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Elevated BMI Is Associated With Decreased Blood Flow in the Prefrontal Cortex Using SPECT Imaging in Healthy Adults

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Obesity is a risk factor for stroke and neurodegenerative disease. Excess body fat has been linked to impaired glucose metabolism, insulin resistance, and impulsivity and may be a precursor to decline in attention and executive cognitive function. Here, we investigated the effects of high BMI on regional cerebral blood flow (rCBF) using single photon emission computed tomography (SPECT) imaging in healthy subjects. A total of 16 adult men and 20 adult women were recruited from the community between January 2003 and July 2009 as part of a healthy brain study (HBS) conducted at the Amen Clinics, a private medical facility. Participants in the study were screened to exclude medical, neurological, and psychiatric conditions, including substance abuse. Subjects were categorized as normal or overweight according to BMI. Using a two sample *t*-test, we determined the effects of BMI on rCBF in normal vs. overweight subjects. Subjects were matched for age and gender. Statistical parametric mapping (SPM) revealed a higher BMI in healthy individuals that is associated with decreased rCBF in Broadmann areas 8, 9, 10, 11, 32, and 44, brain regions involved in attention, reasoning, and executive function ($P < 0.05$, corrected for multiple comparisons). We found that an elevated BMI is associated with decreased rCBF in the prefrontal cortex of a healthy cohort. These results indicate that elevated BMI may be a risk factor for decreased prefrontal cortex function and potentially impaired executive function.

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Over the last decade a growing body of evidence indicates that increased adiposity is associated with decreased brain metabolism and cognitive performance in regions associated with executive function and attention (1–4). The use of imaging tools, such as magnetic resonance imaging and positron emission tomography, have defined specific brain regions where metabolic imbalances occur in individuals with a high BMI. In a study of 1,428 Japanese men using magnetic resonance imaging, a high BMI was associated with significant decreases in gray matter volume in areas including the frontal lobe, bilateral medial temporal lobes, anterior lobe of the cerebellum, and occipital lobe (5). Volkow *et al.* found in healthy adults that a high BMI has been inversely correlated with metabolic activity in the prefrontal cortex and anterior cingulate gyrus using positron emission tomography (1). Taken together, these studies demonstrate the link between excess body mass and decreased brain structure and function. To date, no studies have investigated the regional cerebral blood flow (rCBF) changes in those with high BMI using single photon emission computed tomography (SPECT) imaging. Since obesity has been linked to arterial stiffness, reduced cerebral blood flow velocity (6) and microvasculature dysfunction, SPECT imaging can yield valuable insights into how obesity impacts cerebral blood flow patterns.

Elevated BMI has been associated with biomarkers for myelin abnormalities in the frontal lobe of healthy adults (7). In addition, obesity has been linked to an increased prevalence of attention deficit hyperactivity disorder (ADHD) (8), especially in the morbidly obese (9). ADHD has been associated with lower rCBF in the prefrontal cortex (10). Significant impairments in executive dysfunction have been reported in both healthy adults (4,11) and in a clinical sample of 68 extremely obese individuals (3). These studies suggest a connection between obesity and frontal lobe dysregulation, which may result in impaired focus and increased impulsivity along with decreases in executive function observed in previous studies. The goal of our study was to test the hypothesis that elevated BMI is associated with lower rCBF in the prefrontal cortex using SPECT imaging in a group of healthy age and gender matched adults who are categorized as normal or overweight according to BMI.

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METHODS

A total of 97 subjects were recruited by the Amen Clinics, Newport Beach, CA, to be part of a healthy brain study (HBS) (WIRB # 20021714). Within this group there were 18 subjects who had a BMI >25. These 18 subjects were matched for age and gender with 18 HBS subjects who were within a healthy BMI range (18.5–24.9), giving a total of 36 subjects (20 females, 16 males). The mean age for this sample was 41 years (range 20–82; s.d. = 18). Each subject met the clinical criteria for a healthy brain subject that included the absence of current medical illnesses, past brain trauma, family history of psychiatric illness, current or past drug or alcohol abuse and no current or past evidence of neurological, behavioral or psychiatric issues as measured by a detailed clinical history, Minnesota Multiphasic Personality Inventory and Structured Clinical Interview for Diagnosis for DSM-IV (Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition). The procedures were in accordance with the guidelines of the Helsinki Declaration on human experimentation. The study protocol was approved by Western institutional review board. All subjects were fully informed and gave their written consent.

Each participant of the HBS study was interviewed by a clinician and completed a detailed history. Weight and height were obtained from all participants and BMI was calculated. We followed the standard criteria for BMI categorization as defined by the World Health Organization (12).

Participants underwent high-resolution brain SPECT imaging to measure rCBF. Each subject received an age/weight-appropriate dose of Tc99m hexamethylpropyleneamine oxime intravenously. Subjects were injected in normal lighting while they performed the Conners' Continuous Performance Test II, which measures response inhibition and attention, and is a validated screening tool that assigns a clinical probability of having ADHD. The radiopharmaceutical was injected 3 min after starting the 15-min test. All subjects completed the task. Subjects were then scanned 30 min later using a high-resolution Picker Prism 3000 triple-headed γ-camera with fan beam collimators, acquiring data in 128 × 128 matrices, yielding 120 images per scan with each image separated by 3 degrees spanning 360 degrees.

SPECT data were processed and attenuation correction performed using general linear (Chang) methods. All images were reconstructed and resliced using an oblique reformatting program, according to anterior-posterior commissure line so the final images were similarly aligned for analysis.

Differences in hexamethylpropyleneamine oxime uptake were analyzed using SPM8 software (Wellcome Department of Cognitive Neurology, London, UK) implemented on the Matlab platform (MathWorks, Sherborn, MA). Statistical parametric maps (SPMs) are spatially extended statistical processes that are constructed to test hypotheses about regionally specific effects in neuroimaging data. SPM combines the general linear model and the theory of Gaussian random fields to make statistical inferences about regional effects. The images were spatially normalized using a 12 parameter affine transformation followed by nonlinear deformations to minimizing the residual sum of squares between each scan and a reference or template image conforming to the standard space defined by the Montreal Neurological Institute template. The original image matrix obtained at 128 × 128 × 29 with voxel sizes of 2.16 mm × 2.16 mm × 6.48 mm were transformed and resliced to a 79 × 95 × 68 matrix with voxel sizes of 2 mm × 2 mm × 2 mm consistent with the Montreal Neurological Institute template. Images were smoothed using an 8 mm full-width-at-half-maximum isotropic Gaussian kernel.

We compared the SPECT scans with the normal weight HBS vs. overweight HBS using SPM with a two sample *t*-test which was age and gender matched.

RESULTS

Average BMI in our overweight group was 28.43 ± 2.87 kg/m^2 and in our normal weight group was 21.79 ± 1.69 kg/m^2. Three overweight subjects fit the criteria for being obese (BMI ≥30). Using SPM analysis, the brain SPECT scans showed significant decreases in rCBF in the elevated BMI group at $P < 0.05$ familywise error corrected for multiple comparisons (**Figure 1**). There were global decreases observed across the whole brain at $P < 0.05$. We focused our analysis for this study, however, on regions in the prefrontal cortex that are traditionally associated with focus, impulsivity, and executive function. We identified these regions as Broadmann areas 8, 9, 10, 11, 44, (prefrontal cortex) and 32 (anterior cingulate gyrus). No significant increases were observed.

Linear regression analysis at $P < 0.01$ with no familywise error reveals that when using BMI as a factor, we observe the most significant decreases in rCBF as reported by voxel cluster size in the following regions: (i) left frontal superior orbital (coordinates −14, 34, −30) and right frontal mid orbital cortex (coordinates 20, 56, −14; size 1,729 pixels and $t = 3.87$) followed by (ii) cerebellum (coordinates −46, −46, −36; size 1,263 pixels and $t = 3.48$) and (iii) the right precentral (coordinates 56, −14, 58) and right postcentral cortex (coordinates 66, −12, 42, size 775 pixels and $t = 2.8$). A plot of the regression slope reveals a negative correlation between BMI and rCBF in the prefrontal cortex ($r = -0.39$, $P < 0.01$).

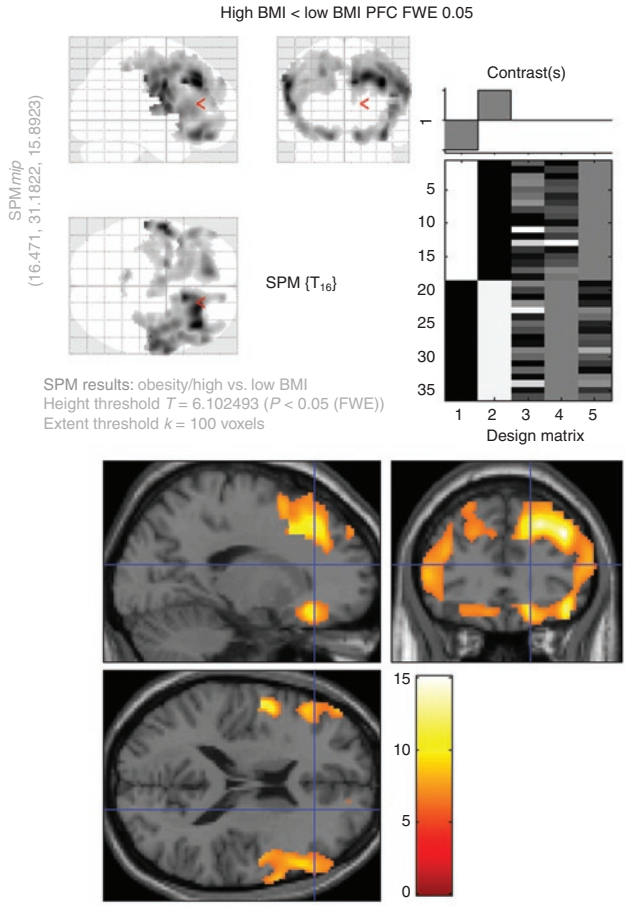

Figure 1 Areas of decreased perfusion on single photon emission computed tomography with elevated BMI in healthy adults at $P < 0.05$ familywise error (FWE). PFC, prefrontal cortex; SPM, statistical parametric mapping.

CONCLUSIONS

Obesity is becoming a world-wide epidemic and is a risk factor for many chronic conditions, including cardiovascular disease, depression, and neurodegenerative disease. According to the 2007–2008 National Health and Nutrition Examination Survey, the prevalence rate of obesity was measured at 33% (13) which suggests that clinicians must be prudent of the risk factors that an elevated BMI has on cognition and brain function. Here, we show in healthy subjects significant decreases in rCBF in the prefrontal cortex and anterior cingulate gyrus in those categorized as overweight. These results suggest that being overweight is associated with lower blood flow to the brain, specifically to the prefrontal cortex, and may negatively impact behaviors associated with this brain region. This is supported by other studies that report diminished metabolic activity in the prefrontal cortex with high BMI (1), and lower gray matter volume in the frontal operculum and frontal gyrus of overweight healthy subjects (14) and in the left orbitofrontal region of older females (4).

The results of this study must be interpreted as an association and not causative. We are not able to determine whether premorbid problems in the prefrontal cortex lead to increased impulsivity and subsequent obesity or whether being overweight or obese directly causes brain changes. Both scenarios may be true. The fact that we used a healthy brain group and specifically excluded ADHD or other behavioral disorders argues against the premorbid hypothesis, but other studies have shown an association between ADHD and obesity (8,9). Still other authors report that adipose tissue directly increases inflammatory cytokines which may have a negative effect on brain structure and function (15).

Nevertheless, these results add to a growing body of literature implicating that decreased function/decreased blood flow in the prefrontal cortex is associated with the problem of obesity and strategies geared to decreasing obesity may be helpful in improving brain function. In addition, strategies geared toward enhancing activity and perfusion in the prefrontal cortex may help obese patients lose weight.

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DISCLOSURE

The authors declared no conflict of interest.

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