

# Implications of Starvation-Induced Change in Right Dorsal Anterior Cingulate Volume in Anorexia Nervosa

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## ABSTRACT

**Objective:** Converging evidence suggests a role for the anterior cingulate cortex (ACC) in the pathophysiology of anorexia nervosa (AN). This study sought to determine whether ACC volume was affected by starvation in active AN and, if so, whether this had any clinical significance.

**Method:** Eighteen patients with active AN and age- and gender-matched normal controls underwent magnetic resonance imaging (MRI). Sixteen patients (89%) with AN had intelligence quotients (IQ) testing at intake, 14 (78%) had repeat MRIs after weight normalization, and 10 (56%) had outcome data at 1-year post-hospitalization.

**Results:** Right dorsal ACC volume was significantly reduced in active AN

patients versus controls and was correlated with lower performance IQ. While ACC normalization occurred with weight restoration, smaller change in right dorsal ACC volume prospectively predicted relapse after treatment.

**Conclusion:** Reduced right dorsal ACC volume during active AN relates to deficits in perceptual organization and conceptual reasoning. The degree of right dorsal ACC normalization during treatment is related to outcome. © 2008 by Wiley Periodicals, Inc.†

**Keywords:** dorsal anterior cingulate; ACC; anorexia nervosa; AN; starvation; weight restoration; cognitive function; performance IQ; MRI

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## Introduction

Brain atrophy in patients suffering with active starvation from anorexia nervosa (AN) is a well-documented finding. In recent years, beginning with Hoffman et al.,<sup>1</sup> a wide body of research using magnetic resonance imaging (MRI) has allowed for detailed analysis of global gray matter (GM) and white matter (WM) atrophy.<sup>2–5</sup> However, the specific brain regions involved in AN have yet to be fully elucidated. Lesion studies have linked structural problems in the dorsal anterior cingulate cortex (ACC) to AN-like behaviors.<sup>6,7</sup> Similarly, abnormal blood flow in this region has been found to

occur in patients with AN<sup>8,9</sup> and remain abnormal even after weight stabilization.<sup>10</sup> A recent study by Mühlau et al., using voxel-based morphometry to assess all brain regions, found that the dorsal ACC region was the only area still abnormally small in recovered patients with AN compared to normal controls.<sup>11</sup>

Most people who develop AN typically have above-average intelligence quotients (IQ).<sup>12</sup> However, during the active phase of AN, 50% of individuals with AN have been found to have mild cognitive impairment on two or more neuropsychological tasks and one-third outright failed two or more tasks.<sup>13</sup> Although there is usually no generalized intellectual compromise as evidenced by premorbid estimates of Wide Range Achievement Test reading levels, several areas of verbal and nonverbal memory were significantly lower than the full scale intelligence quotient (FSIQ). Additionally, performance IQ (PIQ) has been found to be significantly lower than verbal IQ (VIQ) in actively ill patients with AN. Impairments have also been found in several other areas of cognitive functioning including: verbal and visual memory, visuospatial ability, attentional skills, and executive functioning.<sup>14–21</sup> Research focused on cognitive flexibility in patients actively ill with AN reported that deficits exist in set shifting as assessed by the

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Wisconsin Card Sorting Test.<sup>22</sup> Similarly, set shifting difficulties have been found in patients before and after recovery and similar impairments are found in first-degree relatives, suggesting this may represent a specific enduring cognitive deficit in people prone to developing AN.<sup>23</sup> In a study by McDowell and coworkers, the cognitive impairments in actively ill patients with AN were found to be independent of depression severity.<sup>24</sup> Also, in the study by McDowell et al., the memory and psychomotor speed improved the most with weight restoration, whereas a study by Kingston et al.<sup>25</sup> suggested that only attention abilities improved after weight restoration. Although weight restoration during hospitalization is associated with improved cognitive function, McDowell et al.<sup>24</sup> found that changes in cognitive function are not directly correlated to changes in body mass index (BMI), which suggests that weight restoration in and of itself cannot explain changes that occur in the brain. The neural mechanism underlying cognitive deficits that are stable traits and those that are related to starvation during the active phase of AN is still unknown. A large body of literature suggests that the dorsal ACC region of the brain is involved with various aspects of cognition and memory<sup>26,27</sup> and that change in this brain region may be associated with weight-related changes in cognitive functioning in active AN.

It is still unclear whether brain atrophy in patients with AN is completely reversible with weight restoration and whether this has any effect on long-term outcome.<sup>5</sup> Swayze and colleagues reported that total brain GM and WM are significantly reduced in patients with active AN, but appear to normalize with adequate weight restoration. However, evidence of diminished GM after recovery from AN has also been reported.<sup>3</sup> Lambe et al. studied 12 AN patients who maintained normal weight for at least 1 year (range, 1–23 years) and found that although GM/WM restoration occurred in this “weight-recovered” group, they still had significantly greater cerebral spinal fluid and less GM/WM than an age-matched control group.<sup>2</sup> By contrast, Wagner et al. reported no differences between controls and 40 long-term recovered eating disorder patients.<sup>28</sup> However, this study included 10 patients with bulimia nervosa whose BMI was much higher at follow-up compared to AN patients followed in the Lambe et al. study. Relapse rates after weight restoration in AN patients are still very high and many people with this disorder continue to suffer multiple relapses and a chronic course of illness.<sup>29,30</sup> It is still unknown what predicts chronicity and if changes in brain structure and function are related to relapse after full weight restoration.

This study set out to determine whether ACC volume reductions were present in patients hospitalized with active AN compared to age-matched normal controls. Additionally, we assessed the relationship between ACC volume and IQ. Finally, we examined whether ACC volume normalized with weight restoration and whether degree of ACC normalization was related to outcome at 1 year post-hospitalization.

## Method

### *Participants*

The experimental group consisted of 18 Caucasian patients (six males and 12 females), ranging in age from 15 to 41 ( $M = 25.6$  years,  $SD = 7.24$ ), who met DSM-III-R criteria for AN, and received hospitalization in the inpatient eating disorders unit at the University of Iowa Hospitals and Clinics between November 1992 and December 1995. Results from this population have been reported previously in two studies by Swayze et al.<sup>4,5</sup> However, these reports did not include any analysis of specific cortical or subcortical regions of interest other than the cerebellum. Eighteen sex and age-matched and height-equivalent normal controls were selected from a large number of archived control participants available from the Prospective Longitudinal Study of Schizophrenia and the Mental Health Clinical Research Center at the University of Iowa.<sup>31</sup> Controls had a mean age of  $25.5 \pm 7.31$  years (range, 15–42). Demographics are displayed in Table 1. As expected, patients with AN had a significantly lower BMI at intake (i.e., as of the first MRI). The average BMI on admission was 13.5 ( $SD = 2.14$ ) and at time of discharge from the hospital was 20.1 ( $SD = 1.11$ ), which is considered 100% of ideal body weight. This study was conducted at a time when the average length of hospitalization for these patients was 3–4 months and most were able to reach 100% weight restoration prior to discharge. Years of education were significantly lower in the AN group, due to the fact that several patients with AN failed to complete their education after they became ill. A chart review revealed that six of the patients with AN had a history of comorbid major depression and none had a history of comorbid obsessive-compulsive disorder or substance use disorder. Ten patients had either dependent, obsessive-compulsive or cluster C personality traits and one was diagnosed with avoidant and dependent personality disorder. Approximately seven (39%) patients were on an antidepressant upon admission and three (17%) were on Xanax. At time of discharge, seven (39%) were on an antidepressant, one (7%) was still on Xanax, and two (14%) were on Thorazine. A record of interim medications between the last MRI scan

**TABLE 1. Demographic characteristics of patients hospitalized for treatment of anorexia nervosa and age- and gender-matched normal controls**

	AN Patients ( <i>n</i> = 18)		Controls ( <i>n</i> = 18)		<i>p</i> -value
	Mean	SD	Mean	SD	
Age	25.2	7.33	25.5	7.31	.966
Education (years)	12.8	2.00	14.2	1.66	.023
Height (cm)	164.9	9.92	168.4	7.70	.245
BMI (at MRI no. 1)	13.5	2.14	24.1	3.17	.000
BMI (at MRI no. 2)	20.1	1.11	24.2	3.41	.000
Lowest lifetime BMI	12.4	2.24	—	—	—
Duration of illness (years)	6.5	5.32	—	—	—
Age at 1st EDO hospitalization	20.3	5.75	—	—	—
Previous hospitalizations (no.)	3.1	2.98	—	—	—
Inpatient hospital days	106.8	50.9	—	—	—
WAIS-R <sup>a</sup>					
Verbal IQ	100.9	14.09	103.4	9.82	.595
Performance IQ	91.6	11.64	113.1	9.02	.000
Full Scale IQ	96.5	12.85	108.1	8.19	.007
	<i>N</i>	%	<i>N</i>	%	
Gender					
Male	6	33	6	33	1.00
Female	12	67	12	67	
Subtype					
Restricting	7	39	—	—	—
Binge/Purge	11	61	—	—	—
Comorbid MDD	6	33	—	—	—
Follow-up in Partial Hospitalization Program	3	17	—	—	—

Notes: AN, anorexia nervosa; EDO, eating disorder; MRI, magnetic resonance image; MDD, major depressive disorder; BMI, body mass index; SD, standard deviation; WAIS-R, Wechsler Adult Intelligence Scale-Revised.

<sup>a</sup>WAIS-R data available for 16 patients and 14 controls.

and the outcome point at 1 year is unknown. This study was reviewed and approved by the Institutional Review Board at the University of Iowa.

### Procedures

All AN patients (*n* = 18) received MRI scans soon after admission (1–19 days; mean, 6.44). Of these, 14 (78%) patients (four males and 10 females) received a follow-up MRI scan after weight restoration (56–196 days after the initial scan). Among this follow-up MRI group, 11 patients were scanned while still in the hospital, whereas three were scanned shortly after discharge. Examination of the prospective association between longitudinal change in ACC subregion volume with weight restoration and 1-year outcome was made in 10 individuals (56%) for whom outcome data could be obtained. Remission was defined as having a sustained BMI  $\geq$  18.0 kg/m<sup>2</sup> at 1 year posthospitalization as determined by chart review and posthospitalization survey results.

### MRI

All patient and control MRI scans were obtained with a 1.5-T General Electric Signa scanner (GE Medical Systems, Milwaukee, WI). Standard T1-weighted images were obtained using a 3-D spoiled gradient recall acquisition sequence (echo time, 5 ms; TR, 24 ms; flip angle, 40°; number of excitations, 2; FOV, 26; matrix, 256  $\times$  192; slice thickness, 1.5 mm). In addition, all participants received a

fast spin-echo PD/T2 sequence (TE = 32, 96; TR = 3,000; FOV = 26 cm with flow comp) with a 3 or 4 mm contiguous slice thickness to cover the entire brain. MRI data were visually assessed for quality and movement artifacts. The scans were then processed with locally developed BRAINS2 software.<sup>32</sup> Details of the image processing are published in a previous report on this dataset.<sup>5</sup> Briefly, the T1 and PD/T2 images were spatially normalized, aligned, and resampled to 1.0 mm<sup>3</sup> voxels.

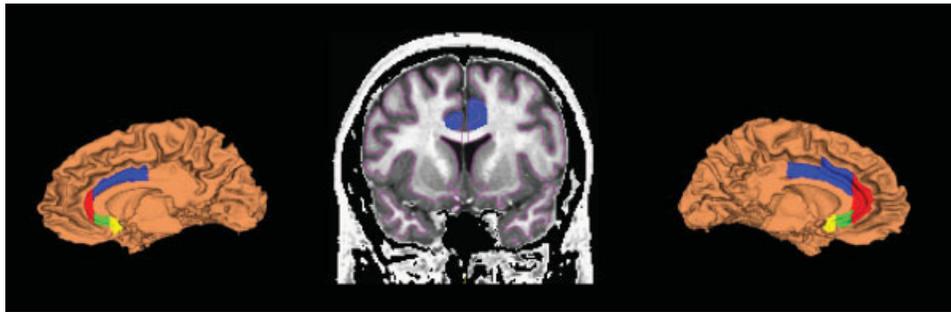
### Definition of ROI

Established manual methods were used to parcellate the ACC into four subregions per hemisphere—left and right dorsal, rostral, subcallosal, and subgenual—resulting in eight regions-of-interest<sup>33</sup> (see Fig. 1). For the 14 patients with both intake and follow-up scans, we carefully reviewed each MRI dataset to ensure that ACC subregions were traced consistently between scans (e.g., on the same number coronal slices).

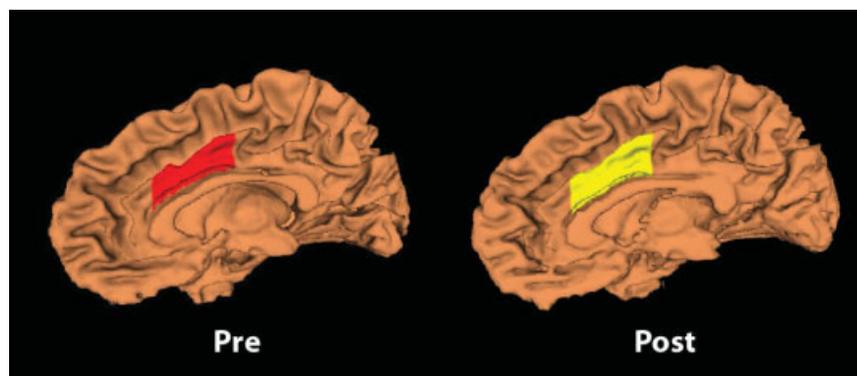
### Neuropsychological Data

For 16 of the 18 AN patients (89%), cognitive function at intake was assessed using the Wechsler Adult Intelligence Scale-Revised (WAIS-R, *n* = 15) or the Wechsler Intelligence Scale for Children (WISC-R, *n* = 1). For simplicity, we will henceforth only refer to the WAIS-R as the main measure used to assess IQ scores. For 14 of these patients, we also obtained age-adjusted scaled scores for the WAIS-

**FIGURE 1.** Anterior cingulate cortex subregions. The dorsal (blue), rostral (red), subcallosal (green), and subgenual (yellow) subregions of the anterior cingulate cortex, as defined by the methods of McCormick et al.<sup>33</sup>



**FIGURE 2.** Dorsal ACC volume before and after weight restoration in anorexia nervosa. The dorsal anterior cingulate cortex changes significantly from starvation during active anorexia nervosa and normalizes with weight restoration.



R verbal subtests of information, comprehension, arithmetic, similarities, vocabulary, and digit span; and for the PIQ subtests of picture completion, picture arrangement, block design, and digit symbol coding. The object assembly performance subtest was not administered and thus the other four PIQ subtests were used to calculate a prorated PIQ score. In addition, we obtained WAIS-R IQ and subtest scores for 14 of the 18 normal controls. Lastly, 13 patients with AN (72%) completed the Beck Depression Inventory (BDI) to assess depression at intake.

### Statistical Analysis

Parametric analyses were used to compare ACC subregion volumes between AN patients and controls, to examine associations between ACC subregion volumes and neuropsychological assessments, and to analyze changes in ACC subregion volumes. Logistic regression was used to examine the association between ACC subregion volume and relapse by 1-year follow-up. An  $\alpha$ -level of 0.05 was used for all analyses.

## Results

Volumetric data from the initial patient scans were compared with the data from scans for the 18 age-

and sex-matched and height-equivalent controls. At intake, right dorsal ACC GM volume was significantly reduced in patients with AN compared to normal controls (**Table 2**). This effect was still present even after controlling for total GM atrophy ( $p < .014$ ) as well as when we covaried for just cortical GM atrophy ( $p < .028$ ). There was no significant difference in any ACC subregion between patients with AN who had comorbid depression and those who did not.

Among the 16 patients who completed the WAIS-R on admission, the average FSIQ was  $96.5 \pm 12.85$ , which comprised a PIQ of  $91.6 \pm 11.64$  and a VIQ of  $100.9 \pm 14.09$ . Thus, there was a significant difference between PIQ and VIQ for the patients with AN ( $p < .005$ ). When we compared WAIS-R scores between patients with AN versus age-matched normal controls, we found significant differences between PIQ ( $91.6 \pm 11.64$  vs.  $113.1 \pm 9.02$ ;  $p < .001$ ) and FSIQ ( $96.5 \pm 12.85$  vs.  $108.1 \pm 8.19$ ;  $p < .007$ ), but not for VIQ ( $100.9 \pm 14.09$  vs.  $103.4 \pm 9.82$ ;  $p < .595$ ). Thirteen AN patients completed the BDI (mean score =  $22.1 \pm 7.47$ ), which indicated a moderate degree of depression during the active phase of AN.

**TABLE 2. Anterior cingulate cortex subregion gray matter volume (ml) for initial scans of patients with anorexia nervosa**

	AN patients ( <i>n</i> = 18) Mean (SD)	Controls ( <i>n</i> = 18) Mean (SD)	<i>t</i>	<i>p</i> -value
Total Cortical GM	637.2 (53.95)	667.3 (49.38)	-1.7	.091
R Dorsal ACC	3.48 (0.51)	4.02 (0.56)	-3.0	.005 <sup>a</sup>
L Dorsal ACC	3.11 (0.73)	3.38 (0.65)	-1.2	.241
R Rostral ACC	2.66 (0.67)	2.98 (0.84)	-1.3	.211
L Rostral ACC	2.12 (1.16)	1.75 (0.80)	1.1	.276
R Subcallosal ACC	0.57 (0.16)	0.58 (0.14)	-0.3	.756
L Subcallosal ACC	0.43 (0.19)	0.44 (0.17)	-0.2	.814
R Subgenual ACC	0.51 (0.08)	0.49 (0.13)	0.5	.598
L Subgenual ACC	0.48 (0.10)	0.50 (0.12)	-0.5	.596

Notes: GM, gray matter; R, right; L, left; ACC, anterior cingulate cortex; SD, standard deviation.

<sup>a</sup> Remained significant after controlling for total cortical GM.

**TABLE 3. Correlations between anterior cingulate cortex subregion gray matter volume and IQ variables in patients with active anorexia nervosa**

	PIQ <i>r</i> ( <i>p</i> )	VIQ <i>r</i> ( <i>p</i> )	FSIQ <i>r</i> ( <i>p</i> )
Total Cortical GM	.43 (.093)	.16 (.552)	.24 (.379)
R Dorsal ACC <sup>a</sup>	.59 (.022) <sup>b</sup>	-.05 (.868)	.22 (.423)
L Dorsal ACC <sup>a</sup>	-.06 (.840)	-.20 (.484)	-.13 (.648)
R Rostral ACC <sup>a</sup>	-.17 (.538)	.14 (.616)	.04 (.891)
L Rostral ACC <sup>a</sup>	-.08 (.791)	.07 (.808)	.04 (.888)
R Subcallosal ACC <sup>a</sup>	.30 (.272)	-.20 (.478)	-.01 (.977)
L Subcallosal ACC <sup>a</sup>	.11 (.687)	.31 (.260)	.23 (.412)
R Subgenual ACC <sup>a</sup>	.17 (.542)	.14 (.609)	.17 (.541)
L Subgenual ACC <sup>a</sup>	.06 (.835)	.27 (.337)	.22 (.429)

Notes: *N* = 16; GM, gray matter; R, right; L, left; ACC, anterior cingulate cortex; PIQ, performance IQ; VIQ, verbal IQ; FSIQ, full-scale IQ.

<sup>a</sup> Covarying for total cortical gray matter.

<sup>b</sup> *p* < .05.

**Table 3** presents correlation analysis between intake ACC subregion volumes and IQ scores in 16 patients with AN (controlling for total cortical GM). Smaller right dorsal ACC volume at intake correlated significantly to lower PIQ. This finding was still present when normal controls were included with education level as a covariate (*p* < .027). PIQ subtest scores were available for 14 of these 16 patients on admission for hospitalization (**Table 4**). Lower scores on block design and digit symbol coding of the PIQ were significantly correlated to lower right dorsal ACC volume. There was also a significant difference in block design (9.0 ± 1.88 vs. 13.0 ± 1.96; *p* < .001) and digit symbol coding (8.6 ± 3.23 vs. 13.5 ± 1.65; *p* < .001) between patients and normal controls, even after controlling for differences in education (*p* < .022).

For the 14 AN patients, who received a second MRI scan after weight restoration, a comparison between baseline and follow-up data found that weight normalization led to a significant increase in total cortical GM and right and left dorsal ACC

**TABLE 4. Correlations between right dorsal anterior cingulate cortex subregion gray matter volume and subscores of the performance IQ in patients with active anorexia nervosa**

PIQ Measure	R Dorsal ACC <sup>a</sup> on admission	
	Rho ( <i>p</i> )	<i>N</i>
Total PIQ	.59* (.022)	16
Picture completion	.31 (.309)	14
Picture arrangement	.09 (.783)	14
Block design	.73** (.005)	14
Digit symbol – coding	.63* (.022)	14

Notes: The Object Assembly subtest was not administered; R, right; L, left; ACC, anterior cingulate cortex; PIQ, performance IQ.

<sup>a</sup> Covarying for total cortical gray matter.

\* *p* < .05

\*\* *p* < .01.

**TABLE 5. Change in anterior cingulate cortex subregion gray matter volume (ml) before and after weight restoration in patients with anorexia nervosa**

	Initial ( <i>n</i> = 14) Mean (SD)	Follow-up ( <i>n</i> = 14) Mean (SD)	<i>t</i>	<i>p</i> -value
Total Cortical GM	632.4 (56.56)	655.7 (54.33)	-2.9	.013
R Dorsal ACC	3.47 (0.53)	3.84 (0.60)	-4.0	.001*
L Dorsal ACC	3.12 (0.78)	3.31 (0.72)	-3.0	.010
R Rostral ACC	2.61 (0.66)	2.70 (0.81)	-1.0	.344
L Rostral ACC	2.25 (1.20)	2.29 (1.21)	-1.0	.316
R Subcallosal ACC	0.57 (0.18)	0.57 (0.15)	-0.1	.926
L Subcallosal ACC	0.43 (0.17)	0.44 (0.20)	-0.9	.389
R Subgenual ACC	0.52 (0.08)	0.53 (0.13)	-0.7	.521
L Subgenual ACC	0.49 (0.11)	0.51 (0.09)	-1.2	.242

Notes: GM, gray matter; R, right; L, left; ACC, anterior cingulate cortex; SD, standard deviation.

\* Remained significant after controlling for change in total cortical GM.

GM volume (**Table 5**). After controlling for change in total cortical GM, only change in right dorsal ACC GM volume remained significant at time of discharge (*p* < .001). To ensure outliers were not driving this finding, we removed the patient with the largest change, and found that these results still remained significant (*p* < .004). To further ensure that this difference did not result from gender effects, we also compared change in right dorsal ACC GM among females only (*n* = 10, controlling for change in total cortical GM), and found that the results remained significant (*p* < .010). See **Fig. 2** for a before and after illustration of this type of change.

The 14 follow-up scans for patients with AN were also compared to the 14 corresponding control scans. The comparison indicated that weight normalization restored all ACC GM areas such that no ACC subregion differed significantly from controls (i.e., all *p*-values > .05). Weight restoration itself as measured by change in BMI was not significantly correlated to restoration of right dorsal ACC volume.

We were able to determine clinical outcome at 1-year posthospitalization for 10 out of 18 AN patients. Of these, the three patients (one male and two females) who had not been rehospitalized and had self-reported normal weight were compared to the seven patients (two males and five females) who had confirmed cases of a drop of BMI < 18.0 kg/m<sup>2</sup> (five of these seven were re-hospitalized within 1 year). Greater normalization of right dorsal ACC volume following weight restoration prospectively predicted sustained remission ( $p < .027$ , covarying for percent change in total GM and  $p < .070$  after controlling for percent change in just total cortical GM change). After controlling for percent change in BMI during hospitalization, the effect of right dorsal ACC volume covarying for total GM change was still significant ( $p < .009$ ) and approached traditional thresholds of significance when covarying for change in cortical GM only ( $p < .079$ ). While there was a significant association between change in BMI and cortical GM during hospitalization, a linear regression analysis of the effect of change in BMI on right dorsal ACC volume controlling for change in cortical GM, revealed no significant association ( $F = 1.3$ ,  $p < .275$ ). The group that sustained remission was older ( $35.2 \pm 7.30$  years) than those who relapsed within the first year ( $21.7 \pm 7.92$ ;  $p < .05$ ). Otherwise, no significant demographic differences were found between outcome groups—including gender, BMI on admission and discharge, lowest lifetime BMI, comorbid depression, number of previous hospitalizations, duration of illness, and age of first hospitalization—even when these were used as continuous variables in a linear regression analysis.

## Conclusion

Although global brain atrophy occurs as a consequence of starvation in patients with active AN, atrophy in the right dorsal ACC appears to occur out of proportion to atrophy in the rest of the brain. Dorsal ACC volume sensitivity to starvation in active AN suggests that this region of the brain is affected by some component of starvation-related adaptation and/or specific nutritional deficiency. It is unknown whether these same findings would be found in normal controls that have lost weight unintentionally and not due to AN. There are case reports of people who have developed the syndrome of AN from unintentional weight loss.<sup>25</sup> Similarly, the Keys et al. study revealed that starvation induced cognitive and behavioral features of AN in people with no prior history of AN.<sup>34</sup> The

process by which malnutrition actually induces these changes may be from something as subtle as thiamine deficiency, which is known to occur in patients with AN.<sup>29</sup> The thiamine deficiency syndrome, known as Beriberi, has several symptoms that overlap with the syndrome of AN, such as loss of appetite, depression, irritability, poor mental concentration, and weight loss. Although the differential effects of alcohol toxicity and thiamine deficiency on the development of Wernicke's encephalopathy and Korsakoff syndrome are not completely resolved, thiamine deficiency without alcohol use is known to affect a number of brain regions including the ACC.<sup>28</sup> There are several case reports of Wernicke's encephalopathy occurring in patients due to starvation alone.<sup>35-37</sup> Rapid institution of thiamine to prevent refeeding damage to the brain can prevent a permanent state of Korsakoff syndrome from occurring<sup>38,39</sup> and may be important for patients with AN hospitalized for weight restoration. If thiamine deficiency occurs in patients with AN and is related to brain abnormalities, not providing rapid replacement of thiamine during weight restoration may further affect brain structure and function.

Dorsal ACC activity has been implicated in the reward circuit for food intake<sup>22</sup> and is linked to several aspects of cognitive functioning<sup>26,27,40-43</sup> and motor activity.<sup>21</sup> Patients affected by starvation from active AN have decreased blood flow to the dorsal ACC.<sup>8-10</sup> Decreased dorsal ACC activity is associated with increased motor activity<sup>44</sup> and abnormal food intake behaviors in people without AN.<sup>45</sup> Since blood flow changes have been related to volume changes,<sup>46</sup> decreased volume in the right dorsal ACC may be related to an increased drive to exercise and decreased appetite. Food deprivation in rats given free access to a running wheel leads to increased motor activity to the extent that these animals will eventually run themselves to death.<sup>47</sup> Thus, many aspects of the active AN syndrome appear to be related to the pathophysiology of starvation-mediated effects on the right dorsal ACC. However, in a recent study by Muhlau et al.,<sup>11</sup> the dorsal ACC was the only region found to be smaller in recovered patients with AN compared to normal controls. While we found this same brain region to be much smaller in the weight-restricted patients with AN, this area normalized with full weight recovery in our sample. It is unknown what degree of weight loss or nutritional deficiency causes decreased right dorsal ACC volume. However, the results from this study suggest that there is no direct correlation between lower BMI and smaller right dorsal ACC volume on admission or between

changes in BMI and right dorsal ACC volume during hospitalization.

ACC involvement in the manifestation of psychiatric symptoms is well established.<sup>26,42,48</sup> The ACC appears to be a recent brain adaptation that is linked with cognitive and emotional processes unique to human beings. This suggestion is based on the fact that ACC volume is larger in humans and contains a unique class of spindle-shaped neurons found only in humans and to a lesser degree in the great apes.<sup>49</sup> These neurons within the ACC develop postnatally and their development is enhanced or diminished due to environmental factors. Global GM atrophy in AN has been related to increased cortisol levels<sup>3</sup> and this effect may be even more pronounced in the right dorsal ACC. Similarly, nutritional deficiencies in thiamine, also known to occur in patients with AN,<sup>29</sup> have been shown to affect the WM tracts between the mammillary bodies and ACC.<sup>50</sup> Thus, there may be a cumulative effect of nutritional deficiency, elevated cortisol levels and/or some other hormonal effect that is involved in GM atrophy specifically in the right dorsal ACC.

Decreased right dorsal ACC volume at intake was correlated to decreased PIQ and, more specifically, the subtest scores of block design and digit symbol coding. To our knowledge, this is the first brain region to be correlated to known cognitive deficits in active AN. PIQ deficits out of proportion to VIQ reductions are known to occur in active AN.<sup>13</sup> While a similar neuropsychological measure of the RBANS (i.e., line orientation) has been shown to improve after weight restoration in AN patients,<sup>25</sup> no follow-up PIQ or subtest data were available to assess the correlation of change in this brain region to change in PIQ. PIQ is considered a global measure of perceptual organization and conceptual reasoning, while block design and digit symbol coding are measures of nonverbal intelligence, and visual-motor speed and short-term visual memory, respectively. Multiple studies have found higher cognitive processes such as executive function to be under the domain of normal dorsal ACC function.<sup>26,27,40–43</sup> Dorsal ACC function also is involved specifically with conceptual reasoning tasks in humans<sup>41</sup> and perceptual organization in rats.<sup>51</sup> Identifying a neural correlate for cognitive deficits in the active phase of AN provides further evidence that hospitalized AN patients may have limited cognitive abilities to fully process psychotherapeutic principles and stop losing weight on their own.

Although not specifically assessed in this study, right dorsal ACC volume reduction and dysfunction also have been found in patients with high alexithy-

mia scores.<sup>52–54</sup> High alexithymia scores, which indicate impairment in one's ability to express emotion and know how one is feeling,<sup>55</sup> also have been reported in patients with AN,<sup>56</sup> and may be related to outcome.<sup>57</sup> Similarly, abnormal function and reduced volume in the dorsal ACC is also found in patients with OCD<sup>30</sup> and may be related to food and body image obsessions and compulsions in patients with AN. Patients with OCD and AN also have similar deficits in executive function tasks.<sup>58</sup> Although none of the patients in this study had a comorbid diagnosis of OCD, reduced right dorsal ACC volume reduction in patients with AN may help explain why obsessions and compulsions related to food and weight are known to increase as a function of decreasing weight in patients experiencing starvation with active AN.<sup>59</sup>

Right dorsal ACC volume normalized after weight restoration in patients with AN. However, weight restoration itself as measured by change in BMI was not significantly correlated to restoration of right dorsal ACC volume. This suggests that there are other factors involved in GM restoration that occur independently of simple weight restoration. These factors may involve brain changes from psychotherapy<sup>26</sup> or possibly a reduction of cortisol or something even simpler such as thiamine replacement. Alternatively, it may reflect the extent to which neuronal regeneration is impacted by the current energy balance such that re-growth is only possible once a positive energy state (more kcal consumed than burned) is achieved. For example, it may actually be that longer inpatient hospitalizations lead to larger gains in right dorsal ACC regeneration. However, we did not find a significant correlation between hospital length and change in right dorsal ACC volume restoration (controlling for change in total cortical GM).

While overall normalization of right dorsal ACC volume after the starvation episode of active AN was ameliorated, the degree of normalization in this region was related to outcome in that greater right dorsal ACC normalization predicted sustained remission at 1 year posthospitalization. This finding was unrelated to BMI or depression severity at admission and changes in these variables were not directly correlated to change in right dorsal ACC volume during hospitalization. While weight restoration also occurs during hospitalization, these results suggest that there are other unknown factors affecting this brain change. These other factors may be related to individual sociocultural or biological differences that affect response to psychotherapeutic processes or something as simple as

age of onset of first starvation episode or differences in nutritional deficiency upon admission. Although there are certainly other biological vulnerabilities underlying temperament and behavior that are related to developing AN, the syndrome of active AN may be due primarily to the many effects of starvation itself. Similarly, while global WM and GM atrophy is found in patients with AN, the specific effects of GM atrophy in the right dorsal ACC may explain some of the syndromal symptoms that are found in the starvation phase of active AN and their relationship to relapse vulnerability. Since the highest incidence of AN occurs during adolescence—a time when the ACC is still developing—the effects of starvation on this brain region may have long-term effects. Furthermore, with increasing pressure from insurance companies to discharge patients with AN before they are weight stabilized, inpatients may increasingly lack adequate time for the brain restoration that is needed to prevent rapid relapse and facilitate ultimate recovery from this often chronic illness.

Strengths of this study include the use of age and gender-matched and height-equivalent normal controls to evaluate brain region volume deficits associated with AN during active illness and after complete weight restoration. Additionally, intake neuropsychological measures were available to compare with the MRI findings in the AN patients suffering from starvation upon admission to the hospital. Limitations of this study include the fact that only a modest proportion (56%) of AN patients had outcome data available at 1 year posthospitalization to assess whether brain changes predicted relapse rates. Also, these findings represent a secondary analysis resulting in limited data available for analyses such as reliable family history, follow-up neuropsychological or clinical symptom scales, and treatment received during the 1-year posthospitalization period.

Larger controlled studies are needed to confirm these findings and assess whether full restoration of the right dorsal ACC volume is a requirement for full recovery from AN and if changes in right dorsal ACC volume are correlated to changes in block design and digit symbol coding of PIQ. It will also be important to further explore the types of nutritional deficiencies and/or biological responses that are related to focal GM reduction in the right dorsal ACC. Finally, it will be important to assess whether developmental delays in the formation of the right dorsal ACC during adolescence and early adulthood remain even after weight restoration compared to normal age-matched controls.

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