

## Brain Tissue Volume Changes Following Weight Gain in Adults with Anorexia Nervosa

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### ABSTRACT

**Objective:** To measure brain volume deficits among underweight patients with anorexia nervosa (AN) compared to control participants and evaluate the reversibility of these deficits with short-term weight restoration.

**Method:** Brain volume changes in gray matter (GM), white matter (WM), and cerebrospinal fluid (CSF) were examined in 32 adult women with AN and compared to 21, age and body mass index-range matched control women.

**Results:** Patients with AN had a significant increase in GM ( $p = .006$ ,  $\eta^2 = 0.14$ ) and WM volume ( $p = .001$ ,  $\eta^2 = 0.19$ ) following weight restoration. Patients on av-

erage had lower levels of GM at low weight ( $647.63 \pm 62.07$  ml) compared to controls ( $679.93 \pm 53.31$  ml), which increased with weight restoration ( $662.64 \pm 69.71$  ml), but did not fully normalize.

**Discussion:** This study suggests that underweight adult patients with AN have reduced GM and WM volumes that increase with short-term weight restoration. © 2010 by Wiley Periodicals, Inc.

**Keywords:** anorexia nervosa; magnetic resonance imaging; brain volume; structural brain abnormality; starvation

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### Introduction

Anorexia nervosa (AN) is a serious psychiatric illness characterized by relentless dieting and weight loss. The starvation promoted by the illness affects multiple physiological systems in the human body causing metabolic, endocrine, and cardiovascular abnormalities.<sup>1</sup> Brain volume deficits and increased cerebrospinal fluid (CSF) observed in underweight individuals with AN suggest that the brain is not spared the deleterious effects of starvation.<sup>2–7</sup> More specifically, one small study ( $N = 13$ ) found that underweight adolescents with AN had

greater ventricular, sulcal, and total CSF volumes and less gray matter (GM) and white matter (WM) volumes compared to healthy control participants.<sup>8</sup> These findings, with the exception of WM deficits, were replicated in another small sample ( $N = 12$ ) of underweight children and adolescents with AN.<sup>9</sup> When this patient sample was evaluated 7 months after weight restoration, there were increases in GM volume and decreases in CSF over time. Similarly, two studies examining changes in adult patients with AN observed decreases in CSF and increases in brain matter immediately following weight restoration,<sup>5,10</sup> and others have observed a reversal of ventricular enlargement with weight restoration.<sup>3,6,7</sup> However, it remains unclear whether brain volume fully normalizes with acute weight restoration.<sup>9–11</sup>

Because many of the existing studies have only examined adolescents with the restricting subtype of AN, the first aim of this study was to examine changes in brain volume accompanied by weight restoration among adult inpatients meeting full criteria for either the restricting or binge/purge subtypes of AN. We hypothesized that patients with AN would experience increases in GM and WM with short-term weight gain. The second aim was to examine how GM and WM volumes in patients with AN at low-weight and normal weight compared to the brain volumes of healthy control participants. We hypothesized that underweight patients would have deficits in GM and WM when

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compared with controls and that these deficits would no longer be present after weight restoration.

## Method

### Participants

Participants were adult women with AN engaged in inpatient treatment on the Eating Disorders service of the General Clinical Research Unit of the New York State Psychiatric Institute at Columbia University Medical Center. Forty patients were recruited to participate in two longitudinal functional magnetic resonance imaging (fMRI) studies examining responses to food. As part of those fMRI studies, standard T1-weighted structural scans were obtained, allowing for brain volume assessments. To be eligible for the study, patients had to (1) meet DSM-IV criteria for AN (except for amenorrhea); (2) have no other Axis I disorder other than major depression; (3) be women between the ages of 18 and 45; (4) be free of psychotropic medication; (5) not be pregnant or lactating; (6) not have any nonremovable metal on their body, or other contraindications for MRI (e.g. claustrophobia); (7) be medically stable; and (8) have no history of suicide attempt or other self-injurious behavior within the previous 6 months.

Twenty-six healthy women control participants were also recruited via flyers to participate. Eligibility criteria for controls included (1) women between the ages of 18 and 45; (2) no current or past psychiatric illness; (3) no history of binge eating or vomiting; (4) body mass index (BMI) between 18 and 23 kg/m<sup>2</sup>; (5) not currently taking medication; (6) no significant medical or neurologic illness; (7) not pregnant or lactating; and (8) no nonremovable metal on their body, or other contraindications for MRI.

The Structured Clinical Interview for DSM-IV was used to diagnose patients and screen controls.<sup>12</sup> Height was measured by stadiometer to the nearest [1/4] in., and weight was measured on a beam balance scale by a research assistant and used to calculate BMI. A psychiatrist (LESM) met with all patients and controls to determine whether they met the additional eligibility criteria. Patients also provided self-report data on duration of illness.

Participants were initially scanned within the first 2 weeks of hospitalization after they were deemed medically stable and before the beginning of the weight-gain phase of treatment. Patients were rescanned after reaching 90% of ideal body weight (IBW) based on the 1959 Metropolitan Life Insurance Tables.<sup>13</sup> Two of the participating patients requested to be discharged from the hospital before reaching 90% of IBW, but had gained a significant amount of weight placing them at a BMI above

18.0 kg/m<sup>2</sup>, and were rescanned before discharge. Controls were also scanned twice. The New York State Psychiatric Institute/Columbia University Department of Psychiatry Institutional Review Board for the protection of human participants approved this study, and informed consent was obtained for all participants.

### MRI Acquisition

High-resolution spoiled gradient-recalled echo T1-weighted axial images (TE/TR 5/19 ms, flip angle 20°, 22 × 17-cm field of view, 256 × 256 × 114 matrix, yielding an in-plane resolution of 0.859 × 0.859 mm and slice thickness 1.5 mm) were acquired on a 1.5T General Electric Twin Speed MRI machine.

### Image Analysis

An optimized voxel-based morphometry procedure was used as described in Ashburner and Friston<sup>14</sup> and Good et al.<sup>15</sup> using SPM5 (Wellcome Department of Cognitive Neurology, London, UK) to derive tissue volumes. Those conducting the segmentation were blind to participant diagnostic status. Individual images were spatially normalized into standardized stereotactic space and segmented into three tissue types using prior probabilities provided by SPM5. Default settings were used for this procedure. During the spatial normalization step, images were corrected by the Jacobian determinant to maintain volumetric information,<sup>15</sup> and each voxel intensity value reflected its true volume. Total volumes were determined by summing across voxel intensity values for each tissue type (i.e., GM, WM, and CSF).

### Statistical Analysis

Data analysis was performed using SPSS 15.0 (Chicago, IL). First, two sets of independent samples two-tailed *t*-tests were conducted to assess potential differences between patients and controls and patients with either binge-purge or restricting subtype of AN on age, height, BMI, and time between scans. For our primary analyses, we performed three two-factor repeated measures ANOVAs to assess changes in GM, WM, and CSF over time and possible interactions between brain volume and participant status (patient vs. control). All ANOVAs included total intracranial volume (derived by summing GM, WM, and CSF) as a covariate. Eta-squared effect sizes are reported for these analyses, and interpretation is based on Cohen's guidelines (small = 0.01, medium = 0.06, and large = 0.14).<sup>16</sup> Significant omnibus tests were followed with tests of simple effects to examine differences in brain volume between patients at low weight compared to controls as well as patients at normal weight compared to controls. Cohen's *d* was calculated as a measure of effect size for these comparisons, and interpretation was based on Cohen's guidelines (small = 0.2, medium = 0.5, and large = 0.8).<sup>16</sup> Finally, Pearson correla-

tions were performed to determine if the GM, WM, or CSF volumes of patients at low weight were associated with BMI and/or duration of illness and if changes in GM, WM, or CSF volumes were correlated with changes in BMI. We used a  $p$ -value of less than 0.05 to denote statistical significance for all analyses.

## Results

Three patients' and one control's follow-up scans could not be reliably segmented into three tissue types (i.e., GM, WM, and CSF) and were therefore excluded from the analyses. Five patients and four controls failed to complete a second scan and so were excluded from the analyses. Thus, data from 32 patients and 21 controls were assessed. Fourteen patients (43.75%) had AN-restricting subtype, and 18 patients (56.25%) had AN-binge/purge subtype. These two subtype groups did not significantly differ on age, height, duration of illness, or BMI at scan 2 (data not shown). The subtype groups did significantly differ on scan 1 BMI ( $p = .01$ ), with the restricting subtype group having a lower BMI (M 15.24 kg/m<sup>2</sup> SD 1.51 vs. M 16.65 kg/m<sup>2</sup> SD 1.40 for the binge/purge subtype group). Both groups were combined into one sample for all of the analyses. The patient group did not differ significantly from the control group on age, height, or BMI after patients had normalized their weight, although the patient group was significantly underweight at the initial scan compared to controls. The difference in age, scan dates, and the second scan BMI violated the equality of variances assumption based on the Levene test, and so  $t$ -tests, degrees of freedom, and significance levels for these variables reflect values based on the Welch-Satterthwaite approach. Demographic and clinical information is presented in **Table 1**.

There was a significant interaction between scan time and participant status (patient vs. control) on GM [ $F(1,50) = 8.28, p = .006, \eta^2 = 0.14$ ], indicating that GM changes differed by participant status. The tests of simple effects were significant when comparing GM volumes between patients and controls at scan 1 (when patients were underweight) ( $p < 0.001, d = 0.56$ ) and at scan 2 (when patients were weight-restored) ( $p = .039, d = 0.30$ ). Patients on average had lower GM volumes at scan 1 compared to controls, which increased over time, but remained significantly lower than controls after weight restoration (see **Fig. 1**).

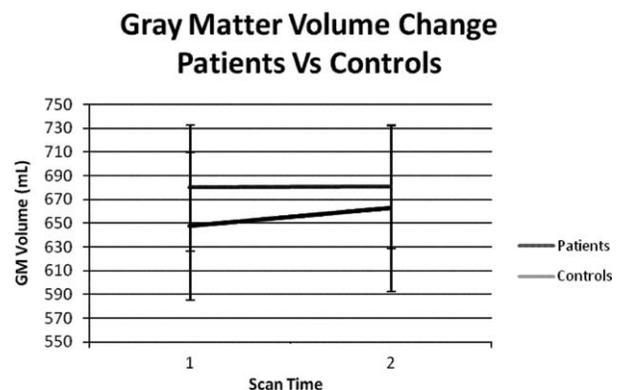
There was a significant interaction between scan time and participant status [ $F(1,50) = 12.01, p = .001, \eta^2 = 0.19$ ], with the patient group experienc-

**TABLE 1. Demographic and clinical variables for patients and controls**

	Patients ( $n = 32$ )		Controls ( $n = 21$ )		Ind Samples $t$ -Test		
	Mean	SD	Mean	SD	$t$	df	$p$
Age (years)	26.91	6.41	25.00	3.18	-1.44	48.12	0.158
Height (in.)	63.61	2.52	64.35	2.30	1.076	51	0.287
Scan 1 BMI (kg/m <sup>2</sup> ) <sup>a</sup>	16.03	1.59	20.82	1.22	10.27	35	0.000
Scan 2 BMI (kg/m <sup>2</sup> )	20.01	0.59	20.60	1.17	2.10	25.13	0.050
Time between scans (days)	50.28	19.07	51.65	37.66	0.151	25.18	0.881
Duration of illness (years)	10.15	6.23					

<sup>a</sup>Significant difference between patients and controls,  $p < 0.05$ .

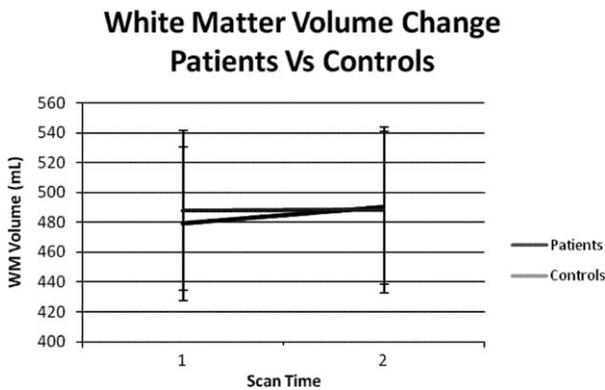
**FIGURE 1. The graph shows mean gray matter volume for patients with anorexia nervosa and controls at scan one and scan two. Error bars represent standard deviations.**



ing an increase in WM over time that was not present in the control group. Tests of simple effects did not reveal significant differences in WM volume between patients and controls at the first scan ( $p = .229, d = 0.17$ ) or the second scan ( $p = .947, d = -.03$ ) (see **Fig. 2**). There was not a significant interaction between scan time and participant status for CSF volumes [ $F(1,50) = 1.30, p = .259, \eta^2 = 0.03$ ]. See **Table 2** for results.

When patients were underweight, BMI was not significantly correlated with GM, WM, or CSF volumes. However, duration of illness was correlated with GM volume at low weight ( $\rho = -.472, p = .007$ ), but not with WM or CSF volumes. The change in BMI between the low weight and weight-restored scans was significantly correlated with the change in GM ( $\rho = .549, p = .001$ ) and the change in WM ( $\rho = .405, p = .022$ ), but not with the change in CSF. Duration of illness was not correlated with any of the brain volume changes.

**FIGURE 2.** The graph shows mean white matter volume for patients with anorexia nervosa and controls at scan one and scan two. Error bars represent standard deviations.



**TABLE 2.** Brain volume comparisons between patients and controls

	Patients (N = 32)				Controls (N = 21)			
	First Scan		Second Scan		First Scan		Second Scan	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
GM (ml) <sup>a</sup>	647.63	62.07	662.64	69.71	679.93	53.31	680.91	52.35
WM (ml) <sup>a</sup>	479.22	51.42	489.99	51.04	488.22	53.68	488.36	55.54
CSF (ml)	276.57	47.61	267.70	49.20	229.05	45.24	229.02	40.82

<sup>a</sup>Significant interaction between patient/control group and scan time,  $p < 0.05$ .

## Discussion

This study confirmed our first hypothesis that adult patients with AN would experience an increase in GM and WM volumes following short-term weight restoration. Our second hypothesis that patients would have GM and WM deficits compared to controls at low-weight, which would resolve after weight-restoration was also partially confirmed. Significant deficits in GM were observed at low weight. These deficits improved with short-term weight restoration, but did not fully normalize. A significant increase in WM volume was also observed, but post hoc tests of simple effects did not reveal significant differences in WM between patients and controls at either scan. However, given that WM increased over time, it appears that WM deficits may have been present when patients were underweight. There was also no significant difference between patients and controls in WM volumes at the second scan. Although this suggests that WM volume may fully normalize with short-term weight gain, the results should be interpreted with caution given the small sample size. Considering all of these findings together, we draw the following conclusions: (1) GM deficits were present at

low weight and GM volume increased with weight gain, but did not fully normalize; (2) WM volume increased with weight gain, suggesting that WM deficits were present at low weight and may normalize with weight restoration.

We were able to replicate Katzman et al.'s<sup>8</sup> observation that adolescent underweight patients with the restricting subtype of AN had deficits in GM when patients were underweight in a larger sample of adult patients with both binge/purge and restricting subtypes of AN compared to controls. However, unlike Katzman et al., we did not detect significant differences in WM when patients were underweight, though our findings suggest that these deficits may exist in our sample as well. The larger sample size of this study improved upon Swayze and colleagues<sup>5</sup> study, which examined an adult sample of patients with AN (though only eight patients met diagnostic criteria for full syndrome AN, and the sample included a male with BN and a male with EDNOS). They failed to find significant differences in GM and WM and attributed this to their small sample size. In a second study of 13 adult patients, Swayze et al.<sup>10</sup> observed increased CSF volume at low weight, but again did not see deficits in total GM. They did however observe deficits in total WM, and while we did not observe this, the increase in WM over time in our sample suggests that WM deficits at low weight were likely present. In addition, we replicated their finding that GM and WM significantly increase following weight restoration.

It will be important for future research to further explore differences in brain volume deficits between adolescent and adult populations and between the different AN subtypes. Castro-Fornieles and colleagues<sup>9</sup> argued that GM is more affected than WM in adolescents, which appears to be true in our sample as well, although we also observed increases in WM. We also detected an inverse correlation between duration of illness and lower volumes of GM at low weight, but no correlation between low weight BMI and brain volume measures. This suggests that greater brain volume deficits are experienced the longer a patient has AN. This is in contrast to Katzman et al.,<sup>8</sup> who observed a correlation between BMI and brain volume, but not duration of illness. This disparity may represent differences in adolescent populations who have not been ill for very long versus adult populations where duration of illness and thus duration at lower weight may prove to be a more important indicator of brain volume loss than current BMI. However, Swayze et al.<sup>10</sup> also saw a significant correlation between initial BMI and all global brain and CSF volumetric measurements and, as we

observed, also detected a significant relationship between changes in volume and changes in BMI. The correlation between BMI and volume changes suggests that starvation plays a central role in brain deficits among patients with AN, although the mechanism through which starvation impacts brain volume remains unclear.

Katzman and colleagues have hypothesized that one mechanism may be cortisol levels.<sup>8</sup> They note that underweight patients with AN have elevated levels of cortisol comparable to those seen in Cushing disease, which is also often accompanied by brain atrophy. Katzman and colleagues have observed a correlation between high levels of cortisol and GM deficits, but because we did not obtain measures of cortisol, we could not assess this relationship in this study. Future research should examine deficits in specific structures particularly vulnerable to excess cortisol, such as the hippocampus.

Although this study evaluated a larger sample size than most other existing studies, it remains limited by a small number of participants. However, there are a number of additional strengths. The study used a longitudinal design that included individuals who met full criteria for both binge/purge and restricting subtypes of AN. The design was also strengthened by the inclusion of age and BMI range-matched controls who were also scanned twice at the same time intervals as patients.

Future research should use longitudinal designs to aim to replicate these findings in a larger adult sample as well as explore potential differences in subtypes of AN. In addition, it will be important to clarify if and when brain volume normalizes with longer term weight maintenance. Lambe et al.<sup>17</sup> examined brain volume after long-term maintenance (between 1 and 23 years) in 12 individuals with a past history of AN-restricting subtype and found that compared to controls, weight-recovered patients had smaller total GM volumes and greater total CSF volumes. No differences in total WM volumes emerged between the groups, but based on our findings, this WM reversal may have occurred early in the recovery process. Similarly, Katzman et al.<sup>18</sup> found that among six adolescent patients with AN who were rescanned 2–3 years after maintaining normal weight, there were no differences in WM when compared with controls, but GM deficits and elevated CSF volumes remained. However, Wagner et al.<sup>19</sup> performed a cross-sectional study comparing 30 adult women with AN who had been recovered for 1 year and did not find any differences in total GM, WM, and CSF between patients and controls. Overall, these findings are mixed, and conclusions based on small sample sizes need to

be interpreted with caution, because the failure to detect differences does not mean real differences do not exist. Finally, although a study of adolescents did not find an association between cognitive deficits and brain volume deficits,<sup>20</sup> the impact of these structural changes on brain function (e.g. cognitive abilities) among adult patients with AN requires additional research. McCormick et al.<sup>21</sup> found that reductions in right dorsal anterior cingulate cortex volume in underweight patients with AN were related to difficulties with perceptual organization and conceptual reasoning. Furthermore, the smaller changes in right dorsal anterior cingulate cortex volume were associated with poorer response to treatment. These findings suggest that future research should focus on regional analyses in addition to overall brain volume.

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