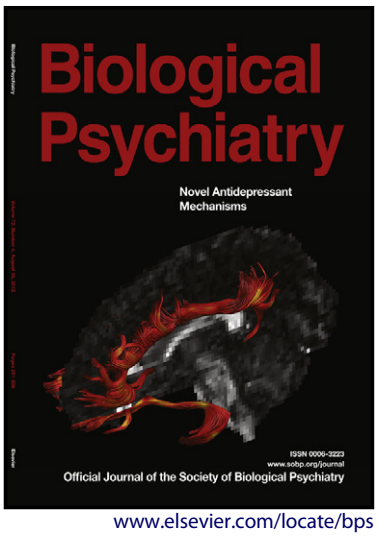

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Global cortical thinning in acute anorexia nervosa normalizes following long-term weight restoration

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Short title: Cortical Thickness in Anorexia Nervosa

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Abstract

Background: Anorexia nervosa (AN) is a serious eating disorder characterized by self-starvation, extreme weight loss and alterations in brain structure. Structural magnetic resonance imaging (sMRI) studies have documented brain volume reductions in acute AN, but it is unclear whether they are 1) regionally-specific or 2) reversible following weight restoration. Here, we measured cortical thickness (CT) for the first time in AN.

Methods: sMRI data was acquired from adolescent and young adult female patients with acute AN (acAN; *n* = 40), recovered patients following long-term weight restoration (recAN; *n* = 34) and an equal number of age-matched healthy controls. Group differences in CT were tested with well-validated procedures implemented in FreeSurfer. The mediating role of clinical variables including body-mass-index and “drive for thinness” were explored. For completeness, we also used FreeSurfer’s subcortical segmentation stream to test group differences in volumes of select gray matter regions of interest (ROIs).

Results: Vertex-wise analyses revealed significant thinning of over 85% of the cortical surface in acAN and normalization in recAN, although normal age-related trajectories were absent in the disorder. This pattern of results was largely mirrored in subcortical volumes. We also observed a strong negative correlation between CT and “drive for thinness” in extrastriate regions involved in body perception.

Conclusions: Structural brain anomalies in AN as expressed in CT and subcortical volume are primarily the consequence of malnutrition and unlikely to reflect premorbid trait markers or permanent “scars”, but longitudinal data are needed.

Introduction

Anorexia nervosa (AN) is a life-threatening eating disorder that usually begins in adolescence in females and is characterized by an intense fear of weight gain, despite severe emaciation, and a perpetual drive for thinness, typically by self-starvation. To elucidate the underlying neurobiology, researchers have long searched for clues in brain structure (1, 2). In acute AN (acAN), reduction of brain mass is often readily visible in individual patients' brain scans and several structural magnetic resonance imaging (sMRI) studies have documented decreases in both gray- and white matter volume (3, 4, 5, 6, 7, 8, 9,10,11). However, recent studies using voxel-based morphometry (VBM) have emphasized regionally-specific differences (3, 7, 8, 9, 13, 14), including volume increases (15, 16,17) and their possible link to AN-specific clinical characteristics (18, 19, 20, 21). Furthermore, while a number of studies have shown differences in acAN to normalize in weight-recovered AN patients (recAN; 7, 22, 23, 24), others have reported persistence of structural alterations (11, 12, 13, 25). Thus, important questions remain regarding 1) the regional specificity of structural brain anomalies in AN and 2) whether they merely reflect state-related consequences of malnourishment or constitute disorder-defining traits (26, 27).

Several factors may contribute to the lack of consistency in the sMRI literature on AN. First, study samples have generally been small ($n < 20$) and heterogeneous, sometimes also including individuals with bulimia nervosa. Also, group inclusion criteria have not been uniformly defined according to diagnostic standards across studies and definitions of "weight recovered" have varied. More critically, some studies have

included patients receiving psychoactive medications which may have a considerable effect on brain morphometry (28). Particularly relevant for the current study, the results of VBM methods can be highly dependent on registration strategies and normalization templates (29, 30). In attempt to gain new insight, the current study employed an alternative approach for the first time in AN, surface-based morphometry (SBM), to measure cortical thickness (CT) in a comparatively large and medication-free sample of young acAN and recAN patients.

Whereas VBM provides generic measures of brain volume inferred indirectly from matter density, SBM utilizes geometric models of the cortical surface to partition its constituent surface area and CT components, which are thought to constitute genetically independent properties (31, 32, 33). Surface-based analysis, especially in the case of CT, has therefore been proposed to constitute a more biologically-informative measure with particular sensitivity to structural changes both in health (34, 35) and disease (36, 37, 38, 39, 40). CT has the added advantage of being a direct measure of gray matter expressed in mm.

Here we use a well-validated, automated surface-based procedure to estimate CT (FreeSurfer; 41, 42, 43, 44*)* in adolescent and young acAN and recAN women and test for group differences relative to age-matched healthy controls (HC). We conducted both vertex-wise analyses of the entire cortical surface and confirmatory region of interest (ROI) comparisons based on the Desikan-Killiany atlas (45). Additionally, we exploited FreeSurfer's subcortical processing stream (46, 47) to explore whether group differences and similarities were also evident in the volumes of select gray matter ROIs.

Methods

Participants

The current sample consisted of 143 female volunteers: 40 acute patients diagnosed with according to DSM-IV criteria (acAN; 12 - 23 years old), 34 recovered former AN patients (recAN; 17 - 28 years old) and 69 healthy control participants (HC; 12 – 28 years old). The study was approved by the Institutional Review Board of the Technische Universität Dresden and all participants gave written informed consent (or their legal guardians, if under 18 years old).

acAN patients were admitted to eating disorder clinics at the departments of Child and Adolesc ent Psychiatry or Psychosomatic Medicine at the Universitätsklinikum Carl Gustav Carus in Dresden, Germany and underwent MRI within 96 hours after beginning nutritional rehabilitation programs. Diagnosis was supported using the Structured Interview for Anorexia and Bulimia Nervosa (SIAB-EX; 48) which requires body mass index (BMI) < 10^{th} age percentile (if younger than 15.5 years) and < 17.5 (if older than 15.5 years). To be considered “recovered”, recAN subjects had to 1) maintain a body-mass-index (BMI; kg/m^2) > 18.5 (if older than 18 years) or > 10^{th} age percentile (if younger than 18 years) 2) menstruate and 3) have not binged, purged, or engaged in restrictive eating patterns for at least six months prior to the study. Further details regarding the AN samples are provided in Table 1 and Supplement 1. HCs were recruited through advertisement among middle school, high school and university students. To be included in the HC group, participants had to be of normal weight and eumenorrhoeic.

Information pertinent to exclusion criteria and possible confounding variables, including menstrual cycle and use of contraceptive medication, were obtained from all participants using the SIAB-EX interview (48), supplemented by our own semi-structured interview. HC participants were excluded if they had any history of psychiatric illness, a lifetime BMI below the 10th age percentile (if younger than 18 years)/BMI below 18.5 kg/m^2 (if older than 18 years), or were currently obese (BMI over 97th age percentile if younger than 18 years; BMI over 30 kg/m^2 if older than 18 years). Participants of all groups were excluded if they had a history of any of the following diagnoses: organic brain syndrome, schizophrenia, substance dependence, psychosis NOS, bipolar disorder, bulimia nervosa or binge-eating disorder. Further exclusion criteria for all participants were intelligence quotient (IQ) < 85, psychotropic medication within 4 weeks prior to the study, current substance abuse, inflammatory, neurologic or metabolic illness, chronic medical or neurological illness that could affect appetite, eating behavior, or body weight, clinically relevant anemia, pregnancy or breast feeding.

Clinical Measures

Eating disorder-specific psychopathology was assessed with the German version of the Eating Disorders Inventory (EDI-2, 49). Depressive symptoms were explored using the German version of the Beck Depression Inventory (50). General levels of psychopathology were gauged with the global severity index of the revised Symptom Checklist 90 (SCL-90-R; 51). IQ was estimated with a short version of the German adaption of the Wechsler Adult Intelligence Scale (WIE; 52) or a short version of the German adaption of the Wechsler Intelligence Scale for Children (HAWIK; 53) for

participants aged 15 years or younger. Demographic and clinical study data were collected and managed using a secure, web-based electronic data capture tool [Research Electronic Data Capture (REDCap); 54].

MRI Acquisition and Processing

All participants underwent MRI scanning between 8 and 9 a.m. following an overnight fast. High resolution 3D T1-weighted structural scans were acquired on a 3.0T scanner (Magnetom Trio, Siemens, Erlangen, Germany) using a rapid acquisition gradient echo (MP-RAGE) sequence with the following parameters: 176 sagittal slices (1 mm thickness, no gap), TR = 1900 ms; TE = 2.26 ms; flip angle = 9˚; voxel size = 1.0 × 1.0× 1.0 mm^3, FoV = 256 × 224 mm^2, bandwidth of 200 Hz/pixel). The data were registered, motion corrected, realigned, averaged and analyzed in an automated manner with the FreeSurfer software suite (http://surfer.nmr.mgh.harvard.edu, version 5.1.0), a well-documented program for cortical surface reconstruction and volumetric segmentation (41, 42, 43, 44, 45, 46, 47). In the current study, we focused on estimations of CT and volumes of the following subcortical regions of interest (ROIs): accumbens, amygdala, caudate nucleus, cerebellum, hippocampus, pallidum, putamen, and thalamus. For details on the implementation of the surface-based and subcortical processing streams according to standard FreeSurfer procedures, see Supplement 1.

Statistical Analyses

Two independent comparisons of age-matched groups were conducted: 1) acAN vs. HC (*n* = 40 in each group) and 2) recAN vs. HC (*n* = 34 in each group). Patients

were individually age-matched to HCs by means of an automated search algorithm for optimal pairs (55) resulting in a maximum difference of 1 year between individual within each pair. This procedure resulted in 9 HCs being included as control subjects for comparisons with both the acAN and recAN groups. The data of 4 HCs for whom no optimal age-match was found or who did not fulfill inclusion criteria were excluded from further analysis.

Vertex-wise cortex-wide analyses of CT were executed with FreeSurfer. To this end, CT data were first mapped to an average template coordinate system using surface-based registration methods and smoothed using a Gaussian kernel with a full-width-at-half-maximum (FWHM) of 10 mm. In order to generate statistical difference maps, we computed general linear models (GLM) focusing on group differences in CT in two separate analyses (both including age as covariate): 1) acAN vs. HC and 2) recAN vs. HC (separately for each hemisphere). The results of these independent tests of age-matched groups were verified against results of an ANCOVA (including age as covariate) with a three-level group factor (acAN, recAN, HC; more details in Supplement 1). We followed-up on group differences revealed by the acAN vs. HC comparison by fitting two additional GLMs incorporating z-standardized 1) age-adjusted BMI standard deviation scores [BMI-SDS; calculated according to Cole (56) and German population reference data (57,58)] and 2) “drive for thinness” values (as gauged by the EDI-2 subscale) as main predictor variables. Based on significant results in the latter analysis, we conducted an analog analysis in the recAN group. For the purpose of these analyses, missing “drive for thinness” values for 2 participants were substituted with group mean values (i.e. z = 0). Additional exploratory analyses of age effects and

duration of recovery in recAN are described in Supplement 1. All vertex-wise CT results were corrected for multiple comparisons using a Monte-Carlo simulation (10,000 repetitions) with an initial vertex-wise threshold of $p < .05$ to test the likelihood of a spatially contiguous area of association (cluster) occurring by chance (cluster-wise probability; *CWP*).

To validate the findings of the vertex-wise analyses, we extracted averaged CT measurements for each subject from each of the 34 labels of the Desikan-Killiany cortical atlas (45) in each hemisphere and empirically-defined ROIs. Due to a lack of hemispheric specificity in the primary vertex-wise results, the label-wise CT measurements were then averaged across hemispheres. Finally, these values were entered into two separate MANCOVAs [one for each age-matched group comparison: 1) acAN vs. HC and 2) recAN vs. HC] controlling for the covariate of age. Additional analyses of the label-wise CT data were conducted to inspect the potentially mediating factors of psychiatric comorbidity and residual symptoms in recAN (Supplement 1).

Similarly, we explored group differences in subcortical volume by averaging the mean volume of each of the 8 ROIs in each hemisphere and subjecting the resulting values to MANCOVAs covarying for age and total intracranial volume (ICV). Given the number of anatomical regions considered in these analyses and the label-wise analyses of CT described above, reported probability values were Bonferroni-adjusted for multiple comparisons.

Results

Demographic and clinical characteristics are summarized in Table 1. Neither the acAN patients nor the recAN participants differed in age or IQ relative to their HC counterparts. In line with group inclusion criteria, BMI was significantly lower in the acAN group relative to the corresponding HCs, but in normal range in the recAN group and did not differ from that of HCs. Overall, despite weight normalization and generally improved psychopathology in the recAN group (as gauged by the global severity index of the SCL-90R), former patients showed some residual eating disorder specific- and affective symptoms (as assessed by EDI-2 and BDI-II, respectively).

Global cortical thinning in acute anorexia nervosa is normalized following long-term weight restoration

A vertex-wise search for differences in CT between the acAN and HC groups revealed widespread thinning in the acute patients (Figure 1; Supplementary Figure S1). Gray matter thickness was reduced in acAN in a total of 86% of the cortical surface (91% in the left hemisphere, 82% in the right hemisphere) with only two regions (based on the Desikan-Killiany atlas; 45) showing no group differences: the bilateral temporal pole and entorhinal cortex. These results were confirmed by label-wise analysis of the CT data (Supplementary Table S1) and were not mediated by comorbidity (Supplement 1).

Demonstrating the reversibility of cortical thinning following weight normalization, an analog vertex-wise analysis of CT measured in the recAN and HC groups revealed no regional differences (*CWP* < .05). Label-wise analysis of the CT data from the recAN

vs. matched HC sample confirmed the lack of any group differences in 33 out of 34 regions (Supplementary Table S1).

Interestingly, however, exploratory analyses of age-related effects suggested that the normal neurodevelopmental trajectory of CT across adolescence and young adulthood is interrupted in AN (Supplementary Figure S2). Specifically, while expected patterns of cortical thinning as a function of increasing age (35, 59, 60, 61) were readily observable in HCs, they were absent in AN patients.

"Drive for thinness" in acute anorexia nervosa correlates with cortical thinning in lateral occipitotemporal cortex

Given the striking reduction of CT in acAN, we asked whether the degree of thinning might be explained either by the degree of bodily emaciation or AN-specific psychopathology. To this end, we conducted additional vertex-wise analyses to explore potential relationships between CT and individual levels of 1) BMI-SDS and 2) "drive for thinness" in the acAN patients (Methods). We found no relationships with BMI-SDS, suggesting that cortical thinning in acAN might not be strongly dependent on the severity of weight loss. However, strong negative correlations between CT and individual levels of "drive for thinness" emerged in two adjacent regions of right lateral occipitotemporal cortex (Figure 2) implicated in a range of higher-level visual functions (62) including representation of the body (63,64). Nonetheless, this relationship is not likely to reflect a biological trait marker in AN, because a follow-up vertex-wise analysis in the recAN group revealed no such correlation.

Substantial subcortical volume reduction in acute anorexia nervosa normalizes with long-term weight restoration

Finally, we explored whether group differences were also expressed in measurements of volume in select subcortical gray matter ROIs (Methods). Volume was notably reduced in acAN patients relative to HCs in the nucleus accumbens, amygdala, cerebellum, hippocampus, putamen, and thalamus (Figure 3; Supplementary Table S2). Normal volume in acAN was observed only in the caudate and pallidum. In contrast, similar to the pattern of normalization revealed in the CT estimations, volume was no longer clearly reduced in recAN in the accumbens, amygdala, hippocampus or putamen (Supplementary Table S2).

Discussion

In this first study to investigate CT in AN, we found widespread thinning of the cortical surface in adolescent and young women in acute illness (acAN) relative to age-matched HC participants. Using identical analysis procedures, no differences were detected in former patients (recAN) relative to HCs – that is, CT normalized following long-term weight rehabilitation. This pattern of globally reduced CT in acAN and normalization in recAN was independent of psychiatric comorbidity and largely mirrored subcortical gray matter volume. However, suggesting that normalization of CT might not be entirely complete, we found evidence that normal neurodevelopmental patterns of cortical thinning across adolescence into young adulthood (35,59,60,61) are disrupted in AN. Together, these findings acquired in comparatively large and medication-free samples deliver novel support for the notion that morphological brain alterations in AN are primarily a consequence of malnutrition associated with self-starvation and

challenge the idea that they constitute premorbid trait markers or permanent scars. Critically, however, the relative normalization observed here in CT and subcortical volume should not be taken to imply that other aspects of brain structure, including grey matter density and white matter volume, are necessarily left unscathed by the illness.

Recent qualitative (21) and quantitative reviews of structural neuroimaging in AN (19,20) concluded that despite the well-established finding of reduced brain mass in acAN, it remains equivocal as to whether such shrinkage (as previously measured in cortical volume) is 1) regionally-specific and 2) to what extent it can be reversed by weight normalization. Given that gray matter volume is a mixed measure comprised of both CT and surface area and these are independent (31,32,33), it would be overly simplistic to draw direct comparisons of the current findings with previous grey matter density or volumetric studies of AN. Nonetheless, they deliver novel insight into brain structure in AN. First, they demonstrate that gray matter reduction is spatially generalized in acAN with only few areas left intact. In our estimations of CT, only relatively small (bilateral) regions of entorhinal cortex and the temporal pole were spared from otherwise global “atrophy”. Not only the spatial expanse, but the magnitude of cortical thinning in acAN is noteworthy. Effect sizes for acAN vs. HC group differences were on average in the large range (Cohen’s *d* = -.87; Supplementary Table S1); considerably greater than those reported in other psychiatric populations with widespread thinning such as schizophrenia (40) and comparable to those found in Alzheimer’s disease (65). Similarly, effect sizes for group differences in subcortical volume were also relatively large (Cohen’s *d* = -.68; Supplementary Table S2) and only

the globus pallidus and caudate remained normal in acAN. It is interesting to note that despite this massive reduction in gray matter, adolescent AN patients typically have little or no cognitive impairment (66,67,68,69). Second, our findings provide new evidence that reduction of gray matter in acAN is largely reversible in recovery. We found no indication of differences between recAN participants and age-matched HCs. Follow-up analyses revealed no correlations with the length of recovery, suggesting that normalization may occur relatively quickly over the course of weight restoration. Despite differences in technology, this particular finding is in line with previous reports of rapid changes in gray matter volume with weight changes in AN (70) and increased volume following short-term weight restoration (11,12,22). Nonetheless, longitudinal data are needed to support this speculation.

Our findings lend new support to previous claims of the reversibility of reduced grey matter in acAN (24,71), but the precise mechanism(s) underlying the “atrophy” and relative normalization in recAN remain a mystery. The topographically unspecific nature of cortical thinning and subcortical volume “loss” in acAN and seemingly rapid normalization in recAN are suggestive of pseudoatrophy – that is, no actual apoptotic neurodegeneration. This interpretation is supported by previous findings of normal levels of neural and glial damage markers in AN (72). One possibility worthy of future investigation is that reduced CT in acAN may reflect changes in the lipid structure of the neuronal cell wall and myelin resulting from diminished fat consumption (73). Although similar effects of reduction and normalization of brain mass might be expected from dehydration and rehydration (74,75), respectively, we hold such an explanation to be

unlikely based on the clinical observation that acAN patients often attempt to manipulate weight measurements by increasing fluid intake. Furthermore, urinalysis prior to scanning indicated normal hydration (Supplement I). Protein energy malnutrition is also an improbable cause, as serum protein values are surprisingly normal in acAN (76) relative to other forms of severe emaciation (77). Given the macroscopic nature of the CT and volumetric measures employed here, detailed discussion of potential microstructural underpinnings of our observations is difficult. Nonetheless, it is tempting to speculate that AN could result in changes in the size of neurons, glia or in metabolic processes (19). Indeed, neurohistological evidence exists suggestive of AN-related alterations in dendritic spine morphology and density (78,79) and a recent MR spectroscopy study found increased concentrations of potentially excitotoxic metabolites (glutamate) selectively in gray matter (80).

Insight into the mechanisms underlying the brain structure alterations observed here might be gained by considering the few regions that were left unaffected (entorhinal cortex/temporal pole, pallidum, caudate). Given that the entorhinal cortex and temporal pole are among the thickest regions of the cortical surface (47), one might speculate that they are protected from the otherwise unspecific pseudoatrophy in acAN. Based on the finding that IQ is often elevated in AN (62) and IQ correlates with CT (81,82), an alternative hypothesis might be that these regions are relatively thick in premorbid AN. Given the known role of the striatum as a central node in the brain reward system (83, 84) and the hypothesis that AN is characterized by aberrant reward-related processing (16,26,85,86,87), it can be speculated, paradoxically, that intact volume of the globus

pallidus and caudate might contribute to AN-specific psychopathology. Although we found no evidence for such relationships, a recent VBM study (17) reported caudate volume to be associated with reward sensitivity in recAN.

Whereas the majority of previous sMRI studies have reported global reductions in brain mass in AN (19), a number of recent studies have emphasized regional group differences. For example, several studies have noted volume reductions in anterior cingulate cortex (7,8,9,13,15,16) and a recent meta-analysis highlighted decreased volume in reward-related regions of the basal ganglia and in somatosensory cortex (20). On the whole, however, regional group differences have been inconsistent in the sMRI literature on AN (18,19,22), with some studies finding volume increases (15,16,17). Frank et al. (17), for example, found orbitofrontal volumes to be elevated both in acAN and recAN. Discrepancies between previous reports of regionally-specific differences and the current findings may be explained by a range of methodological factors, including but not limited to differences in analysis strategies (e.g. SBM vs. VBM), sample sizes, group inclusion criteria, and nutritional state of participants. For example, we only included acAN patients that underwent MRI within 96 hours after beginning nutritional rehabilitation to capture the natural disease state, while some studies have scanned patients after 1-2 weeks of treatment in attempt to avoid effects of acute starvation. While both methods certainly have their advantages, we are confident that our results of regionally unspecific group differences obtained in a large, rigorously matched and unmedicated sample using are robust.

A number of previous sMRI studies have investigated relationships between regional structural anomalies in AN and clinical measures such as BMI (3,13), illness duration (3), and "drive for thinness" in recAN (9), but findings have also been inconsistent (18,19). Although we found no evidence that cortical thinning or subcortical volume reduction in acAN was related to the degree of bodily emaciation (as gauged by age-corrected BMI), we did uncover a relationship between CT and "drive for thinness" in a broad region of the right lateral occipitotemporal cortex. The significance of this correlation is highlighted by the overlap with regions specialized in visual processing of human bodies, the so-called extrastriate and fusiform body areas (EBA and FBA, respectively; 59,60), and the extreme body image distortion in acAN (88). Furthermore, EBA volume has been reported to be particularly reduced in acAN (14) and to show impaired functional connectivity with the FBA (89). Based on these convergent findings, we speculate that structural (and functional) anomalies in body-selective regions of visual cortex may contribute to the maintenance of body image distortion in AN. Caution should be used in interpreting this correlation as a causal relationship, however, as exemplified by the fact that it was not evident in recAN in the current study, despite significant residual "drive for thinness".

In sum, our findings of cortical thinning and decreased subcortical volume in acAN and relative normalization in recAN bring needed clarity to the sMRI literature on AN. We speculate that these alterations are largely state-dependent and unlikely to reflect underlying biological trait markers of the disorder. The magnitude of some regional anomalies such as those observed here in lateral occipitotemporal cortex and previous studies (14) may contribute to the maintenance of AN-related psychopathology.

By carefully building age-matched AN-HC cohorts and covarying for age, we established that these main findings were independent of potentially confounding age-related processes. By specifically exploring age-related effects, we uncovered evidence that AN might disrupt the normal developmental trajectory of CT (59,60,61). Thus, while CT normalizes following long-term weight restoration in AN as gauged by average values, longitudinal observation is needed to conclusively determine whether normalization is truly complete. It should also be emphasized that although our findings send an overall positive message to patients and clinicians alike, the employed technology may not capture certain brain changes associated with AN that may not be reversible. Nonetheless, we believe the current results exemplify the potential neuroscience research has in guiding treatment for AN (90) and encourage therapists to integrate our findings of the reversibility of brain tissue "loss" in psychoeducational interventions that foster a proactive sense of agency (91).

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Tables and Figure Legends

Table 1. Demographic Variables and Clinical Measures of Sample I (acAN*/HC) and Sample II (recAN/HC)**

	N	Sample		Analyses		
	(acAN/HC) *(recAN/HC)*	acAN *recAN*	HC_{acAN} HC_{recAN}	*T*	*df*	*P*
Age (years)	(40/40) *(34/34)*	15.9±2.5 *22.7±2.9*	16.2±2.9 *22.3±2.8*	.5 *.7*	78 *66*	.7 *.5*
IQ	(35/39) *(34/33)*	112.1±11.6 *108.7±9.7*	111.3±10.3 *110.6±8.8*	.3 *.9*	72 *65*	.9 *.4*
BMI (kg/m^2)	(40/40) *(34/34)*	14.8±1.3 *21.0±1.9*	20.8±2.7 *21.6±2.1*	11.6 *1.2*	78 *66*	<.001 *.2*
minimal lifetime BMI	(38/36) *(34/33)*	14.5±1.3 *14.4±1.8*	19.8±2.3 *20.1±2.1*	12.3 *10.3*	75 *65*	<.001 *<.001*
BDI-II	(38/36) *(34/33)*	19.1 ± 11.5 *8.2 ± 8.1*	5.6 ± 5.6 *3.3 ± 4.3*	6.4 *3.1*	72 *65*	<.001 *.003*
SCL-90-R (global severity index)	(35/37) *(31/32)*	.4±.4 *.1±.2*	.1±.2 *.1±.3*	3.7 *.9*	70 *61*	<.001 *.4*
EDI-2 (total score)	(38/40) *(28/30)*	195.1±48.4 *159.2±45.6*	141.4±26.7 *133.7±26.1*	6.1 *2.6*	76 *56*	<.001 *<.01*
(drive for thinness)	(38/40) *(32/34)*	27.0±9.6 *20.4±9.4*	14.1±6.6 *12.7±5.0*	6.9 *4.2*	76 *64*	<.001 *<.001*
(body dissatisfaction)	(38/40) *(32/33)*	33.7±10.9 *30.4±11.5*	24.2±9.3 *23.2±7.5*	4.2 *2.9*	76 *63*	<.001 *.005*
(bulimia)	(38/40) *(33/33)*	10.9±5.1 *9.7±2.9*	10.3±3.1 *9.7±3.2*	.3 *1.0*	76 *64*	.8 *1.0*

Mean values ± SD for each variable and sample are shown. Raw BMI and minimal lifetime BMI scores are displayed, but statistical comparisons are based on BMI-SDS values (Methods) to ensure comparability by age. BDI-2, Beck Depression Inventory, version 2; SCL-90-R, Symptom Checklist-90-Revised. EDI-2, Eating Disorder Inventory, version 2; Group differences were tested using independent samples t-tests with SPSS 21.0.
*The mean age of illness onset in the acAN group was 14.4 ± 1.9 (SD) years and the mean duration of illness was 18 ± 26 months. 36 acAN patients (90%) were of the restrictive subtype and 4 (10%) were binge/purge. 4 acAN patients were diagnosed with comorbid axis I psychiatric disorders (3 depression, 1 social phobia, 1 obsessive-compulsive disorder) and 1 patient received an axis II diagnosis: avoidant personality disorder (see Supplement 1 for details regarding diagnostic procedures).
**The mean duration since weight normalization in the recAN group was 53.3 ± 34 (SD) months. 27 (79.5%) recAN former patients were of the restrictive subtype during illness and 7 (20.5%) were binge/purge. 9 recAN participants (26.5%) were diagnosed with comorbid axis I psychiatric conditions (8 depression, 1 obsessive-compulsive disorder; see Supplement 1 for details regarding diagnostic procedures).
***Smoking status: 8 participants reported smoking 1 or more cigarettes daily in the last 6 weeks (7 recAN, 1 HC; mean 6.6 cigarettes daily). An additional 5 participants reported having smoked 1 or more cigarettes daily in the past, but being abstinent in the last 6 weeks (3 recAN, 2 HC; mean 5.6 cigarettes daily).

Figure 1. Vertex- and label-wise analyses of CT in acute (acAN) and recovered (recAN) anorexia nervosa patients relative to healthy controls (HC). ***A***, Cluster-wise probability corrected (*CWP* < 0.05) statistical map displaying regions of reduced CT in acAN patients relative to age-matched HCs as revealed by vertex-wise analysis is plotted on the inflated surface of the standard average subject. LH, left hemisphere; RH, right hemisphere. Colored outlines correspond to anatomical labels of the Desikan-Killiany atlas (45). An analog analysis of CT in recAN relative to age-matched HCs revealed no group differences. ***B***, Grouped bar graphs show mean CT measurements (mm ± SEM) for each AN group and the pairwise matched HCs (acAN left, recAN right) extracted from selected anatomical labels. Exact values displayed are age-adjusted means obtained with MANCOVAs which revealed a main effect of the group factor for the acAN vs. HC analysis ($F_{34,44}$ = 2.95; p < .001), but not for the recAN vs. HC test ($F_{34,34}$ = 1.67; p = .073 ;see Methods and Supplementary Table S1 for more details). * p < 0.05, ** p < 0.01, *** p < 0.001; Bonferroni corrected.

Figure 2. Correlation between “drive for thinness” and CT in right lateral occipitotemporal cortex in acAN. ***A***, Cluster-wise probability corrected (*CWP* < .05) statistical map

displaying two independent clusters (superior cluster maximum: x = 39, y = -62, z = 10, 1038 mm^2, *CWP* = .01; inferior cluster maximum: x = 47, y = -70, z = -14, 1084 mm^2, *CWP* = .007) in which CT correlated negatively with "drive for thinness" in acAN as revealed by vertex-wise analysis is plotted on the inflated surface (tilted 20°) of the standard average subject. An analog analysis in recAN revealed no significant correlations. ***B***, Mean CT (mm ± SEM) for each AN group and the respective matched HCs (acAN left, recAN right) averaged across the two clusters is shown in panel *A*. Univariate ANCOVAs covarying for age confirmed reduced thickness in these regions in the acAN group ($F_{(2,79)}$ = 18.4; $p < 0.001$), but normal values in recAN ($F_{(2,67)}$ = 1.4; p = .2). *** < 0.001 ***C***, Correlation between individual "drive for thinness" values (z-normalized) and CT measurements averaged across the clusters revealed by the vertex-wise analysis. Each point corresponds to the data from one participant.

Figure 3. Analyses of subcortical volume in acAN and recAN relative to HCs. ***A***, Single-subject results of FreeSurfer's automated subcortical segmentation as exemplified in an acAN participant whose age and BMI (age = 15.9 years; BMI = 15.5) both approximated the group means (see Table 1) and her individually age-matched HC (age = 15.6; BMI = 19.3) are plotted on selected slices of each participants' T1-weighted MRI volume. ***B***, Grouped bar graphs show mean volume measurements (mm^3 ± SEM) for each AN group and the pairwise matched HCs (acAN left, recAN right) extracted from each of the 8 subcortical ROIs. Exact values displayed are adjusted means obtained with MANCOVAs covarying for age and ICV which revealed a main effect of the group factor

for the acAN vs. HC analysis ($F_{8,69}$ = 6.98; p < .001), but not for the recAN vs. HC test ($F_{8,57}$ = 1.32; p = .25; see Methods and Supplementary Table S2 for more details). * p < 0.05, ** p < 0.01, *** p < 0.001; Bonferroni corrected.

Fig 1

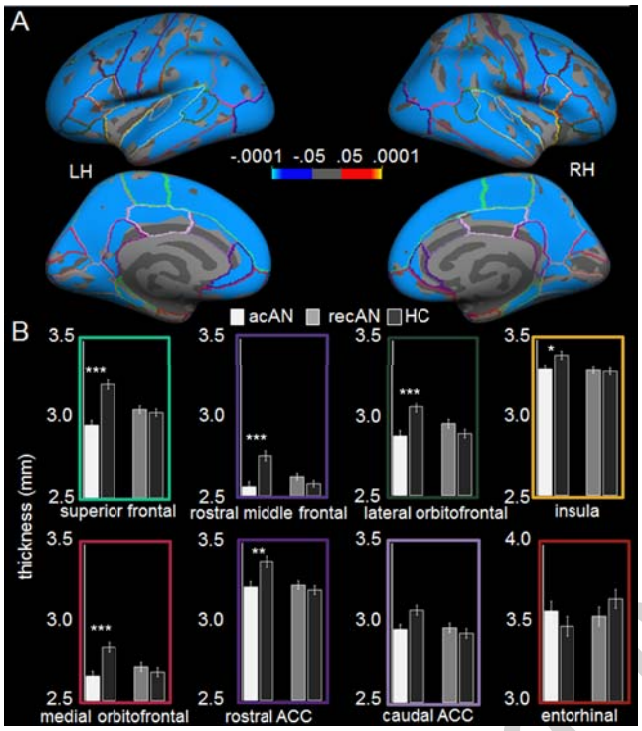

Fig 2

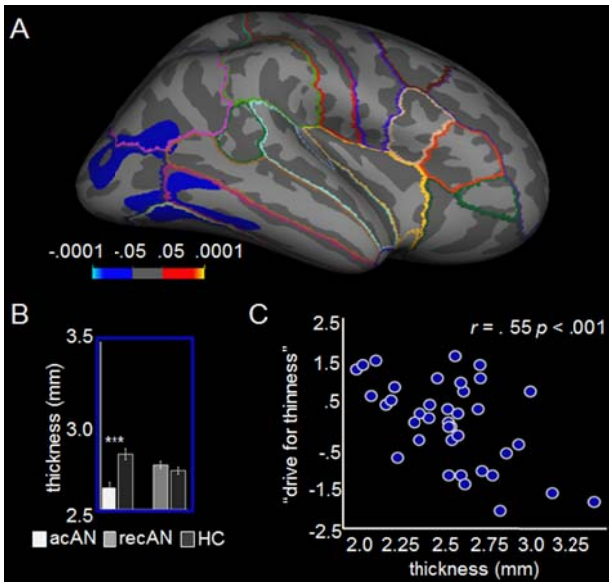

Fig 3