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Voxel-Based Morphometry Reveals Brain Gray Matter Volume Changes in Successful Dieters

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Original Article
CLINICAL TRIALS AND INVESTIGATIONS

Obesity

Voxel-Based Morphometry Reveals Brain Gray Matter Volume Changes in Successful Dieters

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Objective: To compare regional brain volume predictors of percent weight loss (WL) in dieters with obesity (DwO) and in the same participants categorized as "successful" (≥7% WL) or "unsuccessful" dieters (<7% WL).

Methods: DwO (n = 72) and participants with healthy weight (n = 22) completed a structural MRI at baseline and 3 months. All DwO participants were enrolled in a 12-week program consisting of a reduced calorie diet, increased physical activity, and behavioral modification. SPM8-based voxel-based morphometry processing streams were used for measurements of regional gray (GMV) and white matter volume and longitudinal changes in volume. Correlations between WL and baseline brain volume and change in brain volume, as well as differences between groups, were then tested.

Results: %WL was positively correlated with baseline GMV in right parahippocampal and orbitofrontal gyri in DwO. Successful dieters showed greater GMV loss in the left precentral gyrus and the insula compared with unsuccessful dieters. A negative correlation was found between %WL and GMV change from baseline in the left prefrontal regions.

Conclusions: Findings illustrate that WL is related to volumetric changes in brain areas previously linked to interoception and food motivation.

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Introduction

Rates of obesity in the U.S. are steadily climbing, with 30% or more of the adult population having clinical obesity (1). Both overweight (body mass index, BMI, of 25-29.9 kg/m^2) and obesity (BMI ≥30 kg/m^2) are characterized by the accumulation of excessive levels of body fat that contribute to hypertension, heart disease, diabetes, Alzheimer's disease, and some cancers, as well as psychosocial and economic difficulties (2). Positive effects of weight reduction include lowered cardiovascular risk factors and inflammatory markers, improved glucose tolerance, decreased inflammatory markers, and beneficial effects on brain health (3). In individuals with obesity there is a negative correlation between BMI and waist circumference and regional brain volume (BV) (4-6). However, there have been few investigations of the relationship of variations in brain anatomy and successful weight loss (WL).

Previous research has identified brain differences in individuals with obesity compared with those who are lean. Pannacciulli et al. (7) used voxel-based morphology (VBM) to identify structural brain difference in areas of the brain associated with the regulation of taste, reward, and behavioral control in individuals with obesity as compared with lean individuals. Haltia et al. (8) compared the brain structure of individuals, to find that white matter volume (WMV) was greater in those with obesity as compared with the lean individuals in the frontal and temporal regions; brain stem; and cerebellum (bilaterally). Following baseline assessments, the individuals with obesity (i.e., dieters with obesity, DwO) completed a 6-week very low-calorie diet. Findings indicated that the WMV expansion at baseline was partially reversed in the left temporal lobe by WL, while regional GMV did not differ significantly in DwO and lean subjects. Dieting did not affect GMV, and the study did not examine baseline BV predictors of WL. Similarly, Hassenstab et al. (9) found reduced cortical thickness in the cognitive control network (anterior cingulate and posterior parietal cortices) in individuals with obesity, compared with successful weight maintainers and lean individuals.

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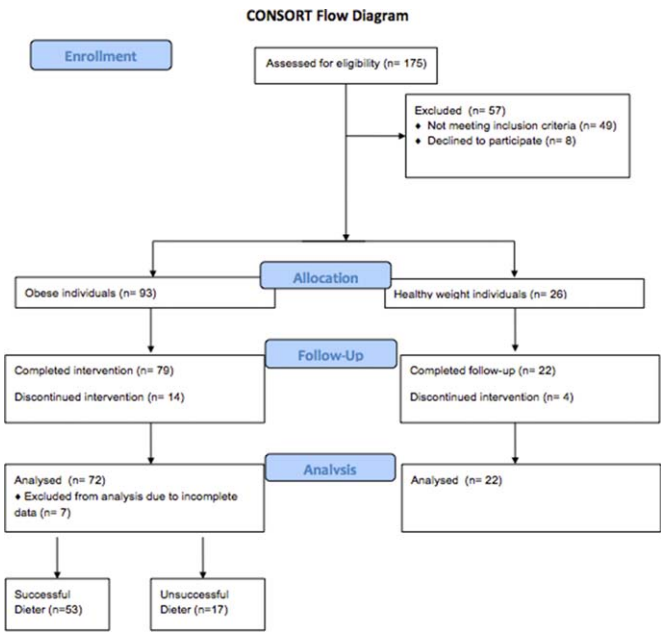

Figure 1 CONSORT flow diagram shows the number of participants at enrollment, allocation, follow-up, and analysis. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Together, these studies demonstrate differences in BV between individuals with obesity and lean brains. Nonetheless, little is known regarding the extent to which baseline differences in BV predict responses to WL interventions.

This study included both healthy weight (HW) controls and DwO participants; the latter participated in a 3-month WL intervention with brain imaging at baseline and post-diet. The aim of the study was first to examine the relationships between baseline GM and WMVs and future %WL at 3 months, as well as to compare longitudinal regional brain changes between categorically defined successful (individuals who lost $\geq$7% of starting weight) and unsuccessful dieters and HW individuals. We hypothesized that future %WL would be associated with an increase in GMV in areas of the prefrontal cortex at baseline, while a comparison between successful, unsuccessful, and HW individuals would show a greater gain in GMV over time in the prefrontal cortex for successful as compared with unsuccessful dieters relative to the HW individuals.

Methods

The details of this investigation have been previously published (10); therefore, a brief description of the methods has been provided.

Participants

DwO individuals (n = 82) were recruited and enrolled in the study. Seventy-nine completed the 12-week diet; however, only 72 had complete data (structural MRI and behavioral) for analyses. Twenty-two HW were also recruited and all had complete data. A CONSORT diagram is available in Figure 1 and baseline demographics and sample characteristics are included in Table 1. Participants were included in the study if they met the following inclusion criteria: (1) age 21 to 55 years; (2) BMI of $<$25 or $\geq$30.0 to 45.0 kg/m^2; (3) able to safely complete an MRI; and (4) received clearance for participation from their primary care physician. This study was approved by the Human Subjects Committees at the University of Kansas Medical Center. We certify that all applicable institutional and governmental regulations concerning the ethical use of human volunteers were followed during this research. Based on the previous research conducted by our group and clinical relevance for these cutoffs (11-13), "successful dieters" were defined as those individuals losing $\geq$7% of their initial body weight during the 12-week WL period, while "unsuccessful dieters" lost $\leq$6.9%.

Intervention

All DwO completed a WL intervention which consisted of attendance to 60-min, in-person, behaviorally based meetings of 5 to 15 individuals that were conducted weekly for 3 months. All meetings used behavioral strategies based on social cognitive theory to promote change in both diet and exercise (14). Average meeting attendance was 83%.

During the WL phase, energy intake was reduced to an approximate goal of 1,200 to 1,500 kcal/day using a combination of commercially available portion-controlled meals (PCM), fruits and vegetables, low-calorie shakes, and noncaloric beverages. Participants were provided with a list of selected PCMs provided by HMR Weight Management Service Corp. (Boston, MA). Fruits and vegetables and noncaloric beverages were allowed *ad libitum*. When combined with a variety of fruits and vegetables, PCMs (entrees + shakes) provide a diet with all necessary nutrients specified by the Dietary Reference Intakes (15). Any participant reaching a BMI of 22 kg/m^2 during the WL phase (n = 1) was transitioned to the prevention of weight maintenance diet.

Participants reported the number of PCMs consumed, fruits and vegetables consumed, minutes of physical activity completed, and the number of steps as recorded on step counters each week to their health educator according to their meeting schedule. Participants weighed on a scale at the clinic site at each clinic meeting. At midpoint between meetings, the same information except weight was also reported via toll-free phone, fax, or email.

Anthropometrics (body weight, height, and BMI)

Body weight was recorded at baseline, and 3 months using a digital scale accurate to +0.1 kg (Befour Inc Model #PS6600, Saukville, WI). All participants were weighed after arriving at MRI appointments in standard hospital scrubs, having fasted for at least 4 h and after attempting to void. Subsequently, height was measured using a stadiometer (Model PE-WM-60-84, Perspective Enterprises, Portage, MI) and BMI (kg/m^2) was calculated.

Wechsler Abbreviated Scale of Intelligence Vocabulary and Matrix Reasoning

The Wechsler Abbreviated Scale of Intelligence (WASI) Vocabulary and Matrix Reasoning were administered to estimate intellectual function.

TABLE 1 Demographic and cognitive characteristics of study group

		Obesity subgroups						
	HW	Obesity group	Successful dieter (≥7%)	Unsuccessful dieter (<6.9%)	*P*			
	n = 22	*n* = 72	*n* = 53	*n* = 17	HW vs. obesity	HW vs. succ	HW vs. unsucc	Succ vs. unsucc
Age	36.8 (10.9)	38.9 (8.2)	40.1 (8.5)	35.6 (6.2)	0.336	0.149	0.667	0.072
Gender (*n* (%female))	18 (81)	49 (68)	34 (64)	13 (76)	0.164	0.106	0.492	0.264
Education	4.59 (1.2)	4.53 (1.3)	4.6 (1.3)	4.2 (1.3)	0.837	0.967	0.387	0.300
BMI (kg/m^2) BL	21.6 (1.6)	35.6 (3.6)	35.6 (3.3)	34.7 (3.8)	0.000	0.000	0.000	0.283
BMI (kg/m^2) 3M	21.5 (1.7)	31.6 (3.4)	31.2 (3.3)	32.9 (3.8)	0.000	0.000	0.000	0.052
% Weight loss	0.02 (1.47)	10.6 (4.9)	12.3 (4.2)	5.01 (1.7)	0.000	0.000	0.000	0.000
IQ	116.1 (9.3)	113.7 (9.8)	114.9 (9.7)	109.9 (9.8)	0.322	0.634	0.051	0.067
Stroop interference BL[a]	24.7 (9.2)	23.5 (8.5)	22.4 (8.4)	27.4 (7.9)	0.596	0.308	0.362	0.050
Stroop interference 3M[a]	24.0 (9.1)	23.7 (7.8)	22.6 (7.3)	27.8 (8.6)	0.890	0.483	0.173	0.030

Values are mean (SD) unless noted otherwise.
[a]Lower scores represent better performance/function.
BMI, body mass index; BL, baseline; HW, healthy weight control; 3M, 3 month follow-up; *n*, number; Succ, successful; Unsucc, unsuccessful.

Stroop Test

The Stroop Test is a measure of speed of information processing and response inhibition (16). A series of colored X's and color words were printed in black and presented on a computer screen. Participants were asked to either say the color or read the word as quickly as possible; in the final task, the color words were printed in different, incompatible, colors, and participant were instructed to say the color of the text, not read the word.

Data and MRI acquisition

The anthropometric, WASI, and Stroop tests were completed at both baseline and 3 months before the MRI scan. Scanning was performed on a 3 Tesla Siemens Allegra scanner (Siemens, Erlangen, Germany) fitted with a quadrature head coil. T1-weighted anatomic images were acquired with a three-dimensional MPRAGE sequence (TR/TE = 2,300/3.06 ms, flip angle = 8°, FOV = 192 × 100 mm, matrix = 192 × 192). Every scan was checked for image artifacts and gross anatomical abnormalities, resulting in the removal of three DwO and two HW participants.

MRI data analysis

Data analysis for 94 subjects, who had completed both baseline and 12-week testing and exhibited no abnormalities, was performed using Statistical Parametric Mapping version 8 (SPM8) algorithms (Wellcome Department of Cognitive Neurology, London, UK) running under MATLAB 7.2 (The MathWorks, Natick, MA) on Linux. Processing for VBM analysis at cross-section was completed by first creating a sample-specific Diffeomorphic Anatomical Registration Through Exponentiated Lie (DARTEL) template algebra (17). A high-dimensional spatial normalization with DARTEL was then applied to normalize images to the DARTEL template, and the unified segmentation ("New Segment") model in SPM8 (18) with priors to output warped, modulated, segmented images. The final images were smoothed with a 10 mm isotropic Gaussian kernel to accommodate inexact spatial normalization (8 mm for WMV).

Longitudinal analysis

First, the 12-week follow-up MRI of a subject was rigidly registered onto the subject's baseline image to remove position differences. Then we used a high-dimensional deformation field to warp the follow-up to the baseline image (19) resulting in a field map describing changes that occurred between baseline and follow-up scans. The local volume change was captured in each voxel with the determinant of the Jacobian matrix of the deformation field. We multiplied the Jacobian determinant voxel-by-voxel with the baseline GM segments to form a GMV change image.

The baseline and follow-up images were then segmented using the unified segmentation ("New Segment") model in SPM8 (18). To compare regional volume change between groups, it was necessary to spatially normalize the baseline segmentation images to a common stereotactic space to ensure that the same voxel in different subjects sampled an approximately corresponding neuroanatomic structure using DARTEL (17).

Segmented GMV maps were then imported into DARTEL and used to create a customized template. The DARTEL template, and the estimated spatial normalization parameters, or flow fields from the template creation, were normalized to Montreal Neurological Institute (MNI) space. The flow fields from the template creation and parameters from normalization to MNI space were then applied to the GMV change images. To preserve the original tissue volumes, the normalized GMV change images were modulated and smoothed with an 8 mm isotropic Gaussian kernel. The normalized, modulated, and smoothed GMV change maps for each individual were then inputted into statistical analysis in SPM8. The same procedure was completed to create normalized, modulated, and smoothed WMV change maps.

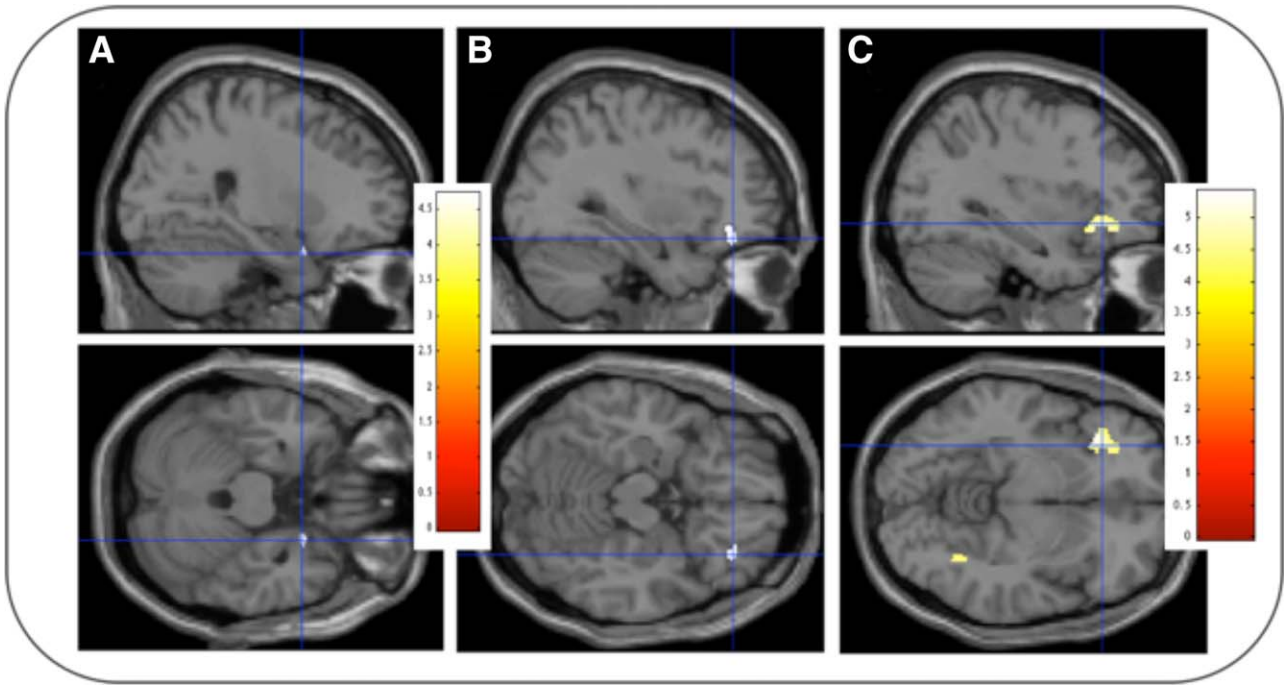

Figure 2 Statistical parametric maps of regions where percent weight loss was significantly correlated with higher (**A,B**) baseline regional GMV and (**C**) regional WMV from VBM analysis, displayed on a standardized spatially normalized MRI. Column A shows significant findings in a right parahippocampal gyrus cluster overlaid on sagittal and axial (lower) views (24, 8, −24). Column B shows significant findings in a right orbitofrontal gyrus cluster overlaid on sagittal and axial (lower) views (33, 36, −15). Column C shows significant findings in a left orbitofrontal/inferior frontal cortex (upper and lower; −38, 24, −9) and right fusiform gyrus (lower; 38, −55, −12). Coordinates given in MNI; color bars represent *Z* scores from SPM8 analysis, SPM8 maps threshold and displayed at $P < 0.05$ FWE corrected; clusters >100. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

GM, WM, and cerebral spinal fluid (CSF) segmentations for baseline and follow-up images were used to calculate total-intracranial volume for both time points, and normalized GMV, WMV, and CSF volume for both time points. Annualized rate of change was calculated by dividing the difference in segmentation volume between time points by the time (in months) between the two scans.

Imaging statistics

Within the DwO alone, we used a General Linear Model full factorial analysis with *post hoc t*-tests to assess the relationship between %WL as a continuous variable and voxel-based longitudinal changes in GMV and WMV. Then, a multiple regression model was utilized within the dieting group to assess the relationship between baseline regional BV as a predictor for %WL as a dichotomous variable (i.e., successful vs. unsuccessful) over the 3 months. For these regression analyses of %WL, we included only age as a covariate (GMV and WMV as global variables where applicable) as there was a significant relationship between sex and %WL, such that in the successful dieting group men had higher %WL ($P < 0.002$; mean %WL in men was 14.6 and mean %WL in women was 11.1) as compared with the unsuccessful dieting group. A General Linear Model full factorial analysis with *post hoc t*-tests was also used to examine longitudinal regional volume differences across successful and unsuccessful dieters, with HW individuals as controls, including age and sex as confounding variables, and GMV as a global variable (WMV for WM analyses). BMI was used as a covariate when HW individuals were included to control for any possible weight change that may have occurred in this nondieting group over the 3-month period.

For all analyses, voxels are reported with reference to the MNI standard space within SPM8 (20). To avoid possible edge effects at the border between GM and WM and to include only relatively homogeneous voxels, we used an absolute threshold masking of 0.05 for each analyses. Results were considered significant at $P < 0.05$ after correction for multiple comparisons (family-wise error, FWE) and had a minimum cluster size of 100 voxels ($k > 100$).

Statistical analyses

SPSS 22.0 was used for all statistical analysis outside of imaging space. Continuous demographic, cognitive, and dieting variables were compared between the HW, and overall DwO using ANOVA with LSD correction for multiple comparisons testing. χ^2 was used to compare categorical variables between groups. For all analyses, results were considered significant at $P < 0.05$ (Table 1).

Results

Subject characteristics

A CONSORT diagram detailing recruitment, allocation, follow-up, and analysis is provided in Figure 1. There was no significant difference between HW and DwO in age, gender, or education (Table 1).

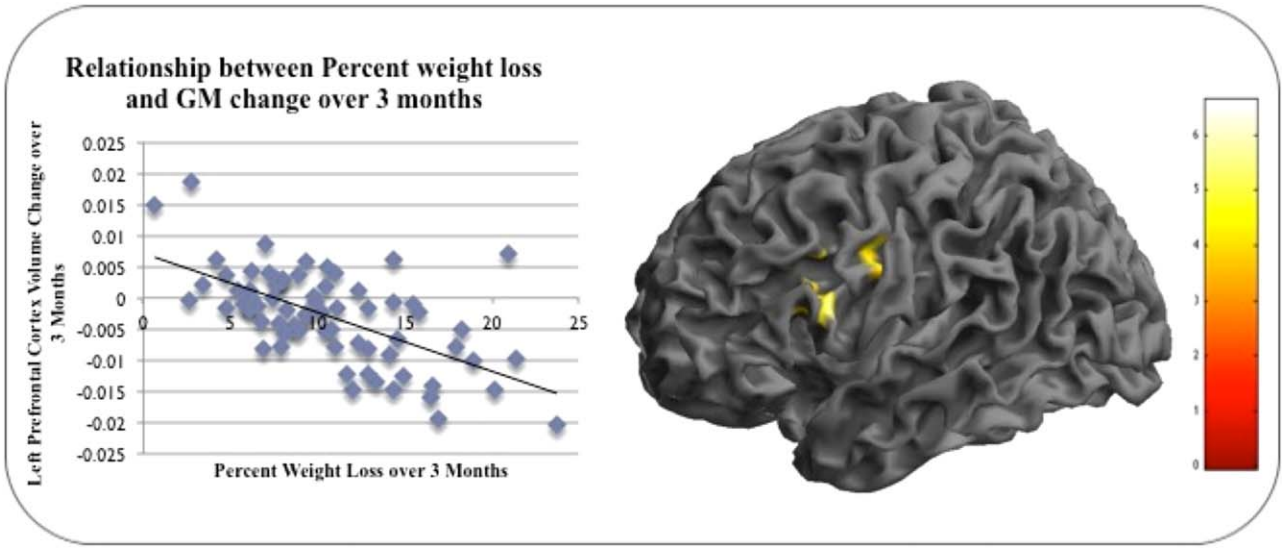

Figure 3 Linear relationship between percent weight loss in dieting individuals with obesity and decrease in gray matter (GM) over 3 months in the left precentral gyrus. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

We found a trend for a difference between HW individuals and unsuccessful dieters in IQ ($P = 0.051$). There was a significant difference between successful and unsuccessful dieters on the Stroop task (interference score) at baseline ($P = 0.05$), and that difference was maintained at 3 months ($P = 0.03$) with the unsuccessful group having significantly higher interference scores than the successful dieter group.

Imaging results

Analysis of baseline GM and WM with %WL. In the VBM regional analysis of baseline GMV in all dieting individuals (the DwO), we found that %WL (i.e., successful dieters) was positively correlated with baseline GMV in two regions: right parahippocampal gyrus ($P < 0.05$ FWE, MNI coordinates (24, 8, −24), $Z = 4.37$) and right orbitofrontal gyrus ($P < 0.05$ FWE, (33, 36, −15), $Z = 4.37$) (Figure 2). We also found a positive correlation between %WL in the dieting group and baseline WMV in left orbitofrontal/inferior frontal gyrus ($P = 0.001$ FWE, (−38, 24, −9), $Z = 4.91$) and in right fusiform gyrus ($P < 0.05$ FWE, (38, −55, −12), $Z = 4.23$) (Figure 2).

Analysis of brain change in successful vs. unsuccessful dieters. When comparing voxel-based regional changes in the brain between successful and unsuccessful dieters, successful dieters had more GMV loss in the left precentral gyrus ($P < 0.05$ FWE, (−54, −15, 21), $Z = 4.67$) than unsuccessful dieters. There were no regions where unsuccessful dieters had more GMV loss than successful dieters. In a multiple regression of %WL against voxel-wise data of regional change in GMV (in only the dieting groups), we found a significant relationship between increased %WL and decreased GMV in two clusters in the left prefrontal cortex, the left middle frontal gyrus ($P < 0.001$ FWE, (−43, 7, 27), $Z = 5.77$) and precentral gyrus ($P = 0.006$ FWE, (−49, −7, 34), $Z = 5.12$) (Figure 3), similar to the comparison between successful and unsuccessful dieters. There were no regions with a significant relationship in the other direction (higher %WL and increased GMV). There were also no significant relationships between %WL and regional change in WMV.

We also independently tested whether baseline IQ and Stroop interference scores were associated with the change in GMV associated with %WL. Stroop interference score was significantly different between successful and unsuccessful dieters at baseline and 3 months ($P = 0.050$ and $P = 0.030$, respectively); however, there was no significant association between GMV change and IQ or Stroop interference score at either time point or with change in Stroop interference score.

Analysis of brain change in successful and unsuccessful dieters compared with HW. For our voxel-based regional analysis of GM and WMV change across all subject groups, we first compared HW individuals (none of whom dieted) with the DwO as a whole, and then the successful and unsuccessful dieters separately. Over 3 months, individuals in the dieting program as a whole showed decreased GMV in the left insula ($P = 0.001$ FWE corrected, (−(1,25,30)), $Z = 5.43$), whether or not they were successful, compared with HW controls. Decreased volume in this same GM region in the insula was significantly different between the HW and unsuccessful dieting group ($P = 0.013$ FWE) when compared individually. Moreover, when comparing the HW and successful dieting group, there were significant decreases in GMV in the dieting group in the left insula ($P < 0.001$ FWE, (−(1,25,31)), $Z = 5.67$), and also the left postcentral gyrus ($P = 0.003$ FWE, (−50, −18, 36), $Z = 5.26$) as well as the left putamen/lentiform nucleus ($P < 0.05$ FWE, (−(6,11,23)), $Z = 4.93$). There were no regions where the DwO as a whole (or the successful and unsuccessful dieting groups) had increased GMV over 3 months compared with HW controls. There were no significant differences between the HW and DwO, or

between the HW and dieting groups (i.e., successful or unsuccessful) individually over 3 months in change in regional WMV.

Discussion

This study found that DwO who lose weight as part of a 3-month dieting program undergo a reduction in GMV in the left prefrontal cortex. Similarly, over the 3-month diet period, overweight and DwO both showed a decreased GMV in the left insula whether or not they were successful, as compared with HW controls. While the longitudinal data were contrary to our hypothesis, we did find that individuals who were considered successful dieters (≥7% of their starting weight) had significantly more GMV change than those who were unsuccessful in these frontal regions of the cortex. Moreover, we found that greater GMV in the orbitofrontal and parahippocampus, and WMV in the orbitofrontal and temporal cortex, was associated with greater success in dieting (greater %WL). There was also observed a decrease in GMV in the insula for DwO in the unsuccessful group, while the successful dieting group showed a decrease in GMV in the left insula, left postcentral gyrus, and left putamen/lentiform nucleus as compared with HW individuals.

Our findings of decreased BV in individuals with substantial WL are in line with a recent study of other human DwO which found a reduction in regional WMV in the left temporal lobe (8). Also, previous research in patients with anorexia nervosa supports our findings that rapid WL is associated with a reduction in GMV in the insular cortex (21-23). This change in insula volume is important to note as the anterior insula provides a representation of taste, temperature, texture of food in the mouth that is independent of hunger (24). Previous research has shown a greater brain activation in the insula relative to taste when comparing individuals with obesity and HW (25) as well as lower GMV in DwO as compared with HW (26). Other research has demonstrated decreased activation in the insula in individuals who had recently lost weight (27). Other studies have shown a significant GMV decrease in the insular cortex at the time of anorexia nervosa diagnosis as compared with HW controls. Although DwO and patients with anorexia are unique in their own right, both groups represent patterns of disordered eating. Therefore, these findings are of particular interest due to the insula's role as part of a neural circuit involved in the analysis of physiological feedback and subjective body image. The insula is involved in interoceptive processing that contributes to the formation of an integrated sense of the physiological condition of the entire body and is important for the self-body representation. Altered interoceptive awareness might be a precipitating and reinforcing factor in obesity as well as other weight-related conditions including anorexia and bulimia (28).

Our longitudinal findings of increased GMV in the orbitofrontal and paraphippocampal cortex and a significant, positive correlation between baseline WMV and %WL in the dieting group in the left orbitofrontal/inferior frontal gyrus are not unexpected, as energy intake and other eating behaviors have been shown to be influenced by homeostatic factors and motivational processing (29-31). Previous research has shown that abnormal activity in these networks may lead to increased eating behaviors, and overeating and obesity may be conceptualized as reflecting failures in impulse control that are associated with unique patterns of brain activation to food stimuli (32-35). Therefore, the increase in GMV in these regions may reflect compensatory recruitment of limbic/paralimbic cortex as the regions are thought to be essential for efficient food procurement and maintenance of energy balance (36). Together, these findings illustrate that WL is related to volumetric changes in areas of the brain associated with interoception and food motivation, which in turn are both modified during a weight management intervention.

We are aware of the positive impact that increases in exercise and fitness can have on brain structure and function (37,38). However, typical weight management programs, the present investigation included, combine both diet and exercise in order to promote WL (3,39). Accordingly, we were unable to distinguish the influence of changes in exercise as compared with changes in diet on brain structure. In addition, cardiorespiratory fitness was not measured. However, our noted associations between WL and increases in GMV are consistent with previous literature suggesting that increases in exercise and fitness result in increases in GMV (37,38).

Conclusion

Ours is the first study to look at the effects of dieting over 3 months on brain anatomy, as well as the first to correlate %WL with baseline and longitudinal measures of BV. Specifically, we found WL was associated with a reduction in GMV in the left prefrontal cortex that appears proportional to the amount of weight lost. Also, individuals in the dieting program as a whole showed decreased GMV in the left insula regardless of WL success. We also found that successful dieters (≥7% of their starting weight) had significantly more GMV change in these frontal cortical regions than those who were unsuccessful and that greater GMV in the orbitofrontal and parahippocampal cortex, and WM in the orbitofrontal and temporal cortex, were associated with greater success at dieting as measured by greater %WL. These brain areas identified are of importance as they are critical for taste, proprioception, and food motivation, all of which can be modified during weight management counseling. Together, these neuroimaging findings support associations between baseline brain morphometry and future WL and unique brain morphometric profiles in successful and unsuccessful dieters. O

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