Title: Brain Structure in Acutely Underweight and Partially Weight-Restored Individuals with Anorexia Nervosa - A Coordinated Analysis by the ENIGMA Eating Disorders Working Group

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Abstract

Background

The pattern of structural brain abnormalities in anorexia nervosa (AN) is still not well understood. While several studies report substantial deficits in grey matter volume and cortical thickness in acutely underweight patients, others find no differences, or even increases in patients compared with healthy controls. Recent weight regain before scanning may explain some of this heterogeneity. To clarify the extent, magnitude, and dependencies of grey matter changes in AN, we conducted a prospective, coordinated meta-analysis of multicenter neuroimaging data.

Methods

We analyzed T_1-weighted structural MRI scans assessed with standardized methods from 685 female AN patients and 963 female healthy controls across 22 sites worldwide. In addition to a case-control comparison, we conducted a three-group analysis comparing healthy controls to acutely underweight AN patients (n = 466), and to those in treatment and partially weight-restored (n = 251).

Results

In AN, reductions in cortical thickness, subcortical volumes, and, to a lesser extent, cortical surface area, were sizable (Cohen's *d* up to 0.95), widespread and co-localized with hub regions. Highlighting the effects of undernutrition, these deficits associated with lower BMI in the AN sample and were less pronounced in partially weight-restored patients.

Conclusion

The effect sizes observed for cortical thickness deficits in acute AN are the largest of any psychiatric disorder investigated in the ENIGMA consortium to date. These results confirm the

importance of considering weight loss and renutrition in biomedical research on AN and underscore the importance of treatment engagement to prevent potentially long-lasting structural brain changes in this population.

Introduction

Anorexia nervosa (AN) is an eating disorder characterized by low weight, severe restrictive eating, and a high mortality due to starvation-related complications (1). Although the pathomechanisms are unknown, biological underpinnings are widely recognized (2).
In acutely underweight patients (i.e., patients at the very beginning of weight restoration treatment), sulcal widening and grey matter (GM) thinning are sometimes visible on computed tomography or magnetic resonance images (MRI). However, the spatial distribution and extent (and even direction, see e.g. (3,4)) of alterations varies across studies, complicating efforts to identify the mechanisms underlying MRI-observed structural brain changes in AN (5,6). Possible reasons for these heterogeneous findings include different analytic approaches (e.g. voxel- versus vertex-based morphometry), small samples (typically between 20 to 40 individuals per group) and clinical heterogeneity between studies (6). Recent work suggests that weight gain is closely linked to normalization of GM reductions, and that adolescents show normalized brain structure after partial weight restoration (7,8). Therefore, GM changes in AN may reflect nutritional status (as opposed to trait-level alteration) and time (i.e., weight gain) between initiating weight-gain focused treatment and MRI scanning may substantially affect the extent and magnitude of structural brain changes.

To characterize GM differences several metrics from T_1-weighted MRI scans can be derived, including regional cortical thickness (CT), cortical (SA) and volume. Although CT and SA were reported to have opposing underlying genetic factors and show different developmental trajectories (9,10), only three studies have investigated SA in AN (4,11,12). Recent large-scale coordinated research efforts have facilitated investigations of structural brain abnormalities with such metrics in multiple psychiatric disorders (13). Through these international collaborations, researchers have carried out prospective meta-analyses — i.e. analyses that were designed a priori using predefined study selection criteria, hypotheses, standardized data and analysis protocols and did not rely on

published findings, hence reducing publication bias (14). By including data collected from several research sites without the need to share individual-level data, these efforts can generate more generalizable and rigorous findings compared to a single large study and enable transdiagnostic comparisons. For example, combining data from thousands of patients with schizophrenia and unaffected controls, two recent prospective coordinated meta-analyses reported small deficits in subcortical volumes, widespread (small to moderate) cortical thinning and equally widespread, although weaker reductions in SA (15,16). Similar, but often smaller and more localized effects were reported for major depression, bipolar disorder, PTSD, and other psychiatric disorders (13,17).

We formed the ENIGMA Eating Disorders Working Group (http://enigma.ini.usc.edu/ongoing/enigma-eating-disorders/) to characterize brain alterations in eating disorders (e.g. AN and bulimia nervosa) using the same imaging analysis, quality control and statistical analysis methods across a large number of independently collected case-control samples. Given the heterogeneity of AN studies and the possible effect of weight gain, we a priori decided to use two complementary approaches in the current study: 1) a case-control two-group comparison maximizing sample size and 2) a three-group comparison. In the latter, we subcategorized participants with AN into acutely underweight and partially weight-restored patients (i.e., patients who had already been in treatment for some time and/or gained some weight prior to MRI scanning). We then used the ENIGMA Toolbox (18) to contextualize patterns of altered CT across micro- and macroscales of brain organization. Specifically, we tested whether structural abnormalities were related to 1) histological information, e.g. cell density and/or distribution across the cortex (19), 2) regional cytoarchitectonic properties, e.g. the five von Economo and Koskinas structural types of isocortex (20), and 3) normative connectome properties, e.g. the spatial distribution of hubs (i.e., brain regions with many connections (21)). Based on prior studies (8,22,23), we predicted a priori that GM volume, CT and SA reductions would be apparent in acute AN, but would be less pronounced in partially weight-restored AN. As with previous neurodegenerative

(24,25), psychiatric (26), and neurological (27) diseases, we also predicted that highly connected hub regions would be more susceptible to disease-related effects.

Methods

Study samples

We aggregated data from 22 cohorts included in institutional review board-approved studies with a combined sample of n=685 patients with AN and n=963 healthy controls (HC_2; SM Table 1 and SM Figure 1). Patients in the two-group case-control comparison had to be female and meet DSM IV-TR, DSM-5, or ICD-10 criteria for AN including a body mass index (BMI, kg/m^2) <17.5 (adults) or <10th age-adjusted BMI percentile (adolescents). HCs were females with a BMI >17.5 (adults) or >10th age-adjusted BMI percentile (and no current or lifetime diagnosis of any eating disorder). For exclusion criteria, previous publications on a selection of data used in the current study, as well as the a priori consensus process regarding the definitions of patients and groups, see SM section 1.1-1.2.

To disentangle the impact of weight gain from diagnosis on brain structure, we also carried out analyses in up to 12 cohorts based on three groups: underweight patients acutely ill with AN ('acAN'; n=466), partially weight-restored patients with AN ('pwrAN'; n=251) and healthy controls (HC_3; n=874; SM Table 1 and SM Figure 1). The inclusion of the pwrAN group in a cross-sectional design was an attempt to assess how partial/short-term weight gain might be associated with brain structure. Of note, the HC sample in the three-group comparison (denoted as HC_3) differed from that in the two-group comparison (HC_2), as not all cohorts contributed data to the three-group analysis (see SM Table 1). In contrast to the 'AN' group from the two-group comparison, 'acAN' cases were defined using more stringent treatment and recent weight gain criteria (SM section 1.2).

Case-control (two-group comparison)

We aggregated data from 22 cohorts with a combined sample of n=685 patients with AN and n=963 HC_2 (SM Table 1 and SM Figure 1). Sample size-weighted mean age across cohorts was 21

years (range: 15 to 27 years). Patients with AN were younger than HC_2 in six cohorts. Weighted mean BMI was 15.40 kg/m^2 (range: 14.32 to 16.91) in AN and 21.61 kg/m^2 in HC_2 (range: 20.81 to 23.48). In all 22 cohorts, BMI was lower among participants with AN than controls. Age-adjusted BMI, available in 15 cohorts, was also lower in AN (weighted mean group difference -2.83; range: -3.83 to -1.61) compared to HC_2 (weighted mean -0.20; range: -0.09 to 0.61). Mean age of AN onset was 16 years (range: 13 to 18 years). Mean illness duration was 5 years (range: 1 to 13 years). Between 0 to 58% of patients per site received antipsychotic or antidepressant medication (SM Table 1).

Acutely ill, partially weight-restored patients and controls (three-group comparison)

In up to 12 cohorts, data from n=251 pwrAN were available and contrasted with n=874 HC_3 and n=466 acAN (SM Table 1 and SM Figure 1). pwrAN were on average 20 years old (range: 14 to 33 years) and did not differ from acAN in age but were younger than HC_3 in three cohorts. The difference in weighted mean BMI was larger between pwrAN and HC_3 than between pwrAN and acAN (see SM Table 1 and SM section 2.1, SM Figure 2). In pwrAN, mean age of onset was 15 years (range: 13 to 16 years). Mean illness duration was 5 years (range: 1 to 20 years).

Image acquisition and processing

All sites processed T_1-weighted structural brain scans using FreeSurfer (28) and extracted, per hemisphere, subcortical volumes for eight regions (see SM section 1.3 and SM Table 3), and CT and SA for 34 Desikan-Killiany atlas regions (29), as well as left and right hemisphere mean thickness and total SA (see SM Table 4 and 4). For our main models, measures for the 8 subcortical and 34 cortical regions were averaged across hemispheres. However, we list all hemisphere-specific findings in the SM Tables 3-13. Cohort-specific details on the number of scanners, vendor, strength, sequence, acquisition parameters, and FreeSurfer version run are provided in SM Table 2.

Statistical meta-analyses and follow up analyses

At the site level, group differences for each of the 42 regions within each sample were examined using univariate linear regression. We used R's linear model function *lm* for the two-group contrast and the *glht* function from the multcomp R package to assess all pairwise contrasts for the three-group comparison using the 'Tukey' method. Bilateral ROI mean volume, mean CT or total SA measures were predicted by group (AN vs HC_2), controlling for linear and quadratic age effects (and intracranial volume when the outcome was subcortical volumes; model A, SM Table 15). To further assess whether group differences in CT and SA showed regional specificity, the analyses were repeated including global mean CT or total cortical SA as covariates in addition to age and age^2 (model B). To test for potential associations between partial/short-term weight gain and structural brain measures, we also included models using three groups (acAN, pwrAN and HC_3), covarying for age and age^2 (model C). In patients (separately in AN, acAN and pwrAN), we also analyzed partial correlations between BMI and brain structure, correcting for linear and quadratic effects of age (model D). At the site level, analysis of multi-scanner cohorts (n=5) included binary dummy covariates for n-1 scanners. Each site conducted analyses of their sample's individual subject data using R code created within the ENIGMA collaboration. Per model, only individuals with complete data were analysed.

Site-level regression statistics were then combined in random-effects meta-analyses of the Cohen's *d* statistics (for group differences) and partial correlation effect sizes (to assess associations with BMI) for each of the 42 brain regions. Meta-analyses were performed in R (version 3.5.1) using the metafor package (version 2.1-0) with site as a random effect and a restricted maximum-likelihood estimator. These same methods were applied to assess the effects of antidepressant or antipsychotic medication use, AN subtype (restrictive or binge-purge), depressive symptoms, illness duration, MRI field strength or age as potential moderators. Moderators were included in these

models through the 'mods' flag in metafor. In all models, the intercept was included to assess differences between different levels of each moderator (e.g., clinical subtype) on the association between AN and brain structure. Throughout the manuscript, we report FDR-corrected results separately for each modality (i.e., volume, CT and SA) and Bonferroni-corrected results across all 42 brain regions (i.e. $p<0.0012$).

Lastly, CT findings were contextualized across micro- and macroscales using the ENIGMA Toolbox ((18), see SM section 1.4). Briefly, to gain insights on the microstructural properties of the significantly affected cortical regions, we 1) produced density plots of two BigBrain statistical moments (i.e., mean, indexing cellular density, and skewness, indexing cellular distribution asymmetry), and 2) computed the average effect sizes across each of the five von Economo and Koskinas cytoarchitectural types. To test whether reductions in CT preferentially localized to hub regions, we obtained normative functional and structural connectivity data and assessed spatial similarity between atrophy patterns and hub distributions. Statistical significance was assessed using spin permutation tests.

Results

Widespread reductions in brain volumes and cortical thickness, but weaker alterations in surface area of patients with AN compared to controls *(two-group comparison)*

Subcortical brain volumes

We observed volume alterations in all eight subcortical structures (model A; SM Table 3 and Figure 1A), with largest effects in the thalamus (Cohen's *d* = -0.69; 95% CI: [-0.86; -0.52]). The lateral ventricles were the only structures enlarged in AN with all other areas showing lower volume in AN. Mean absolute effect size across these regions was *d* = 0.42 (SD = 0.15). Effects across hemispheres correlated strongly (r=0.99, p<0.001).

Cortical thickness

We also observed widespread reductions in CT in 29 regions passing Bonferroni correction (and 30 regions passing FDR-correction; model A; SM Table 4 and Figure 2A). Largest effects were in the superior (*d* = -0.95; 95% CI: [-1.20; -0.69]) and inferior parietal gyrus (*d* = -0.94; 95% CI: [-1.20; -0.67]). Mean effect size across these 29 regions was *d* = -0.65 (SD = 0.18). Effects across hemispheres correlated strongly (r=0.94, p<0.001). When additionally correcting for global mean thickness (model B), only 12 regions showed differences after Bonferroni adjustment (n=18 regions with FDR correction; Figure 2A, SM section 2.2 and SM Table 6), suggesting that differences in region-specific CT between patients and controls were to some extent related to global thickness reductions.

Cortical surface area

We also observed reductions in cortical SA in 16 regions passing Bonferroni correction (n=16 with FDR-correction; model A; SM Table 5 and Figure 2B). Largest effects were in the transverse temporal gyrus (d = -0.29; 95% CI: [-0.42; -0.15]) and pars opercularis (d = -0.28; 95% CI: [-0.38; -0.17]). Mean effect size across these 16 regions was d = -0.23; roughly a third of that observed for reductions in CT and half of that found for volumetric reductions. Effects across hemispheres correlated moderately (r=0.53, p=0.001). When additionally correcting for global mean SA (model B), only the paracentral and transverse temporal gyrus showed a significant difference (Figure 2B, SM section 2.2 and SM Table 7), suggesting that differences in region-specific cortical SA between AN and HC_2 were to a large extent driven by global reductions in SA.

Reductions in volume, thickness and surface area are less severe in partially weight-restored patients than in acutely ill patients *(three-group comparison)*

Subcortical brain volumes

Compared to the volumetric differences between acAN and HC_3 (mean $d_{acAN\text{-}HC}$ = 0.49; SD = 0.18), differences between pwrAN and HC_3 were reduced by 36% (mean $d_{pwrAN\text{-}HC}$ = 0.31; SD = 0.12), suggesting that volume reductions in pwrAN were smaller than in acAN (model C). pwrAN also had larger subcortical volumes than acAN (mean $d_{acAN\text{-}pwrAN}$ = 0.28; SD = 0.09; Figure 1B, SM section 2.3 and SM Table 8). Overall, these findings suggest that reductions in subcortical volumes in pwrAN were smaller than those observed between acAN and HC_3.

Cortical thickness

Compared to the thickness reductions in acAN ($d_{acAN\text{-}HC}$ = 0.67; SD = 0.15), differences between pwrAN and HC_3 were reduced by 36% ($d_{pwrAN\text{-}HC}$ = 0.43; SD = 0.17; Figure 3A). CT in pwrAN

was also larger than in acAN ($d_{acAN\text{-}pwrAN}$ = 0.49; SD = 0.14). This suggests again that CT reductions in pwrAN were less severe than in acAN compared to HC_3 (i.e., indicating partial normalization of thickness during weight restoration). The reductions appeared to be largely driven by global CT reductions. Once controlled for global thickness, effects were reduced by 75% (acAN-HC_3), 63% (pwrAN-HC_3) and 86% (acAN-pwrAN; SM Table 9, SM section 2.3).

Cortical surface area

Effect sizes for SA reductions were on average 52% smaller contrasting pwrAN to HC_3 ($d_{pwrAN\text{-}HC}$ = 0.10; SD = 0.05) compared to reductions in acAN ($d_{AN\text{-}HC}$ = 0.26; SD = 0.07; Figure 3B). This suggests again that cortical SA reductions in pwrAN were less severe than in acAN compared to HC_3 (i.e. indicating partial normalization). These reductions seem to be largely driven by global SA reductions. Controlling for global SA reduced effects sizes from d = 0.26 to d = 0.08 for acAN-HC_3, from d = 0.10 to 0.05 for pwrAN-HC_3 and increased only slightly from d = 0.07 to 0.08 for acAN-pwrAN (SM Table 10 and SM section 2.3).

Multiscale neural contextualization

Patterns of CT reductions in AN corresponded to regions with greater, and more evenly distributed (across the layers), cellular densities ((19); Figure 4A), particularly converging in parietal and frontal cytoarchitectonic classes ((30); Figure 4B). Leveraging connectivity data from the Human Connectome Project (31)), AN-related atrophy implicated functional and structural cortico-cortical hub regions more strongly than nonhub (i.e., locally connected) regions (Figure 4C and 4D).

Reductions in grey matter volume and thickness are associated with BMI

In patients with AN, BMI was positively associated with volumes in the thalamus, putamen, amygdala and hippocampus after Bonferroni-correction (as well as the accumbens and pallidum after FDR-correction; model D; SM Table 11). The mean effect was r = 0.20 (SD = 0.03) with largest associations in the amygdala (r = 0.23; 95% CI [0.12; 0.35]).

Compared to the volumetric findings, associations between BMI and CT were larger with a mean effect of r = 0.32 (SD = 0.06), significant across 25 regions (n=28 after FDR correction; SM Table 12). For SA, associations with BMI were the weakest (r = 0.18; SD = 0.04) with only 5 significant regions (n=7 after FDR; SM Table 13). Together, these findings suggest that CT (and subcortical volumes and SA, albeit to a lesser extent) in AN might be related to BMI, and therefore weight status. Effects were similar – and in the case of volume and CT slightly stronger – when using age-adjusted BMI (SM Tables 11-13).

Moderator effects

The two-group differences in volume, thickness and SA remained stable when covarying for the proportion of antidepressant or antipsychotic medication use, AN subtype (restrictive or binge-purge), depressive symptoms, illness duration, scanner field strength or age (SM section 2.5). Furthermore, almost none of these clinical or technical variables showed moderating effects after FDR correction (SM section 2.5 and SM Table 14). However, samples with a larger proportion of patients with a restrictive subtype were characterized by reduced thickness in the insula and reduced volume in the putamen and nucleus accumbens.

Discussion

In this prospective coordinated meta-analysis combining scans from 685 patients with AN (total n=1,648, including controls), we found widespread and sizable reductions in CT and subcortical volume in the underweight state of AN. SA was also reduced but effect sizes were smaller. Comparison of patients acutely ill with AN, partially weight-restored patients with AN, and HC indicated a substantial positive association between partial weight gain and all three structural brain metrics. This represents the largest structural neuroimaging study in AN to date. Taken together, results suggest that AN is associated with global GM reductions (and no increases) and that these reductions might be highly state-dependent, i.e. related to lower BMI.

In line with some, but not all, previous (smaller) studies (3–5,7,11,22), reductions in CT and subcortical volume in AN were on average moderate (mean Cohen's d of 0.65 and 0.42, respectively). Although cross-disorder comparisons should be considered with caution (also given the possible reversibility of these changes in AN), these reductions were between two to four times larger than in other psychiatric disorders that are often comorbid with AN, including depression and OCD (effect sizes between 0.10 to 0.31; (13), see also SM Figure 5). In fact, until now the largest effects among all ENIGMA studies in psychiatric disorders (apart from the 22q11 deletion syndrome, which is characterized by hypertrophy) have been found in schizophrenia with Cohen's d effect sizes ranging between 0.12 to 0.46 for subcortical structures and up to 0.53 for CT (13,15,16). Although smaller than the effects observed in neurodegenerative diseases such as Alzheimer's disease (32), the effects found here in AN are higher than those in schizophrenia, and can therefore be considered the largest among psychiatric disorders.

We observed strongest effects in the superior and inferior parietal gyrus. These regions are associated with the integration of bodily stimuli (33,34) and form an attention network in synergy with temporal and prefrontal regions (35) that were also associated with AN in the current study.

This might indicate that body-environment integration and attentive processes might be altered in AN, in line with previous functional neuroimaging research (36). Embedding our findings within a multiscale framework (37) revealed that patterns of CT reductions primarily affected regions with greater cellular densities as well as densely connected hub regions. Even though our connectivity networks were derived from data on healthy young controls making inferences about altered network architecture in AN less straightforward, our findings are in line with previous psychiatric and neurological disorders (27,38), suggesting that the high metabolic demands and increased connectional flow of hub regions may account for their selective vulnerability in the manifestation of AN-related atrophy. While it is possible that these findings indicate actual cell loss (39), higher cellular density may also provide more opportunity for neuronal remodelling, which is a current hypothesis regarding the mechanisms underlying the dynamic brain changes in AN (6).

Unlike our findings of larger alterations in volume and CT compared to other disorders, SA reductions were similar in size (mean Cohen's d, 0.23) compared to those in other psychiatric disorders such as OCD or schizophrenia (Cohen's d between 0.16 to 0.33) and slightly smaller than those in depression (0.26 to 0.57; (13)). Even though effects for SA were smaller, they followed a similar pattern as for CT.

In line with this and previous studies (40), BMI showed small to moderate associations with subcortical volumes and CT (and to a smaller degree with SA). The moderating effect of AN subtype may also be related to this, since patients with a restrictive subtype are often characterized by more rapid and extensive weight loss (41–43). Interestingly, abnormally high body weight has also been also associated with lower GM and bariatric surgery seems to reverse some of these effects (44). Underlining the importance of state effects such as weight loss and gain, our three-group comparison showed that partial weight recovery was associated with an attenuated reduction in all three GM metrics (36-52% smaller differences compared to acAN). Although caution regarding causality is warranted, reversibility of "pseudoatrophy" in AN, i.e. increases in GM volume and CT

(and even gyrification) following weight restoration, has been reported in previous cross-sectional investigations of long-term weight recovered former AN patients (11,22,45–47) and a small number of longitudinal studies (7,48–50). However, recent research suggests that normalization is easier to achieve in younger patients (23). Importantly, however, the current findings go beyond previous studies by supporting these effects across many cohorts in a coordinated meta-analytic design. Overall, these findings highlight the need to control for clinical state (acute vs. already gaining weight) in the study of AN, i.e., the drastic impact on the brain is strongly related to undernutrition and therefore rapidly changes with weight gain or treatment.

Results should be interpreted in the light of the following limitations: first, based on the neuroimaging method employed, microstructural changes cannot be detected. Therefore, we cannot exclude the persistence of irreversible scars after weight restoration at the microstructural level. This is important, as recent studies have shown elevated neuronal and glial damage markers in AN (39,51). Second, we aggregated data from different study sites, but differences in MRI scanners and acquisition protocols can introduce non-biological variations (52). However, we covaried for potential scanner differences (within each study site) and found little evidence for moderating effects across sites. Third, we did not assess or control for comorbidities (e.g. OCD, depression), but prior studies indicated generally smaller effects of these psychiatric disorders on brain structure (17,53). Hence, it is unlikely that our findings were better accounted for by comorbid conditions. Fourth, our study included a few HC from a single site with a BMI as low as 17.5. It is possible that these individuals also showed some subthreshold eating disorder symptoms and were therefore more similar to pwrAN than to HC. Similarly, the reported findings may also be dependent on the acAN group definition (and potential changes of their respective nutritional/hydration status within the first two weeks of therapy) and other results might be obtained with different cut-offs. However, our analysis indicated that BMI had a similar association with brain structure as diagnostic group, suggesting that misclassification biases were unlikely. Fifth, given the cross-sectional design, our inferences regarding the effect of partial weight rehabilitation warrant replication in longitudinal

studies. Last, we assume that differences on T_1-weighted MRI measurements relate to true variations in brain morphology rather than errors or artefacts.

In summary, based on the largest and most representative sample to date, the current results indicate that acutely underweight individuals with AN have sizable and widespread reductions of subcortical volumes and CT and, to a lesser extent, cortical SA. Effect sizes for CT reductions are the largest detected among psychiatric disorders (13). These effects are attenuated in partially weight-restored patients and all metrics of structural brain changes (especially cortical and subcortical GM) associate with current BMI, which mirrors the clinical state of AN. Our findings underline the importance of considering weight loss and renutrition in biomedical research on AN and the importance of effective early intervention and treatment engagement to prevent long-lasting structural brain changes.

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Disclosures

The authors report no conflict of interest.

Data availability

All data produced in the present study are available upon reasonable request to the authors.

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Legends

Figure 1. Subcortical volume reductions in anorexia nervosa. Differences (Cohen's *d*) between A) patients with Anorexia Nervosa (AN) and healthy controls (HC_2) and B) all groups, including acute (acAN) and partially weight-restored patients (pwrAN). Color scale: Warmer colors indicate lower volumes (Cohen's *d*; averaged across the left and right hemispheres, but depicted on the right side of the brain) in patients compared to controls. Error bars are 95% confidence intervals.

Figure 2. Reductions in A) cortical thickness and B) surface area between patients with Anorexia Nervosa (AN) and healthy controls (HC_2). Results, which are uncorrected for global measures, are shown on the left in each panel. Results, which are corrected for global measures, are shown on the right in each panel. Color scale: Warmer colors indicate reductions (Cohen's *d* effect size; averaged across the left and right hemispheres, but depicted on the right side of the brain) in patients compared to controls.

Figure 3. Pairwise reductions, shown as Cohen's d effect sizes, in A) cortical thickness and B) surface area between acute patients with Anorexia Nervosa (acAN), partially weight-restored patients (pwrAN) and healthy controls (HC_3). Color scale: Warmer colors indicate reductions (Cohen's d; averaged across the left and right hemispheres, but depicted on the right side of the brain).

Figure 4. Neural contextualization of cortical thickness case-control differences. Cohen's d effect sizes in the context of: A) regional cytoarchitecture, specifically overall cellular density (A; top panel) and laminar differentiation (A; lower panel); B) cytoarchitectonic classes based on postmortem work

by von Economo and Koskinas; and degree centrality according to C) functional and D) structural connectivity.