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Cerebral cortical thickness and surface area in adolescent anorexia nervosa: Separate and joint analyses with a permutation-based nonparametric method

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Abstract

Objective: Reduction in cerebral volume is often found in underweight patients with anorexia nervosa (AN), but few studies have investigated other morphological measures. Cortical thickness (CTh) and surface area (CSA), often used to produce the measure of cortical volume, are developmentally distinct measures that may be differentially affected in AN, particularly in the developing brain. In the present study, we investigated CTh and CSA both separately and jointly to gain further insight into structural alterations in adolescent AN patients.

Method: Thirty female AN inpatients 12–18 years of age, and 27 age-matched healthy controls (HC) underwent structural magnetic resonance imaging. Group differences in CTh and CSA were investigated separately and jointly with a permutation-based nonparametric combination method (NPC) which may be more sensitive in detecting group differences compared to traditional volumetric methods.

Results: Results showed significant reduction in in both CTh and CSA in several cortical regions in AN compared to HC and the reduction was related to BMI. Different results for the two morphological measures were found in a small number of cortical regions. The joint NPC analyses showed significant group differences across most of the cortical mantle.

Discussion: Results from this study give novel insight to areal reduction in adolescent AN patients and indicate that both CTh and CSA reduction is related to BMI. The study is the first to use the NPC method to reveal large structural alterations covering most of the brain in adolescent AN.

KEYWORDS

adolescent, anorexia nervosa, cortical surface area, cortical thickness, magnetic resonance imaging, nonparametric combination, permutation testing

1 | INTRODUCTION

Cerebral structural alterations are consistently found in acutely ill patients with anorexia nervosa (AN), and most frequently reported is cerebral volume reduction (Bomba et al., 2013; Fonville, Giampietro, Williams, Simmons, & Tchanturia, 2014; Frank, Shott, Hagman, & Yang, 2013; Gaudio et al., 2011; Mainz, Schulte-Ruther, Fink, Herpertz-Dahlmann, & Konrad, 2012; Seitz et al., 2015). Findings regarding the

dispersion of structural alterations vary; most studies report that clusters scattered across the cortical mantle are reduced in AN compared to healthy control (HC) participants, but the findings only moderately overlap (Seitz, Herpertz-Dahlmann, & Konrad, 2016). A few studies show regionally larger volumes in AN patients (Frank et al., 2013). The inconsistent results may be due to differing methodology and sample characteristics (King, Frank, Thompson, & Ehrlich, 2018), and the question is unsettled as to whether the observed volume reduction is a regionally specific or global phenomenon.

Cortical volume is often measured as the product of cortical surface area (CSA) and cortical thickness (CTh). These measures reflect two genetically and developmentally distinct measures with individual life span trajectories and different association with cognitive development and disorder (Fjell et al., 2015; Winkler et al., 2010). The combination of these two metrics may be imprecise as it does not account for the unique contribution of area and thickness (Panizzon et al., 2009). During childhood and adolescence, the development of CTh follows a linear curve, while CSA seem to follow a curvilinear trajectory with a later peak (Wierenga, Langen, Oranje, & Durston, 2014). Full syndrome AN normally develops after CTh peak, but early-onset AN may develop before CSA peak in some cortical regions. As CTh is steadily decreasing in adolescents, and CSA may still be expanding, the effect of AN may differ for CTh and CSA in adolescents.

As AN patients may be subject to both cerebral volume increase and decrease, the combination of CSA and CTh may result in "cancelling" out effects and thus mask structural alterations. Separately, these measures may be more specific in detecting cortical changes (Winkler et al., 2010). While several studies have investigated cerebral volume in AN, few have studied CTh and CSA separately.

One study of CTh in adolescent AN reports widespread thinning (King et al., 2015). Studies of adult patients with AN have yielded small group differences and conflicting results; One study reported lower CTh in frontal and temporal lobes (Nickel et al., 2018), while another one reported greater thickness in several frontal regions (Lavagnino et al., 2018). A more recent study found widespread CTh reduction in adult patients with acute AN that mostly normalized after weight rehabilitation and was negatively associated with age (Kaufmann et al., 2020).

CSA is associated with cortical volume (Winkler et al., 2010) consistently found to be reduced in AN (Seitz et al., 2016). However, two studies investigating CSA in adult AN patients compared to HC report small (Leppanen, Sedgewick, Cardi, Treasure, & Tchanturia, 2019) and no group difference (Miles, Voineskos, French, & Kaplan, 2018). Results from a meta-analysis of studies investigating cerebral volume indicate that adolescent AN patients have a greater volume loss than adult AN patients (Seitz et al., 2016) giving cause to investigate adolescent and adult AN patients separately. To our knowledge, no studies have examined surface area in adolescent AN patients.

Traditionally, measuring volume is done by voxel-by-voxel classification of tissue or based on surface registration, multiplying area by thickness at each vertex. The first method is known to be sensitive to artifacts (Ashburner & Friston, 2000) and the latter is likely to under- or overestimate volume (Winkler et al., 2018). A recently proposed method allows the combination of thickness and surface area metrics as an alternative to the traditional volume analyses. The permutation-based nonparametric combination (NPC) method is a multivariate statistical method that utilizes permutations, first testing metrics separately and recording results for each permutation. Subsequently, resulting *p*-values are combined into a joint and more powerful statistic. In this manner, very few assumptions are made about the data and over or underestimation is less likely. As the method is nonparametric it does not assume independence between the two metrics studied, which is an advantage as CTh and CSA share the same environment (Winkler et al., 2016). In summary, the NPC method accounts for the combined effect of CTh and CSA, and is less prone to the drawbacks of traditional volumetric methods and may thus give a more precise measurement of structural alterations in adolescent AN.

In the present study, we investigated CTh and CSA separately and jointly. Based on previous findings of cortical thinning and volume reduction, we hypothesize that both surface area and thickness are affected in adolescent patients with AN. As CTh and CSA peak at different ages and in different regions, we expect to find some differences regarding regions affected. The newly proposed NPC method offers an advantage in detecting affected areas that may be subject to alterations in both CTh and CSA. We expect that separate analyses reveal cortical thinning and surface area decrease in adolescent AN patients, and that the combined analyses reveal that more of the cortex is affected than what has been previously found using traditional volume methods.

2 | METHODS

2.1 | Study design and sample

Participants were inpatients at the regional center for eating disorders at the university hospital of North Norway in Tromsø, and Oslo University Hospital. In total, 31 female patients with AN (Age: M = 15.7 SD = 1.8) and 27 female healthy age-matched controls (Age: M = 16.1, SD = 1.9) were included (10 patients and 10 controls were tested and scanned at the Oslo clinic and the remaining were included in Tromsø). HC were recruited from local high schools in Tromsø and Oslo, respectively. Inclusion criteria for AN patients were DSM-5 criteria for restrictive AN (no history of binge-purge episodes). Upon admission, patients were set on a meal plan and started psychotherapy (family-based treatment for eating disorders). Two of the patients were tube fed in the period between admission and inclusion in the study. Exclusion criteria for all participants were history of brain injury, neurological disorder, bulimia nervosa, schizophrenia or psychotic episodes and use of antipsychotic medication. Additional exclusion criteria for HC were lifetime or current eating disorders or obesity (BMI > 30). Most of this sample was also included in our previous study (Myrvang et al., 2018). Norwegian versions of the Beck's Depression Inventory (BDI-II; Beck, Steer, & Carbin, 1988), and the State-Trait Anxiety Inventory (STAI; Spielberger, Gorusuch, & Lushene, 1970) were used to measure symptoms of depression and

anxiety. The Eating Disorder Examination Questionnaire (EDE-Q; Fairburn & Beglin, 2008) was used to measure eating disorder symptoms. The EDE-Q consists of four subscales (restriction, concerns about eating, weight and figure) and a global scale.

2.2 | Ethics

The study was approved by The Norwegian Committee for Medical and Health Research Ethics (REC), under protocol number 302969. Informed, written consent was obtained from all participants. Written consent was also obtained from parents of participants <16 years of age.

2.3 | Image acquisition

A 3T Siemens Magnetom Skyra in Tromsø and a Phillips Achieva 3T scanner in Oslo was used for MR imaging. Scanners were equipped with 64 channel head coils and high-resolution 3D T1-wheighted images were acquired at both sites. Both sites used an ADNI protocol for the 3D T1 sequence (Jack et al., 2008). In Tromsø a magnetization-prepared rapid gradient-echo (MPRAGE) sequence was utilized, with the following parameters: Orientation = Sagittal; No. of slices = 176; Voxel size = 1 × 1 × 1; Slice thickness = 1 mm; repetition time (TR) = 2,300 ms; echo time (TE) = 2.98 ms; field of view (FOV) = 256 × 256; Flip angle = 9°; and inversion time (TI) = 900 ms, parallel excitation factor 2 (GRAPPA). In Oslo, a 3D-TFE sequence was used for acquisition with the following parameters: Orientation = Sagittal; No of slices = 184; Voxel size = 1 × 1 × 1; Slice thickness = 1 mm; TR/TE/T1 = 3000/2.3/853 ms; FOV = 256 × 256; Flip angle = 8°; and, parallel excitation factor 2 (SENSE). To test for the potential effect of scanner site, a group analysis (Oslo > Tromsø) was conducted using only participants from the HC group.

2.4 | Image processing

Surface reconstruction and volumetric segmentation was performed with the FreeSurfer v6.0 software (http://surfer.nmr.mgh.harvard.edu) version 6.0 (FS 6.0); (Fischl et al., 2002; Fischl et al., 2004) with the recon-all processing pipeline. The pipeline includes motion correction, normalization to Talairach space, intensity bias correction, skull-stripping, surface registration and segmentation. Two of the authors (TRV and ADM) visually inspected image registration results and manually corrected when necessary. Minor corrections were performed on about 1/3 of the sample, and the majority of corrections were of skull stripping errors leading to inclusion of dura mater, and in a few cases, parts of the skull.

2.5 | Statistical analyses

Analyses of group differences in descriptive variables were performed with IBM SPSS 24 using analysis of variance (ANOVA).

The statistical analyses of CTh and CSA were performed within the software package Permutation Analysis of Linear Models (PALM; Winkler, Ridgway, Webster, Smith, & Nichols, 2014). The preprocessing of the cortical surfaces was performed in the mris_preproc module in FS 6.0. The design matrixes for the permutation analyses consisted of group (HC vs. AN patients) whereas age was treated as a continuous covariate. The variable "age" was mean centered before the analyses. The permutation analyses were performed with 5,000 iterations, and threshold-free cluster enhancement (Smith & Nichols, 2009) was used to correct for multiple comparisons (Winkler et al., 2016), and a family-wise error rate (FWER) corrected $p < .05$ was considered significant. All contrast were two-tailed. The joint analyses of surface and CTh were performed in PALM with nonparametric combination (NPC; Winkler et al., 2018) using Fisher's method for combining p-values (Fisher, 1934). The Desikan-Killiany atlas incorporated in FS 6.0 (Desikan et al., 2006) was used for annotation of the cortices. All analyses were performed in two stages; a model testing contrast between groups (HC > AN) regressing out the effect of age was firstly performed. Secondly, the effect of body mass index (BMI) was included in the model to test the positive effect of BMI on CTh, CSA, and in the joint analysis of thickness and area. Both BMI and BMI-SDS were investigated, and results were similar. Results from analyses with BMI are displayed. In the patient sample, associations between morphometrics and symptoms of depression, anxiety and eating disorders, measured by BDI-II, STAI (Y1 and Y2), and EDE-Q, were investigated with similar statistical methods as described above.

3 | RESULTS

3.1 | Sample characteristics

The AN group had significantly higher scores on self-report measures of symptoms of depression (BDI-II) and anxiety (STAI, Y1, & Y2) and eating disorder symptoms (EDE-Q). Patients had significantly lower BMI and BMI-SDS compared to HC (Table 1).

3.2 | Group comparisons—Imaging data

3.2.1 | Cortical thickness

Group differences (HC > AN) were found in several anatomical regions (Desikan et al., 2006) in both hemispheres (Figure 1). Clusters of significant group differences ($p < .001$) were located in the pre- and paracentral area, precuneus, superior- and inferiorparietal, superiortemporal and superiorfrontal area. Only a few frontal and inferior frontotemporal areas such as the medial and lateral orbitofrontal and rostral middle frontal, entorhinal and parahippocampal areas were lacking significant group differences.

Effect sizes (Cohen's d) above 0.2 were found in all of the anatomical areas where significant group differences were observed (Figure S1) and ranged from small (Cohen's $d > 0.2$) to high (Cohen's $d > 0.8$).

TABLE 1 Sample characteristics

	AN Mean (SD)	HC Mean (SD)	*F*-value (*p*)
N	31	27	
Age	15.7 (1.8)	16.1 (1.9)	0.78 (.382)
BMI	16.3 (1.6)	22.0 (3.1)	83.0 (<.001)
BMI-SDS	−2.4 (1.3)	0.4 (1.0)	88.2 (<.001)
BMI-gain	0.9 (0.6)	—	—
Drugs (SSRI/GH)	5/2[a]	0/0	—
Weeks inpatient	5.1 (4.2)	—	—
Years since first GP visit	1.6 (1.5)	—	—
Psychiatric symptoms screening			
BDI II[b]	22.4 (11.7)	4.3 (5.2)	53.7 (<.001)
STAI Y1[b]	49.9 (13.8)	30.2 (9.2)	37.7 (<.001)
STAI Y2[b]	52.1 (14.8)	32.2 (10.3)	31.4 (<.001)
EDE-Q restriction[b]	3.0 (2.0)	0.3 (0.5)	43.9 (<.001)
EDE-Q eating[b]	2.3 (1.7)	0.2 (0.5)	36.1 (<.001)
EDE-Q weight[b]	3.0 (1.8)	0.7 (0.8)	37.6 (<.001)
EDE-Q figure[b]	3.9 (1.9)	0.7 (0.9)	61.1 (<.001)
EDE-Q global[b]	3.0 (1.7)	0.5 (0.5)	55.8 (<.001)

Note: One-way ANOVA. BMI: Body mass index. BMI-SDS: Standardized BMI values based on Norwegian norms for children. BMI-gain: Difference between BMI at scan day and BMI at admission.
[a]Five participants used Serotonin reuptake inhibitors (SSRI), two used growth hormones (GH). Weeks inpatient: Weeks between admission and scanning. Years since first GP visit = Consultation concerning eating disorder symptoms. BDI: Becks Depression Inventory II. STAI 1 & 2: State Trait Anxiety questionnaire form Y1 (State anxiety) and Y2 (Trait anxiety). EDE-Q: Eating Disorder Examination Questionnaire (index scores are reported).
[b]AN *N* = 27.

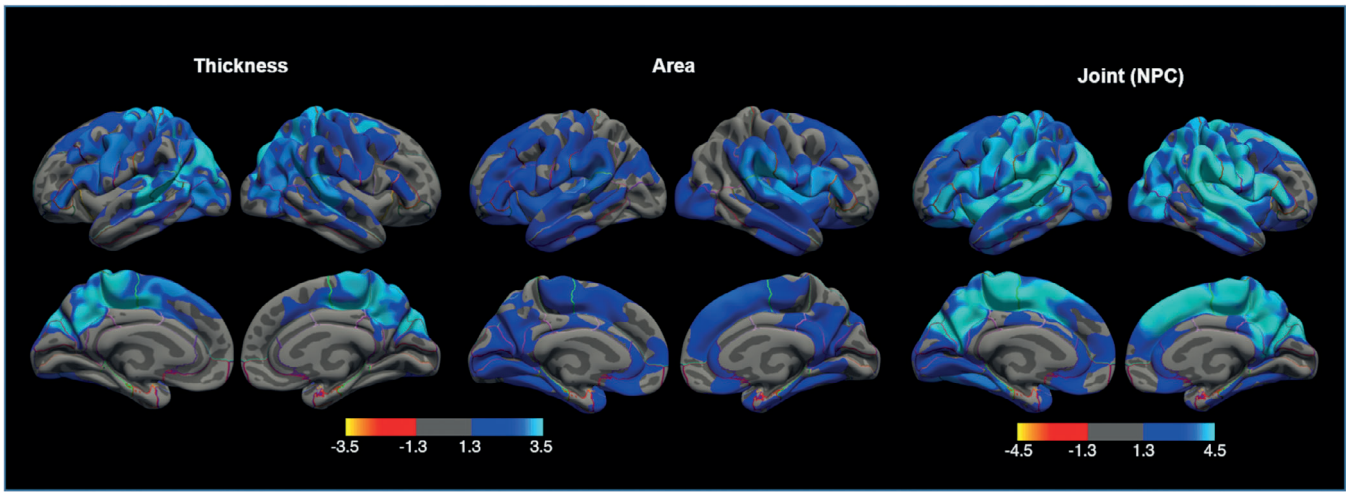

FIGURE 1 Group differences in separate and joint, two-tailed analysis (age adjusted) of cortical thickness and area, showing reduced thickness, area and combination in AN compared to HC. Images are thresholded with $p < .05$ and FWER corrected for multiple contrasts and modalities. Color bar indicate $-\log_{10}(p)$ thresholds for individual results. Thickness: Main body of significant clusters are located in temporal, parietal and superiorfrontal areas. Area: Main body of significant clusters are located in temporal, parietal and frontal areas. NPC: Significant clusters were found in all anatomical regions. AN, anorexia nervosa; FWER, family-wise error rate; HC, healthy controls; NPC, nonparametric combination [Color figure can be viewed at wileyonlinelibrary.com]

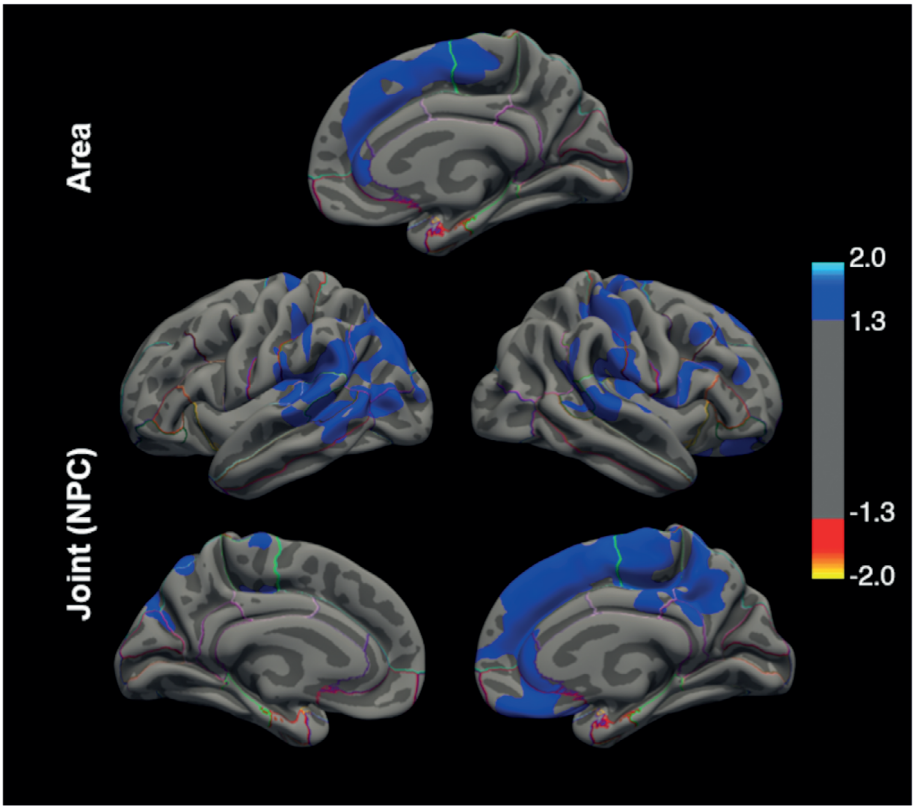

FIGURE 2 Group differences in joint (NPC), two-tailed analysis of cortical thickness and area adjusted for age and BMI, showing smaller combined cortical thickness and surface area in AN compared to HC. Images are thresholded with $p < .05$ and FWER corrected for multiple contrasts and modalities. Color bars indicate $-\log_{10}(p)$ thresholds. AN, anorexia nervosa; FWER, family-wise error rate; HC, healthy controls; NPC, nonparametric combination [Color figure can be viewed at wileyonlinelibrary.com]

When BMI was included as a covariate, none of the observed group differences remained significant.

3.2.2 | Surface area

Significant group differences were found in several anatomical regions (Desikan et al., 2006) in the central brain including all temporal and parietal regions except for the superior parietal region in both hemispheres (Figure 1). Significant clusters mainly encompassed the temporal (superior- and middle temporal), frontal (lateraorbitofrontal, rostral- and caudal middlefrontal and the insula) and parietal (post- and paracentral) lobes. Peak areas of significant group differences ($p < .001$) were found in parietal and prefrontal areas such as the pre- and postcentral gyri, insula and the inferior frontal gyri (pars triangularis and opercularis). The only prominent difference between the two hemispheres was that significant clusters were found in the right lateral occipital area and not the left. When BMI was included as a covariate, only the observed group differences in the right superiorfrontal area remained significant (Figure 2). Medium to high effect sizes (Cohen's *d*) were found in most anatomical labels where there were significant group differences, for both analyses steps (Figures S1 and S2).

3.2.3 | Joint NPC of CTh and CSA

The joint analyses of CTh and CSA (Figure 1) showed a significant effect of group (HC > AN) in most of the cortex. Significant differences ($p < .001$) were observed in all cortical regions (Desikan et al., 2006), the only exception being the frontal pole and three orbitofrontal regions in the right hemisphere. The largest clusters encompassed several regions in the temporal, occipital, parietal lobes. When adjusting for BMI, significant group differences were found in two clusters including temporal and parietal regions with peak coordinates ($p < .05$) in the superiorparietal region in the left hemisphere (Figure 2). In the right hemisphere clusters in the parietal and frontal cortex were significantly reduced in AN patients. Peak coordinates ($p < .001$) were found in the superiorfrontal, and precentral area.

3.2.4 | Scanner effect

To investigate the potential confounding effect of two different scanners, we performed analyses of all three morphometrics in HC only with scan site as group variable. No significant effect of scan site was found.

3.2.5 | Cerebral morphology and psychopathology in patients

In order to test the impact of symptoms of depression and anxiety and eating disorder symptoms on cerebral morphology, we tested the association between CSA and CTh and combination measure and scores on BDI-II, STAI Y1, and EDE-Q global scale. No significant associations with morphometrics and clinical variables were found.

The effect of BMI increase between admission and scan day was also tested, but no significant association between weight gain and morphometrics was found.

4 | DISCUSSION

Both CTh and CSA were independently reduced in AN compared to HC. Cortical thinning and areal reduction were found predominantly in the temporal, parietal and frontal lobes, but affected regions within the lobes differed somewhat between the two morphometrics. No areas were found to be larger in AN patients. When adjusting for BMI, the group effect observed for CTh and CSA was no longer significant, indicating that BMI largely explain the group effect. For the joint NPC analyses, some clusters including parietal and frontal regions remained significant when adjusting for BMI.

4.1 | Cortical thickness

Results showed reduced CTh in adolescent AN covering an extensive area in the posterior brain, bilaterally. Compared to a previous study in the same age group, also uncovering extensive cortical thinning (King et al., 2015), results from our study appear not to include the frontal areas to similar extent. A reason for this discrepancy may be that participants in our study had a higher BMI than participants in the study of King and colleagues. It has been suggested that normalization of anatomical changes starts within 3 months (Bernardoni et al., 2016), and it is plausible that brains of the patients in our study, who had been admitted for several weeks, were in a process of regeneration.

4.2 | Cortical surface area

We found an a real reduction in AN patients in large parts of the frontal cortex, most prominently in the rostral middle frontal, parsorbital, parstriangular and insular areas. Previous findings in adult AN patients have been limited to smaller areas (Leppanen et al., 2019) or no CSA reduction (Miles et al., 2018), and our results may imply that adolescent patients are more affected. A similar discrepancy between adults and adolescents have been reported in major depressive disorder (MDD; Schmaal et al., 2016). As suggested for adolescents with MDD, the reason for the surface area decrease in adolescent AN may be a delay in cortical maturation (Schmaal et al., 2016) as a result of illness debut in a critical period in brain development. The lack of such findings in adults may suggest that the cortex eventually matures in spite of the disturbance in adolescence. However, as in many studies in this field, the methods used differ substantially which may contribute to the discrepancies in findings reported.

As the mechanisms underlying volume reduction in AN are mostly unknown (King et al., 2018), an important first step may be to distinguish the two morphometrics that constitute volume. Results from the present study show that CTh and CSA reduction mostly overlap. However, some significant group differences were found in separate areas. For example, areal reduction, but not thickness reduction was found in the fusiform, entorhinal and parahippocampal areas. Studies have shown volume reduction in these areas (Amianto et al., 2013; Brooks et al., 2011; Fonville et al., 2014), and results from this study suggest that areal reduction is driving this decrease. The discrepancies in results in CTh and CSA may be due to the different developmental trajectory of these two metrics and future studies should investigate in a larger sample where there is possible to examine the relationship between age and morphometrics in AN patients in a more detailed manner, particularly including the youngest patients that may not have reached CTh and CSA peak. A study in adult AN patients found that restoration of CTh during weight rehabilitation was negatively associated with age, indicating that older patients had a lower rate of regeneration, perhaps due to reduced plasticity (Kaufmann et al., 2020). This finding indicates that CTh alterations in AN may be age dependent and future studies should investigate the relationship with age and development in other morphometrics.

4.3 | Nonparametric combination

The combined analyses show widespread cerebral reduction in AN patients, covering most of the cortical mantle. Few studies, independent of metrics studied, have found cortical alterations to this extent. Many of the studies investigating brain volume in adolescent AN have included few participants ($N < 20$), which may explain the discrepancy. However, one comparable study found global alterations, but in smaller clusters (Seitz et al., 2015). Superiority of the NPC method was demonstrated in a study of participants with very low birth weight, where NPC revealed more extensive structural alterations that was not detected using thickness or surface measure alone (Winkler et al., 2018). Results from this study may indicate that the NPC method is more reliable in detecting group differences in patients with AN, but direct comparisons to other methods are necessary to conclude.

Some clusters in the left posterior and the right parietal–frontal brain were still significant when adjusting for BMI suggesting that these areas are associated with other factors than weight. The areas that remained significant when adjusting for BMI in the left occipital temporal brain are associated with somatosensation and imagery. King et al. (2015) found clusters in the same area to be associated with "drive for thinness." It is possible that this area is more closely linked to eating disorder specific symptoms such as body image disturbance. In the present study, the relationship between morphometrics and eating disorder symptoms (measured by global EDE-Q scores) was only tested in the patient group with nonsignificant results, and thus could not explain the mass reduction nonrelated to BMI. Future studies should include other and more precise measures of eating disorder symptoms such as subscales of standardized interviews or questionnaires.

4.4 | Strengths and limitations

Strengths to this study comprises the use of up-to-date software, robust methods and stringent controls for multiple comparisons, a larger sample size than in most other studies in the field, a narrow age range, and sub-analyses of potential confounding variables like scan site, age, drug use and weight gain during inpatient care. As for the latter, the patients were not in the most critical and catabolic phase of their illness at the time of testing. The benefit to this approach was that the effects of extreme malnutrition were reduced. Moreover, the nonsignificant association between BMI increase score (subtracting the BMI at admission from the BMI at the day of the scan) and morphometrics indicate that our results would have been more or less the same had participants been included upon admission at a lower weight.

In the field of structural neuroimaging in AN patients it has been recommended (King et al., 2018) to control for the effects of pubertal stage, oral contraceptives and duration of illness. This was not done in the present study, and our question about the first time the participants visited their general practitioner (year) was a too crude variable to be informative in analyses. The possible effect of two different scan sites was not tested in the AN group, because the mean weight in the Tromsø and Oslo group differed somewhat. Although not statistically significant, this could have a confounding effect on a between site analyses, and therefore this was only conducted in the HC group.

5 | CONCLUSION

This study strengthens previous findings of global cortical thinning, provides novel insight to CSA reduction in adolescent AN, and indicates that both morphometrics are strongly related to BMI reduction. Compared to traditional volume analyses, the more powerful joint NPC analytic strategy shows that mass reduction in adolescent AN may be even more extensive than previously shown. To extend our knowledge on cortical changes in AN, and their relation to BMI, this analytic strategy may be recommended for longitudinal studies in recovering AN patients to investigate potential reductions remaining after weight rehabilitation. Such studies are important to understand for instance why body dissatisfaction tend to be more resilient to treatment compared to more behavioral symptoms of AN.

CONFLICT OF INTEREST

The authors have no conflict to declare.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author, ADM, upon reasonable request.

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REFERENCES

Amianto, F., Caroppo, P., D'Agata, F., Spalatro, A., Lavagnino, L., Caglio, M., … Fassino, S. (2013). Brain volumetric abnormalities in patients with anorexia and bulimia nervosa: A voxel-based morphometry study. *Psychiatry Research—Neuroimaging*, *213*(3), 210–216. https://doi.org/10.1016/j.pscychresns.2013.03.010

Ashburner, J., & Friston, K. J. (2000). Voxel-based morphometry—The methods. *NeuroImage*, *11*(6), 805–821. https://doi.org/10.1006/NIMG.2000.0582

Beck, A. T., Steer, R. A., & Carbin, M. G. (1988). Psychometric properties of the Beck depression inventory: Twenty-five years of evaluation. *Clinical Psychology Review*, *8*(1), 77–100. https://doi.org/10.1016/0272-7358(88)90050-5

Bernardoni, F., King, J. A., Geisler, D., Stein, E., Jaite, C., Nätsch, D., … Ehrlich, S. (2016). Weight restoration therapy rapidly reverses cortical thinning in anorexia nervosa: A longitudinal study. *NeuroImage*, *130*, 214–222. https://doi.org/10.1016/J.NEUROIMAGE.2016.02.003

Bomba, M., Riva, A., Veggo, F., Grimaldi, M., Morzenti, S., Neri, F., & Nacinovich, R. (2013). Impact of speed and magnitude of weight loss on the development of brain trophic changes in adolescents with anorexia nervosa: A case control study. *Italian Journal of Pediatrics*, *39*(1), 14. https://doi.org/10.1186/1824-7288-39-14

Brooks, S. J., Barker, G. J., O'Daly, O. G., Brammer, M., Williams, S. C. R., Benedict, C., … Campbell, I. C. (2011). Restraint of appetite and reduced regional brain volumes in anorexia nervosa: A voxel-based morphometric study. *BMC Psychiatry*, *11*(1), 179. https://doi.org/10.1186/1471-244X-11-179

Desikan, R. S., Ségonne, F., Fischl, B., Quinn, B. T., Dickerson, B. C., Blacker, D., … Killiany, R. J. (2006). An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. *NeuroImage*, *31*(3), 968–980. https://doi.org/10.1016/j.neuroimage.2006.01.021

Fairburn, C. G., & Beglin, S. J. (2008). Eating disorder examination questionnaire (6.0). In C. G. Fairburn (Ed.), *Cognitive behavior therapy and eating disorders*. New York: Guilford Press.

Fischl, B., Salat, D. H., Busa, E., Albert, M., Dieterich, M., Haselgrove, C., … Dale, A. M. (2002). Whole brain segmentation: Automated labeling of neuroanatomical structures in the human brain. *Neuron*, *33*(3), 341–355. https://doi.org/10.1016/S0896-6273(02)00569-X

Fischl, B., Van Der Kouwe, A., Destrieux, C., Halgren, E., Ségonne, F., Salat, D. H., … Dale, A. M. (2004). Automatically parcellating the human cerebral cortex. *Cerebral Cortex*, *14*(1), 11–22. https://doi.org/10.1093/cercor/bhg087

Fisher, R. A. (1934). *Statistical methods for research workers* (5th ed.). Edinburgh & London: Oliver and Boyd.

Fjell, A. M., Grydeland, H., Krogsrud, S. K., Amlien, I., Rohani, D. A., Ferschmann, L., … Walhovd K. B. (2015). Development and aging of cortical thickness correspond to genetic organization patterns. *Proceedings of the National Academy of Sciences*, *112*(50), 15462–15467. http://dx.doi.org/10.1073/pnas.1508831112

Fonville, L., Giampietro, V., Williams, S. C. R., Simmons, A., & Tchanturia, K. (2014). Alterations in brain structure in adults with anorexia nervosa and the impact of illness duration. *Psychological Medicine*, *44*(9), 1965–1975. https://doi.org/10.1017/S0033291713002389

Frank, G. K. W., Shott, M. E., Hagman, J. O., & Yang, T. T. (2013). Localized brain volume and white matter integrity alterations in adolescent anorexia nervosa. *Journal of the American Academy of Child and Adolescent Psychiatry*, *52*(10), 1066–1075.e5. https://doi.org/10.1016/j.jaac.2013.07.007

Gaudio, S., Nocchi, F., Franchin, T., Genovese, E., Cannatà, V., Longo, D., & Fariello, G. (2011). Gray matter decrease distribution in the early stages of anorexia nervosa restrictive type in adolescents. *Psychiatry Research: Neuroimaging*, *191*(1), 24–30. https://doi.org/10.1016/j.pscychresns.2010.06.007

Jack, C. R., Bernstein, M. A., Fox, N. C., Thompson, P., Alexander, G., Harvey, D., … Weiner, M. W. (2008, April). The Alzheimer's Disease Neuroimaging Initiative (ADNI): MRI methods. *Journal of Magnetic Resonance Imaging*, *27*, 685–691. NIH Public Access. https://doi.org/10.1002/jmri.21049

Kaufmann, L. K., Hänggi, J., Jäncke, L., Baur, V., Piccirelli, M., Kollias, S., … Milos, G. (2020). Age influences structural brain restoration during weight gain therapy in anorexia nervosa. *Translational Psychiatry*, *10*(1), 126. https://doi.org/10.1038/s41398-020-0809-7

King, J. A., Frank, G. K. W., Thompson, P. M., & Ehrlich, S. (2018). Structural neuroimaging of anorexia nervosa: Future directions in the quest for mechanisms underlying dynamic alterations. *Biological Psychiatry*, *83*(3), 224–234. https://doi.org/10.1016/J.BIOPSYCH.2017.08.011

King, J. A., Geisler, D., Ritschel, F., Boehm, I., Seidel, M., Roschinski, B., … Ehrlich, S. (2015). Global cortical thinning in acute anorexia nervosa normalizes following long-term weight restoration. *Biological Psychiatry*, *77*(7), 624–632. https://doi.org/10.1016/j.biopsych.2014.09.005

Lavagnino, L., Mwangi, B., Cao, B., Shott, M. E., Soares, J. C., & Frank, G. K. W. (2018). Cortical thickness patterns as state biomarker of anorexia nervosa. *International Journal of Eating Disorders*, *51*(3), 241–249. https://doi.org/10.1002/eat.22828

Leppanen, J., Sedgewick, F., Cardi, V., Treasure, J., & Tchanturia, K. (2019). Cortical morphometry in anorexia nervosa: An out-of-sample replication study. *European Eating Disorders Review*, *27*(5), erv.2686. https://doi.org/10.1002/erv.2686

Mainz, V., Schulte-Ruther, M., Fink, G. R., Herpertz-Dahlmann, B., & Konrad, K. (2012). Structural brain abnormalities in adolescent anorexia nervosa before and after weight recovery and associated hormonal changes. *Psychosomatic Medicine*, *74*(6), 574–582. https://doi.org/10.1097/PSY.0b013e31824ef10e

Miles, A. E., Voineskos, A. N., French, L., & Kaplan, A. S. (2018). Subcortical volume and cortical surface architecture in women with acute and remitted anorexia nervosa: An exploratory neuroimaging study. *Journal of Psychiatric Research*, *102*, 179–185. https://doi.org/10.1016/j.jpsychires.2018.04.010

Myrvang, A. D., Vangberg, T. R., Stedal, K., Rø, Ø., Endestad, T., Rosenvinge, J. H., & Aslaksen, P. M. (2018). Hippocampal subfields in adolescent anorexia nervosa. *Psychiatry Research: Neuroimaging*, *282*, 24–30. https://doi.org/10.1016/J.PSCYCHRESNS.2018.10.007

Nickel, K., Joos, A., Tebartz van Elst, L., Matthis, J., Holovics, L., Endres, D., … Maier, S. (2018). Recovery of cortical volume and thickness after remission from acute anorexia nervosa. *International Journal of Eating Disorders*, *51*(9), 1056–1069. https://doi.org/10.1002/eat.22918

Panizzon, M. S., Fennema-Notestine, C., Eyler, L. T., Jernigan, T. L., Prom-Wormley, E., Neale, M., … Kremen, W. S. (2009). Distinct genetic influences on cortical surface area and cortical thickness. *Cerebral Cortex*, *19*(11), 2728–2735. https://doi.org/10.1093/cercor/bhp026

Schmaal, L., Hibar, D. P., Sämann, P. G., Hall, G. B., Baune, B. T., & Jahanshad, N. (2016). Cortical abnormalities in adults and adolescents with major depression based on brain scans from 20 cohorts worldwide in the ENIGMA major depressive disorder working group. *Nature Publishing Group*, *22*, 900–909. https://doi.org/10.1038/mp.2016.60

Seitz, J., Herpertz-Dahlmann, B., & Konrad, K. (2016). Brain morphological changes in adolescent and adult patients with anorexia nervosa. *Journal of Neural Transmission*, *123*(8), 949–959. https://doi.org/10.1007/s00702-016-1567-9

Seitz, J., Walter, M., Mainz, V., Herpertz-Dahlmann, B., Konrad, K., & von Polier, G. (2015). Brain volume reduction predicts weight development in adolescent patients with anorexia nervosa. *Journal of Psychiatric Research*, *68*, 228–237. https://doi.org/10.1016/j.jpsychires.2015.06.019

Smith, S. M., & Nichols, T. E. (2009). Threshold-free cluster enhancement: Addressing problems of smoothing, threshold dependence and localisation in cluster inference. *NeuroImage*, *44*(1), 83–98. https://doi.org/10.1016/j.neuroimage.2008.03.061

Spielberger, C. D., Gorusuch, R. L., & Lushene, R. E. (1970). *Manual for the state-trait anxiety inventory*. Palo Alto, CA: Consulting Psychologists Press.

Wierenga, L. M., Langen, M., Oranje, B., & Durston, S. (2014). Unique developmental trajectories of cortical thickness and surface area. *NeuroImage*, *87*, 120–126. https://doi.org/10.1016/j.neuroimage.2013.11.010

Winkler, A. M., Greve, D. N., Bjuland, K. J., Nichols, T. E., Sabuncu, M. R., Håberg, A. K., … Rimol, L. M. (2018). Joint analysis of cortical area and thickness as a replacement for the analysis of the volume of the cerebral cortex. *Cerebral Cortex*, *28*(2), 738–749. https://doi.org/10.1093/cercor/bhx308

Winkler, A. M., Kochunov, P., Blangero, J., Almasy, L., Zilles, K., Fox, P. T., … Glahn, D. C. (2010). Cortical thickness or grey matter volume? The importance of selecting the phenotype for imaging genetics studies. *NeuroImage*, *53*(3), 1135–1146. https://doi.org/10.1016/J.NEUROIMAGE.2009.12.028

Winkler, A. M., Ridgway, G. R., Webster, M. A., Smith, S. M., & Nichols, T. E. (2014). Permutation inference for the general linear model. *NeuroImage*, *92*, 381–397. https://doi.org/10.1016/j.neuroimage.2014.01.060

Winkler, A. M., Webster, M. A., Brooks, J. C., Tracey, I., Smith, S. M., & Nichols, T. E. (2016). Non-parametric combination and related permutation tests for neuroimaging. *Human Brain Mapping*, *37*(4), 1486–1511. https://doi.org/10.1002/hbm.23115

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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