIQ scores in the obese group ($P = 0.07$) (Table 2).

Mean accuracy (\pm s.d.) on the verbal 2-Back task was $80.1 \pm 11.8\%$ correct responses and mean reaction time (\pm s.d.) was $1,107 \pm 299$ ms. The performance of the three groups was not different for accuracy ($F(2,27) = 0.345, P = 0.711$) and reaction time ($F(2,27) = 0.541, P = 0.588$). Mean 2-Back-related brain activation differed among the BMI groups in the right parietal cortex, BA 40/7 ($F(2,29) = 5.26, P = 0.011$) (Table 3). *Post hoc* comparisons revealed that obese BMI group had significantly lower activation than the normal ($P = 0.016$) and overweight ($P = 0.047$) BMI groups. 2-Back-related activation differences did not reach the threshold for statistical significance in any other *a priori* ROIs, but there was a trend toward significance for the middle frontal gyrus ($F(2,29) = 4.68, P = 0.018$). When FSIQ was added to the model as a covariate, group differences in 2-Back-related activation in the right parietal cortex remained significant ($F(3,28) = 4.48, P = 0.011$). With the addition of FSIQ, the trend toward significance in the middle frontal gyrus was substantially attenuated ($F(3,28) = 2.62, P = 0.071$).

Within the right parietal cortex, 2-Back-related activation was associated with higher task accuracy ($r = 0.38, P = 0.040$), but not with reaction time ($r = -0.17, P = 0.383$).

In accordance with Baron and Kenny's model for mediation (24), BMI group was significantly associated with insulin sensitivity ($F(2,29) = 9.49, P = 0.001$). Insulin sensitivity was significantly correlated with mean 2-Back-related activation in the right parietal cortex ($F(1,30) = 24.41, P = 0.000$). Finally, the fully adjusted mediation model successfully predicted mean 2-Back-related activation in the right parietal cortex ($F(3,28) = 9.03, P = 0.000$). Insulin sensitivity was significantly associated with greater 2-Back-related activation ($\beta = 0.611, P = 0.001$). However, BMI group no longer significantly accounted for any unique variance ($\beta_1 = 0.100, P = 0.610, \beta_2 = 0.242, P = 0.146$), indicating a significant mediation effect (Table 4). The significance of the mediational effect was confirmed by the 95% confidence intervals (95% confidence interval range -2.548 to -0.468) derived by

Table 4 Regression models for the effect of BMI group and insulin sensitivity on right parietal activation

	Predictors	R ²	Standardized	P value
Model 1	BMI group 1	0.266	0.531	0.006
	BMI group 2		0.445	
Model 2	Insulin sensitivity	0.449	0.670	0.000
Model 3	BMI group 1	0.492	0.100	0.610
	BMI group 2		0.242	
	Insulin sensitivity		0.611	

Preacher and Hayes' (25) bootstrapping method for detecting indirect effects.

DISCUSSION

To our knowledge, this is the first study to examine the relationship between BMI and working memory-related brain activation using fMRI. We found that obesity, as measured by BMI, was associated with lower task-related activation in the right parietal cortex. The relationship between obesity and activation in this region was significant even within our study population of apparently healthy and cognitively intact middle-aged adults. These results could not be explained by age, education level, or blood pressure because these factors did not vary between normal, overweight, and obese groups. Additionally, controlling for IQ did not alter the results.

Our finding of altered brain activation during a working memory task is consistent with the existing literature reporting obesity-related alterations of cognition (4,5) and brain structure (6). Obesity during middle age has been identified as a risk factor for dementia in later life (4). Even in the absence of dementia, obesity is associated with poorer performance on neuropsychological tests (5). Gross alterations in brain structure such as greater temporal lobe atrophy have also been observed in nondemented obese adults (6). Additionally, a recent positron emission tomography study found a negative association between resting prefrontal cortex metabolism and BMI (26). The present study extends the literature by providing evidence of obesity-associated alterations in parietal cortex activation during working memory in healthy middle-aged adults with no evidence of cognitive impairment.

Parietal cortex activation is a common finding across working memory studies (15,22,27). In addition to short-term memory storage, activation in this region has been associated with higher cognitive load (15). This particular region is thought to be part of a frontoparietal executive system involved in regulating attention, switching attentional focus and task preparation (27). This interpretation is supported by our present finding that activation in this region was associated with better performance on the 2-Back, a task with high attentional demands. Additionally, metabolic abnormalities in this area have been noted in cognitively intact individuals at genetic risk for dementia (28), indicating that parietal cortex may be particularly vulnerable to disruption by pathological processes.

In the present study, we found that parietal task-related activation was significantly related to early dysregulation of glucose metabolism as reflected by insulin sensitivity. In agreement with previous literature (20), BMI was strongly related to insulin sensitivity. Most importantly, the inclusion of insulin sensitivity in the model abolished the significant relationship between BMI and right parietal activation, indicating successful mediation. This finding was further confirmed by the bootstrapping methods for assessing indirect effects (25). Taken together, these findings are consistent with the notion that insulin exerts numerous effects on the central nervous system (9–10,29) including cognitive function (30,31).

Within the central nervous system, insulin is an important factor for the successful operation of several processes related to learning and memory such as glucose metabolism, neurotransmitter release, and long-term potentiation (10,29). Insulin from the periphery has been shown to cross the blood–brain barrier in a dose-dependent manner (32). However, chronic hyperinsulinemia and insulin resistance are believed to cause insulin receptors on the blood–brain barrier to downregulate, inducing an insulin deficit state in the brain and negatively affecting neurophysiological processes critical to cognitive functioning (29). In keeping with these findings, rats with diet-induced obesity and insulin resistance display impairments in spatial memory and reduced hippocampal synaptic plasticity (30). Similarly, humans with diabetes mellitus exhibit impaired declarative memory and hippocampal atrophy (33). Last but not least, insulin resistance is implicated in the pathogenesis of Alzheimer's type dementia through stimulation of cellular release of amyloid- β and reduction in amyloid- β clearance (29).

Although dysregulation of glucose and insulin metabolism are most often discussed in the context of declarative memory impairment, effects on attention-executive functions have also been noted. Diabetes mellitus has been shown to negatively affect working memory, psychomotor speed, and executive performance (34). Additionally, lack of glycemic control has been associated with cerebral atrophy in brain areas crucial for attention and executive control (33). While the mechanisms linking insulin dysregulation to attention-executive impairment have not been formally established, endothelial dysfunction may be a potential mediator (35). Due its regulation of nitric oxide production in endothelial cells, insulin acts as a vasodilator (36). Even in the early stages of insulin resistance, impairments in endothelial function are evident (36). Endothelial dysfunction has been linked to cerebral microvascular damage in older patients with cardiovascular disease (37) as well as lower functional working memory activation in middle-aged adults (38). Thus, the deleterious effect of impaired insulin sensitivity on endothelial function may result in microvascular damage and impairments in executive function. In support of this hypothesis, diabetes and impaired glucose tolerance are related to increased risk for vascular dementia (31).

The limitations of the present study must also be considered. These include the small sample size and cross-sectional design of the study. Although our findings make an important contribution to the growing body of evidence indicating

that obesity and decreased insulin sensitivity are associated with altered brain function and cognition, the cross-sectional design limits the scope of the inference we can make from our data. Future longitudinal studies will be instrumental in determining if the observed alterations in brain activation are predictive of future cognitive decline. Further studies are also needed to determine if a dose-dependent relationship exists between impairments in insulin sensitivity, alterations in brain activation during cognition and behavioral performance. Another limitation of the present study is the relatively small sample size. Insulin sensitivity is only one of many factors related to obesity to be implicated in cognitive decline. Exploring the contribution of elevated cholesterol, triglycerides, and inflammation to alterations in functional brain response to cognition, alone or in addition to changes in insulin sensitivity is a very important future direction. Our study was not sufficiently powered to explore such complex interactions. Future studies with larger sample sizes should explore the unique and combined effect of insulin sensitivity with other physiological factors that are known to relate to obesity and cognitive impairment.

In conclusion, we found that working memory-related task activation was significantly different in the right parietal cortex between obese and nonobese individuals. The group difference was independent of age, IQ, education level, and blood pressure. Whereas future longitudinal studies are warranted to determine the long-term implications of these findings, our results add to a growing body of literature indicating that obesity may have a deleterious impact on cognition and cerebral health. Additionally, our study found evidence that insulin sensitivity mediated the relationship between BMI and differential brain activation during working memory. Future investigations on this topic are of great public importance considering the increasing prevalence of obesity and other conditions associated with insulin dysregulation. A better understanding of the mechanisms contributing to obesity- and insulin-related cognitive decline may aid the development of new treatments and inventions. In particular, lifestyle modifications such as diet and exercise may prove important components for maintaining cognitive health and functional ability across the lifespan.

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DISCLOSURE

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REFERENCES

1. National Center for Health Statistics. *Chartbook on Trends in the Health of Americans*. Public Health Service: Hyattsville, MD, 2006.
2. Baumgartner RN, Heymsfield SB, Roche AF. Human body composition and the epidemiology of chronic disease. *Obes Res* 1995;3:73–95.
3. Jurdak N, Lichtenstein AH, Kanarek RB. Diet-induced obesity and spatial cognition in young male rats. *Nutr Neurosci* 2008;11:48–54.
4. Whitmer RA, Gunderson EP, Quesenberry CP Jr, Zhou J, Yaffe K. Body mass index in midlife and risk of Alzheimer disease and vascular dementia. *Curr Alzheimer Res* 2007;4:103–109.
5. Elias MF, Elias PK, Sullivan LM, Wolf PA, D'Agostino RB. Lower cognitive function in the presence of obesity and hypertension: the Framingham heart study. *Int J Obes Relat Metab Disord* 2003;27:260–268.
6. Gustafson D, Lissner L, Bengtsson C, Björkelund C, Skoog I. A 24-year follow-up of body mass index and cerebral atrophy. *Neurology* 2004;63:1876–1881.
7. Bassett SS, Yousem DM, Cristinzio C et al. Familial risk for Alzheimer's disease alters fMRI activation patterns. *Brain* 2006;129:1229–1239.
8. Bruce-Keller AJ, Keller JN, Morrison CD. Obesity and vulnerability of the CNS. *Biochim Biophys Acta* 2009;1792:395–400.
9. Unger JW, Livingston JN, Moss AM. Insulin receptors in the central nervous system: localization, signalling mechanisms and functional aspects. *Prog Neurobiol* 1991;36:343–362.
10. Doyle P, Cusin I, Rohner-Jeanrenaud F, Jeanrenaud B. Four-day hyperinsulinemia in euglycemic conditions alters local cerebral glucose utilization in specific brain nuclei of freely moving rats. *Brain Res* 1995;684:47–55.
11. Shepherd PR, Kahn BB. Glucose transporters and insulin action—implications for insulin resistance and diabetes mellitus. *New Engl J Med* 1999;341:248–257.
12. de Luca C, Olefsky JM. Inflammation and insulin resistance. *FEBS Lett* 2008;582:97–105.
13. Srinivasan SR, Myers L, Berenson GS. Predictability of childhood adiposity and insulin for developing insulin resistance syndrome (syndrome X) in young adulthood: the Bogalusa Heart Study. *Diabetes* 2002;51:204–209.
14. World Health Organization. *Physical status: the use and interpretation of anthropometry*. In *WHO Technical Report Series 854*. World Health Organization: Geneva, Switzerland, 1995.
15. Braver TS, Cohen JD, Nystrom LE et al. A parametric study of prefrontal cortex involvement in human working memory. *Neuroimage* 1997;5:49–62.
16. American Diabetes Association. Diagnosis and classification of diabetes mellitus. *Diabetes Care* 2004;27:S5–S10.
17. Lezak M, Howieson D, Loring D, Hannay H, Fischer J. *Neuropsychological Assessment*, 4th edn. Oxford University Press: New York, NY, 2004.
18. Beck AT, Steer RA, Brown GK. *Manual for the Beck depression Inventory-II*. Psychological Corporation: San Antonio, TX, 1996.
19. Spielberger CD, Gorsuch RL. *STAI Manual for the State-Trait Anxiety Inventory ("Self-Evaluation Questionnaire")*. Consulting Psychologists Press: Palo Alto, CA, 1970.
20. Katz A, Nambi SS, Mather K et al. Quantitative insulin sensitivity check index: a simple, accurate method for assessing insulin sensitivity in humans. *J Clin Endocrinol Metab* 2000;85:2402–2410.
21. Cox RW. AFNI: software for analysis and visualization of functional magnetic resonance neuroimages. *Comput Biomed Res* 1996;29:162–173.
22. Owen AM, McMillan KM, Laird AR, Bullmore E. N-back working memory paradigm: a meta-analysis of normative functional neuroimaging studies. *Hum Brain Mapp* 2005;25:46–59.
23. Talairach J, Tournoux P. *Co-planar Stereotaxic Atlas of the Human Brain*. Thieme: Stuttgart, 1988.
24. Baron RM, Kenny DA. The moderator-mediator variable distinction in social psychological research: conceptual, strategic, and statistical considerations. *J Pers Soc Psychol* 1986;51:1173–1182.
25. Preacher KJ, Hayes AF. SPSS and SAS procedures for estimating indirect effects in simple mediation models. *Behav Res Methods Instrum Comput* 2004;36:717–731.

26. Volkow ND, Wang GJ, Telang F *et al.* Inverse association between BMI and prefrontal metabolic activity in healthy adults. *Obesity (Silver Spring)* 2009;17:60–65.
27. Ravizza SM, Delgado MR, Chein JM, Becker JT, Fiez JA. Functional dissociations within the inferior parietal cortex in verbal working memory. *Neuroimage* 2004;22:562–573.
28. Johnson KA, Albert MS. Perfusion abnormalities in prodromal AD. *Neurobiol Aging* 2000;21:289–292.
29. Craft S, Watson GS. Insulin and neurodegenerative disease: shared and specific mechanisms. *Lancet Neurol* 2004;3:169–178.
30. Stranahan AM, Norman ED, Lee K *et al.* Diet-induced insulin resistance impairs hippocampal synaptic plasticity and cognition in middle-aged rats. *Hippocampus* 2008;18:1085–1088.
31. Curb JD, Rodriguez BL, Abbott RD *et al.* Longitudinal association of vascular and Alzheimer's dementias, diabetes, and glucose tolerance. *Neurology* 1999;52:971–975.
32. Schwartz MW, Sipols A, Kahn SE *et al.* Kinetics and specificity of insulin uptake from plasma into cerebrospinal fluid. *Am J Physiol* 1990;259:E378–E383.
33. Gold SM, Dziobek I, Sweat V *et al.* Hippocampal damage and memory impairments as possible early brain complications of type 2 diabetes. *Diabetologia* 2007;50:711–719.
34. Kodl CT, Seaquist ER. Cognitive dysfunction and diabetes mellitus. *Endocr Rev* 2008;29:494–511.
35. Convit A. Links between cognitive impairment in insulin resistance: an explanatory model. *Neurobiol Aging* 2005;26 (Suppl 1): 31–35.
36. Muniyappa R, Iantorno M, Quon MJ. An integrated view of insulin resistance and endothelial dysfunction. *Endocrinol Metab Clin North Am* 2008;37:685–711, ix.
37. Hoth KF, Tate DF, Poppas A *et al.* Endothelial function and white matter hyperintensities in older adults with cardiovascular disease. *Stroke* 2007;38:308–312.
38. Gonzales MM, Tarumi T, Tanaka H *et al.* Functional imaging of working memory and peripheral endothelial function in middle-aged adults. *Brain Cogn* 2010;73:146–151.