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RESEARCH ARTICLE

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Associations of age, body mass index and biochemical parameters with brain morphology in patients with anorexia nervosa

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Abstract

OBJECTIVE: Accumulating evidence shows that patients with anorexia nervosa (AN) have globally reduced brain mass, including lower cortical volume and thickness, which largely normalizes following weight restoration. The underlying mechanisms for these processes are unknown, and how age and severity of emaciation are associated with brain morphology in AN is poorly understood. We investigated associations of age, body mass index (BMI) and biochemical parameters with brain morphology among patients in treatment.

METHOD: We included 85 patients (94% female) aged 12–48 (mean = 23) years with quality controlled magnetic resonance imaging (MRI) data. T1-weighted MRI images, clinical characteristics and biochemical parameters were retrospectively collected from hospital records. Brain morphology was measured using FreeSurfer, and associations investigated using regression models and correlations.

Abbreviations: AN, Anorexia nervosa; ANCOVA, Analysis of covariance; ANOVA, Analysis of variance; BMI, Body mass index (kg/m2); BMI SDS, Body mass index standard deviation score; CRP, C-reactive protein; EVF, Erythrocyte volume fraction; GM, Gray matter; ICV, Intracranial volume; LD, Lactate dehydrogenase; MRI, Magnetic resonance imaging; pCO_2, Partial pressure of carbon dioxide; WM: White matter.

RESULTS: Controlling for BMI, age showed significant associations with brain morphology generally concordant with typical brain developmental patterns. Controlling for age, BMI showed significant positive associations with cortical volume and thickness. There were no significant interaction effects between age and BMI. None of the biochemical parameters correlated significantly with brain morphology.

CONCLUSION: Our findings suggest the presence of typical neurodevelopmental patterns in AN. Importantly, we showed that severity of emaciation is related to brain morphology reductions, underscoring the importance of weight restoration.

KEYWORDS
anorexia nervosa, biochemistry, body mass index, brain, growth and development

1 | INTRODUCTION

Accumulating evidence shows that patients with anorexia nervosa (AN) have globally reduced grey matter (GM) and white matter (WM) brain volumes compared to healthy individuals (Seitz, Herpertz-Dahlmann, & Konrad, 2016; Titova, Hjorth, Schioth, & Brooks, 2013; Van den Eynde et al., 2012). The GM reductions comprise both cortical and subcortical tissues and especially thinning of the cerebral cortex (Bär, de la Cruz, Berger, Schultz, & Wagner, 2015; Cascino et al., 2020; King et al., 2015; Miles, Voineskos, French, & Kaplan, 2018; Nickel et al., 2018). Some studies have also found greater cortical volume and thickness in local regions (Boghi et al., 2011; Brooks et al., 2011; Frank, Shott, Hagman, & Mittal, 2013; Lavagnino et al., 2018).

Evidence from longitudinal studies indicates that AN-related brain alterations largely normalize during weight restoration treatment (Bernardoni et al., 2016; Bomba et al., 2015; Kaufmann et al., 2020; Mainz, Schulte-Rüther, Fink, Herpertz-Dahlmann, & Konrad, 2012). Accordingly, recovered patients with normal body weights typically show no significant differences in gross brain morphology compared to healthy individuals (Bang, Rø, & Endestad, 2016; Bernardoni et al., 2016; Cascino et al., 2020; Lázaro et al., 2013; Wagner et al., 2006), although some studies report persistent small local alterations (Castro-Fornieles et al., 2019; Frank et al., 2013; Lavagnino et al., 2018). Collectively, these findings suggest the alterations in brain morphology are secondary to emaciation and largely reversible with weight restoration.

The underlying neurobiological mechanisms of the dynamic brain morphology alterations in AN remain unknown. Several hypotheses have been proposed, including dehydration, loss of neuronal or glial cells and hormonal changes (King, Frank, Thompson, & Ehrlich, 2018). Few studies have investigated associations between biochemical/hormonal parameters and brain morphology, which could shed light on mechanistic relations. Preliminary evidence supports a relationship between brain morphology and hormonal levels, including cortisol (Castro-Fornieles et al., 2009; Mainz et al., 2012) and follicle-stimulating hormone (Mainz et al., 2012). In contrast, two previous studies considered serum albumin and hydration indices as measures of dehydration and fluid shifts, but found that these were within normal range and thus unlikely to contribute to brain alterations (Bernardoni et al., 2016; King et al., 2015). Given the dearth of studies, there is a need to consider additional biochemical parameters known to be affected in AN, such as electrolyte and acid-base imbalances (Winston, 2012), and their associations with brain morphology. Shedding light on these relationships may advance our understanding of the

Highlights

- Age showed significant associations with brain morphology generally concordant with known typical brain developmental patterns
- Body mass index showed significant positive associations with cortical volume and thickness
- There were no significant interaction effects between age and body mass index on brain morphology, and none of the biochemical parameters correlated significantly with brain morphology

mechanisms underlying the dynamic brain morphology alterations in AN.

The extent to which severity of emaciation and age are related to brain morphology alterations in AN is poorly understood. While some studies report positive associations between body mass index (BMI, kg/m^2) and cortical volume and thickness (Lavagnino et al., 2016; Nickel et al., 2018), others have not found similar relations (Curzio et al., 2020; Fuglset et al., 2016; King et al., 2015). It is therefore unclear whether increased AN severity is related to greater brain morphology alterations. Moreover, age and neurodevelopment constitutes an additional factor that may influence the extent of brain morphology alterations among patients, but few studies have investigated this. It is well documented that typical neurodevelopment from childhood to adulthood involves GM volume decreases, cortical volume and thickness decreases, and WM volume increases with increasing age (Lebel & Beaulieu, 2011; Mills et al., 2016; Tamnes et al., 2017). A previous study (King et al., 2015) reported an absence of the expected age-related changes in cortical thickness among patients with AN, indicating disrupted neurodevelopment. Similarly, one review concluded that the reductions in brain mass appear to be larger among adolescent as opposed to adult patients with AN (Seitz et al., 2016), raising concerns about the influence of emaciation on neurodevelopment. It was also recently reported that restoration of brain morphology during treatment is age dependent, with younger patients recuperating faster than older patients (Kaufmann et al., 2020). Thus, exactly how age influences brain morphology in AN and whether neurodevelopment is disrupted is unclear. One possibility is that age moderates the relationship between BMI and brain morphology, such that low body weight is associated with greater brain mass reductions among younger as compared to older patients. Studies attempting to untangle the complex relationships between age, BMI and brain morphology are thus critically needed.

The current study investigated the relationship between brain morphology and clinical characteristics in a large sample of patients with AN receiving weight restoration treatment. Our primary aim was to estimate the associations of age and BMI with brain morphology. We hypothesized that age would exhibit negative associations with cortical volumes and thickness and positive associations with WM volumes, in line with known typical neurodevelopmental patterns. We hypothesized that BMI would exhibit positive associations with brain morphology, in line with prior studies showing normalization of brain tissues following weight restoration. Additionally, we hypothesized an interaction effect between age and BMI, which would indicate the presence of a moderating effect of age on the association between BMI and brain morphology. A secondary aim was to explore potential biochemical correlates of brain morphology in order to elucidate mechanisms underlying brain alterations. As these analyses were considered exploratory, we had no formal hypotheses.

2 | METHODS

2.1 | Participants

This study utilized hospital records to retrospectively identify patients with AN who had completed a magnetic resonance imaging (MRI) examination of their brain during treatment at Oslo University Hospital (Norway). Patients were eligible if: (a) they had been admitted to Oslo University Hospital with a primary AN diagnosis and (b) they had completed a T1-weighted MRI examination of their brain.

A total of 212 eligible patients were identified; but only 85 patients were included in the final sample, for which both clinical information and quality controlled neuroimaging data were available (see MRI analysis and quality control below for details regarding excluded patients). Included patients had a primary AN diagnosis according to ICD criteria and had been admitted to one of two specialized treatment units at Oslo University Hospital between 2007 and 2018. Both units provide in- and outpatient treatment to patients with eating disorders, with weight rehabilitation as a primary goal of treatment. One unit admits patients of all ages, and the other admits patients under the age of 18.

Patients with AN who are admitted to these units are routinely referred to a clinical MRI examination of their brain, to rule out organic causes of their disordered eating. The timing of the MRI examination varies, but typically occurs about one month after admission (due to medically unstable patients or wait-list for the MRI scanner). All MR images acquired from patients are stored, allowing us to retrospectively access these years after they were collected. The study was approved by the Regional Committee for Medical and Health Research Ethics (#2017/716) and given an exempt from the normal requirement of informed consent.

2.2 | Clinical information

Clinical information was acquired from patient records and included details about the patients and their treatment. Information regarding BMI was extracted and converted to standard deviation scores (SDS, adjusted for

age and gender) using national Norwegian references (Júlíusson et al., 2013). Patients older than 19 years were assigned an age of 19 years for calculating Body mass index standard deviation score (BMI SDS).

Information on biochemical parameters measured by clinical lab analyses of venous blood samples was collected from patient records. As few studies have considered the influence of such parameters on brain morphology in AN, we included all parameters available to us, in order to provide preliminary evidence regarding their associations with brain morphology. Specific biochemical parameters were missing for many patients (i.e., they were not collected at the time of the MRI examination), so we only included parameters that were available for 25 patients or more. These included levels of electrolytes (calcium, sodium, potassium, chloride, phosphate, bicarbonate), albumin, base excess, partial pressure of carbon dioxide (pCO_2), C-reactive protein, erythrocyte volume fraction, lactate dehydrogenase, pH and haemoglobin. Analyses of blood samples were performed as part of routine clinical evaluation at Oslo University Hospital.

As height, weight, biochemical parameters and MRI data were originally collected for clinical purposes, they were not necessarily collected on the same day. We only included height/weight measurements that were performed within 31 days of the MRI examination, and biochemical parameters that were performed within 7 days. Patients were weighed on average 4 days before the MRI examination, and biochemical parameters were collected on average 0.11 days before the MRI examination (see Table 1).

2.3 | MRI acquisition

Neuroimaging of the final sample was attained on eight separate whole body scanners from GE medical systems (one 3T scanner), Siemens (four 1.5T scanners) and Philips Medical Systems (two 1.5T and one 3T scanners). The specific sequences within each scanner varied, as they were based on clinical protocols. See Tables S1 and S2 for an overview of the various MRI scanners and sequences and brain morphology estimates for each scanner, respectively. Figures S1–S3 present visual depictions of age distributions, BMI and brain morphology estimates across scanners.

2.4 | MRI analysis and quality control

A total of 212 patients were eligible for inclusion, and T1-weighted datasets from these patients underwent processing and quality control. Datasets were processed using the automatic software suite FreeSurfer 6.0, documented and freely available online (http://surfer.nmr.mgh.harvard.edu/). The technical details of the procedures have previously been described in detail (Dale, Fischl, & Sereno, 1999; Fischl, 2012; Fischl et al., 2002; Fischl, Sereno, & Dale, 1999). In short, FreeSurfer performs volumetric segmentations and cortical surface reconstructions, including the 'pial' (grey/cerebrospinal fluid boundary) and 'white' (grey/WM boundary) surface. Cortical thickness was computed as the shortest vertex-wise distance between the white and pial surface, while cortical surface area, based on the white surface, was computed by the amount of vertex-wise contraction and expansion required to fit a common template (fsaverage). Acknowledging the limitations in pooling clinical neuroimaging data from several scanners, we focussed on global brain morphology measures, including cortical volume, cortical thickness, cortical surface area, total subcortical volumes, cerebral WM volume, cerebellar GM volume, cerebellar WM volume and ventricular volumes (the combined volume of the lateral ventricles, the inferior lateral ventricles and the third ventricle). All MRI variables were summed (or averaged for cortical thickness) across hemispheres.

As the MRI data were collected in a clinical context, the data quality varied extensively. FreeSurfer was only able to successfully process 147 of the total 212 eligible MR images. The resulting 147 FreeSurfer processed scans were subjected to both manual and automatic quality control. First, all images and segmentations were visually inspected post-processing by a trained operator (Christian Krog Tamnes) for accuracy and rated as acceptable or not acceptable. Second, Qoala-T 1.2 (Klapwijk, van de Kamp, van der Meulen, Peters, & Wierenga, 2019) was used to automatically assess the quality of segmented data (see Figure S4 for results from Qoala-T quality control), yielding recommendations for inclusion or exclusion. The overlap between the two methods was very high, with the same recommendation for 142 of the 147 scans. In cases of disagreement between the manual and the automatic quality control, a second visual inspection was performed to decide on whether to include or exclude the scan. A total of 56 scans were excluded. Six additional patients were excluded as it was discovered that necessary clinical information was unavailable, yielding a total of 85 patients with quality controlled MRI data for the final sample.

To explore whether the 56 patients excluded during quality control differed from the 85 patients included in the final sample, we compared groups on key variables. Of the excluded patients, 91% were female, 93% were inpatient, 20% were committed involuntarily and 14%

TABLE 1 Clinical characteristics

	Mean ± SD	Median (range)	*n*
Age	23.43 ± 8.04	21.42 (12.92; 48.17)	85
Admission BMI	15.04 ± 2.03	14.75 (10.16; 19.93)	84
Admission BMI SDS	−3.83 ± 1.79	−3.58 (−9.70; −0.72)	83
BMI at MRI	15.93 ± 2.08	15.64 (9.71; 20.73)	80
BMI SDS at MRI	−3.16 ± 1.69	−3.06 (−10.61; −0.38)	80
Days from admission to MRI	44.73 ± 49.19	31.00 (1; 308)	85
Days between weighing and MRI	4.17 ± 8.36	1.00 (−14; 31)[a]	80
Days between blood sample and MRI	0.11 ± 1.67	0.00 (−7; 3)[a]	76
	Count (%)		***n***
Gender	80 (94) female		85
In- or outpatient admission?	77 (91) inpatient		85
Patient committed involuntarily?	18 (21) yes		85
On psychoactive medication?	22 (26) yes		85

Abbreviations: BMI, body mass index (kg/m^2); BMI SDS, body mass index standard deviation score; MRI, magnetic resonance imaging; SD, standard deviation.

[a]Negative values indicate weight/blood sample was collected after the MRI examination.

were on psychoactive medications. These proportions were similar to the included patients (X^2 and Fisher's exact tests: all p's > 0.07). Excluded patients had a mean age of 20.93 (SD = 7.88) years and a mean BMI SDS of −2.77 (SD = 1.58), see Figure S5 for distributions. While BMI SDS did not differ significantly between excluded and included patients (analysis of covariance [ANCOVA]: $p = 0.28$ while controlling for age), excluded patients were significantly younger (ANCOVA: $p = 0.047$, while controlling for BMI SDS). Further inspection showed that a larger proportion of excluded compared to included patients were < 18 years of age (46% vs. 26%), which may have contributed to poor image quality due to increased movement during MRI examinations in younger individuals.

2.5 | Statistical analyses

Pearson r correlations were used to investigate associations between age, BMI, treatment duration and estimated intracranial volume (ICV). ANCOVAs were performed to describe differences between patients on psychoactive medications to patients who were not, with regard to brain morphology (controlling for age, BMI SDS and ICV), age (controlling for BMI SDS) and BMI SDS (controlling for age). Alpha-levels for these tests were not adjusted for multiple comparisons, as they were not related to our primary aims.

To investigate associations of age and BMI with brain morphology, linear multiple regression analyses were performed. Age and BMI SDS were entered as independent variables (both mean-centred), and an interaction term between age and BMI SDS was included to explore presence of moderating effects. ICV was included as a covariate, as we were interested in associations of age and BMI with brain morphology relative to ICV. Additionally, MRI scanner was included as a covariate to control for the effects of multiple scanners. The model is summarized in the following equation:

$$Y = A + \beta_{\text{age}} + \beta_{\text{BMI SDS}} + \beta_{[\text{age}\times\text{BMI SDS}]} + \beta_{\text{ICV}} + \beta_{\text{scanner}}$$

Y represents the measures of brain morphology and A is the intercept. Alpha-levels were corrected for multiple comparisons according to a Bonferroni–Holm adjustment corresponding to number of independent variables of interest ($n = 3$) for each measure of brain morphology. To ease interpretation, we report adjusted p-values, with $p < 0.05$ considered statistically significant. In Table S3, we also present regression models without ICV as a covariate (i.e., absolute brain morphology), as it has been recommended that such results are made available to show the impact of ICV on results (Mills & Tamnes, 2014).

To investigate associations between biochemical parameters and brain morphology, partial Pearson

r correlations (controlling for ICV) were performed. Alpha-levels were corrected for multiple comparisons according to a Bonferroni–Holm procedure, corresponding to the number of biochemical parameters of interest ($n = 15$). We report adjusted p-values, with $p < 0.05$ considered statistically significant. All analyses were performed in R version 3.6.1 (R Core Team, 2019).

3 | RESULTS

3.1 | Clinical characteristics

Table 1 presents clinical characteristics of the 85 patients included in the analyses. Twenty-two patients (26%) were < 18 years of age, and five were male. Patients had been admitted for an average of 45 days prior to the MRI examination. Between admission and the MRI examination, there was a mean weight gain of 2.66 kg, corresponding to 0.89 BMI and 0.67 BMI SDS units. There was a small but significant positive correlation between treatment duration and BMI SDS at the time of the MRI ($r = 0.27$, $p = 0.02$), illustrating that patients gained weight during treatment. Eighty-two percent of patients had a BMI < 18.5 and 76% a BMI SDS corresponding to underweight at the MRI examination. No significant correlation existed between age and BMI SDS ($r = -0.17$, $p = 0.14$). There was also no significant correlation between ICV and BMI SDS ($r = 0.15$, $p = 0.18$) or age ($r = -0.03$, $p = 0.79$). Approximately 26% ($n = 22$) of patients were on psychoactive medications, including antipsychotics ($n = 10$), antidepressants ($n = 4$), antihistamines ($n = 3$), hypnotics ($n = 2$), benzodiazepines ($n = 1$) and a combination of two or more of these ($n = 2$). ANCOVAs showed that those on medications were similar in age and BMI SDS to those not on medications (p's > 0.54). Patients on medications had larger cortical thickness estimates ($p = 0.02$), but groups were not significantly different with regard to remaining brain morphology measures (p's > 0.07), although some comparisons were trending towards significance (i.e., $p < 0.10$). Because of this, we assessed the impact of including medication status as a covariate in the regression models (see additional covariates below).

3.2 | Associations between age and brain morphology

Age showed significant negative associations with cortical volume, cortical thickness and a significant

TABLE 2 Results from regression models

	BMI SDS			Age			Interaction BMI SDS × Age		
	β (95% CI)	SE	p	β (95% CI)	SE	P	β (95% CI)	SE	p
Cortical volume	8115.50 (3975.78; 12255.23)	2074.56	<0.001[a]	−1719.20 (−2668.14; −770.27)	475.55	0.001[a]	−366.32 (−1036.50; 303.86)	335.85	0.28
Cortical thickness	0.027 (0.014; 0.041)	0.007	<0.001[a]	−0.004 (−0.007; −0.001)	0.002	0.02[a]	−0.001 (−0.003; 0.001)	0.001	0.27
Cortical surface area	1869.29 (−700.69; 1836.25)	1118.31	0.20	−493.92 (−475.74; 105.80)	256.08	0.17	−71.43 (−254.20; 156.51)	182.77	0.70
Subcortical volumes	−188.76 (−609.07; 231.56)	210.64	0.75	−109.34 (−205.69; −12.99)	48.28	0.08	−6.25 (−74.29; 61.80)	34.10	0.86
Cerebral WM volume	−985.48 (−5013.29; 3042.33)	2018.48	1.00	1263.03 (339.74; 2186.31)	462.69	0.02[a]	140.60 (−511.47; 792.66)	326.77	1.00
Cerebellar GM volume	58.70 (−1160.22; 1277.62)	610.84	1.00	−62.14 (−341.55; 217.27)	140.02	1.00	−280.87 (−298.32; 109.89)	113.79	1.00
Cerebellar WM volume	−25.64 (−680.85; 629.57)	328.35	1.00	−24.56 (−174.75; 125.63)	75.27	1.00	36.24 (−69.84; 142.31)	53.16	1.00
Ventricular volumes	−891.23 (−1990.76; 208.30)	551.01	0.33	201.86 (−50.18; 453.90)	126.31	0.33	34.22 (−143.79; 212.22)	89.20	0.70

Notes: All models included estimated intracranial volume and scanner as covariates (df = 68). Cortical thickness expressed in millimetres, cortical surface area in millimetres^2 and remaining variables in millimetres^3. p-values are adjusted according to a Bonferroni–Holm correction.

Abbreviations: BMI SDS, body mass index (kg/m^2) standard deviation score; CI, confidence interval; GM, grey matter; SE, standard error; WM, white matter.

[a]Statistically significant.

positive association with cerebral WM volume (Table 2). No other significant associations were evident, although we note that the negative association between age and subcortical volumes was significant ($p = 0.03$) prior to alpha-level correction for multiple comparisons. These results imply that increasing age (while controlling for BMI) is associated with tissue specific changes in brain morphology in patients with AN, generally in accordance with typical patterns of structural brain development (Mills et al., 2016; Tamnes et al., 2017).

3.3 | Association between BMI and brain morphology

BMI SDS showed a significant positive association with both cortical volume and thickness (Table 2). This indicates that lower BMI (while controlling for age) is associated with reduced cortical volume and thickness. These effects were larger than the effects of age. No other significant associations were evident. As no relationship was found between BMI SDS and cortical surface area, the association between BMI SDS and cortical volume is likely driven by differences in cortical thickness.

3.4 | Interaction effect age * BMI

The interaction term was not significant in any of the models (Table 2), indicating that the influence of age and BMI on brain morphology highlighted above constitute independent effects. Thus, we found no evidence of moderating effects.

3.5 | Additional covariates

To explore whether medication status and days between weighing and MRI influenced the associations of age and BMI with brain morphology, regression models were rerun with these variables as covariates. Analysis of variance tests showed that model fit did not improve as a result of this (p's > 0.13), and results did not change.

Scatterplots depicting the significant associations of BMI SDS and age with brain morphology are presented in Figure 1 (Figures S6–S7 present all scatterplots). Note that scatterplots show associations unadjusted for ICV. Inspection of these identified one patient whose cortical volume and thickness estimates were extremely low, and this patient also had the lowest BMI. To rule out the possibility that this patient was driving the observed associations between BMI and brain morphology, we excluded this patient and reran the regression models. This did not alter the statistical outcomes of the models. Regression models were also performed after excluding the five male patients, which had no effect on the statistical outcomes of the models.

3.6 | Correlations between biochemical parameters and brain morphology

Biochemical parameters for most patients were within reference intervals (Figures S8–S9 present distributions of all biochemical parameters). However, albumin, bicarbonate, pCO_2 and base excess were above the reference intervals for a considerable proportion of patients. Additionally, pH was below the reference interval for approximately 50% of patients. Table 3 shows all pairwise partial correlations between biochemical parameters and brain morphology variables. No significant correlations were evident, and the majority of correlation coefficients were of small magnitude. These correlations were also non-significant prior to alpha-level correction. Excluding the five male patients had no effect on the statistical outcomes of the correlations.

4 | DISCUSSION

The current study showed that age and BMI are independently associated with brain morphology in AN. Age-related effects were observed for several measures of brain morphology and were generally concordant with prior studies of typical neurodevelopment. Lower BMI was associated with greater reductions to cortical volume and thickness, indicating a relationship between severity of emaciation and brain alterations. However, we did not find evidence to support an interaction effect between age and BMI. Moreover, none of the biochemical parameters were associated with brain morphology.

Our finding that increasing age is associated with decreased cortical volume and thickness and increased cerebral WM volume align with prior studies of typical neurodevelopment (Lebel & Beaulieu, 2011; Mills et al., 2016; Tamnes et al., 2017). These results generally indicate typical neurodevelopmental patterns among patients with AN. Interestingly, a previous study of patients with AN failed to find a relationship between age and cortical thickness (King et al., 2015), which the authors suggested may be related to interrupted neurodevelopment. Another study (Kaufmann et al., 2020) reported that age correlated with restoration of cortical thickness during treatment, with younger patients recuperating faster than older patients. This may reflect increased brain plasticity among younger patients and together with our findings

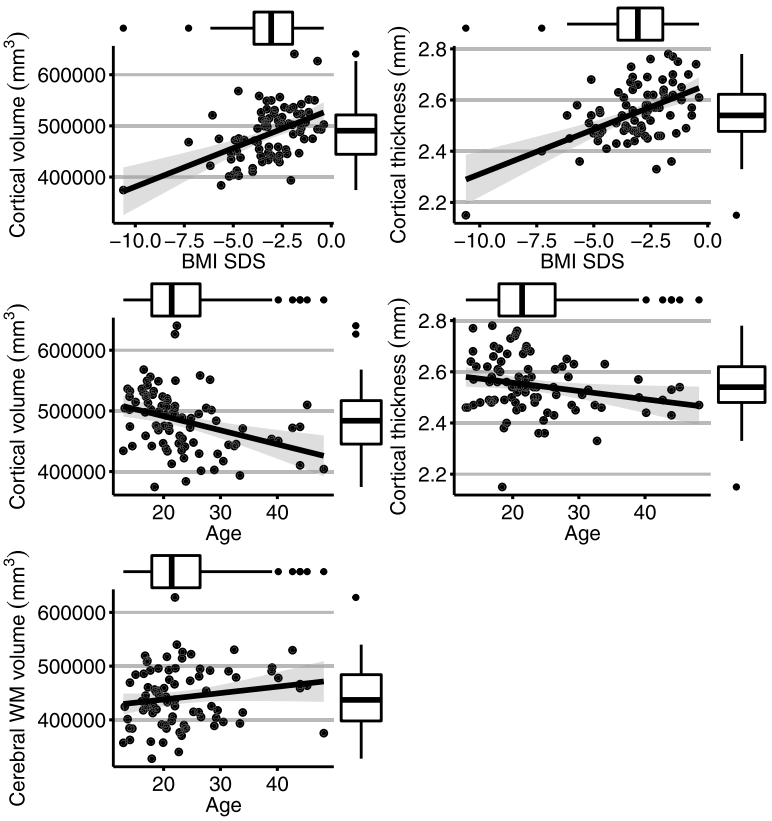

FIGURE 1 Scatterplots showing associations of BMI SDS and age with brain morphology. Only associations significant in regression models are shown. BMI SDS, body mass index (kg/m^2) standard deviation score; Mm, millimetres; WM, white matter

highlights the need for future longitudinal studies to consider individual development of brain morphology in AN. One caveat of our study is that we were unable to disentangle age effects from duration of AN, but prior studies have reported that duration of AN is unrelated to brain morphology (Bernardoni et al., 2016; Kaufmann et al., 2020; Nickel et al., 2018).

Lower BMI was associated with decreased cortical volume and thickness, indicating that severity of emaciation is related to brain mass reductions. These associations corresponded to 0.03 mm decrease in cortical thickness for each unit decrease in BMI SDS and 0.12 dl decrease in cortical volume for each unit decrease in BMI SDS (in absolute terms). The effects of BMI were larger than the effects of age, in line with prior reports (Bernardoni et al., 2016). Previous studies have produced inconsistent results regarding whether severity of emaciation is significantly associated with brain morphology, with some supporting this association (Lavagnino et al., 2016; Nickel et al., 2018) while others do not (Cascino et al., 2020; Curzio et al., 2020; Fuglset et al., 2016; King et al., 2015). The reasons for this discrepancy are unclear, though statistical power may constitute one important factor. Our study included a large sample of patients who varied considerably in BMI, which may have provided sufficient statistical power. Our findings align with converging evidence from longitudinal studies of the strong influence of weight restoration on cortical volume (Bernardoni et al., 2016; Kaufmann et al., 2020; Mainz et al., 2012; Roberto et al., 2011) and thickness (Bernardoni et al., 2016; Kaufmann et al., 2020). Of note, we focussed on global measures of brain morphology and were unable to investigate associations between BMI and local measures of brain morphology. Some studies have reported increased local brain volume and cortical thickness among individuals with AN (Frank et al., 2013; Lavagnino et al., 2018; Leppanen, Sedgewick, Cardi, Treasure, & Tchanturia, 2019), raising the possibility of negative associations between BMI and local measures of brain morphology that we were unable to characterize.

In contrast, we found no evidence of an association between BMI and other measures of brain morphology, including subcortical volumes and WM volumes. Reductions of these volumes are well documented in AN (Bernardoni et al., 2016; Miles et al., 2018; Titova et al., 2013). One possible reason for these null findings is that severity of emaciation is not as directly related to these tissues. We also showed that BMI was significantly associated with cortical thickness but not cortical surface area. Few studies have investigated cortical surface area in AN and current findings are inconsistent, with one study reporting similar cortical surface area (Miles et al.,

TABLE 3 Correlations between biochemical parameters and brain morphology

	Cortical volume	Cortical thickness	Cortical surface area	Subcortical volumes	Cerebral WM volume	Cerebellar GM volume	Cerebellar WM volume	Ventricular volumes
Albumin $n = 64$	0.07 $p = 1.00$	0.06 $p = 1.00$	0.07 $p = 1.00$	0.02 $p = 1.00$	−0.02 $p = 1.00$	0.11 $p = 1.00$	0.09 $p = 1.00$	−0.15 $p = 1.00$
CRP $n = 64$	0.18 $p = 1.00$	0.09 $p = 1.00$	0.14 $p = 1.00$	0.05 $p = 1.00$	−0.03 $p = 1.00$	0.07 $p = 1.00$	0.04 $p = 1.00$	0.04 $p = 1.00$
Sodium $n = 77$	−0.16 $p = 1.00$	−0.17 $p = 1.00$	−0.08 $p = 1.00$	0.17 $p = 1.00$	0.05 $p = 1.00$	0.21 $p = 1.00$	0.13 $p = 1.00$	−0.05 $p = 1.00$
Potassium $n = 78$	−0.04 $p = 1.00$	0.08 $p = 1.00$	−0.10 $p = 1.00$	0.03 $p = 1.00$	−0.00 $p = 1.00$	−0.17 $p = 1.00$	0.02 $p = 1.00$	−0.28 $p = 0.15$
Chloride $n = 37$	−0.12 $p = 1.00$	0.00 $p = 1.00$	−0.14 $p = 1.00$	0.11 $p = 1.00$	0.04 $p = 1.00$	0.17 $p = 1.00$	0.08 $p = 1.00$	0.01 $p = 1.00$
Phosphate $n = 78$	0.18 $p = 1.00$	0.15 $p = 1.00$	0.10 $p = 1.00$	−0.04 $p = 1.00$	−0.06 $p = 1.00$	0.14 $p = 1.00$	0.15 $p = 1.00$	0.01 $p = 1.00$
Calcium $n = 67$	0.03 $p = 1.00$	−0.17 $p = 1.00$	0.20 $p = 1.00$	−0.04 $p = 1.00$	0.00 $p = 1.00$	0.23 $p = 1.00$	0.05 $p = 1.00$	−0.05 $p = 1.00$
Calcium corrected[a] $n = 53$	−0.16 $p = 1.00$	−0.36 $p = 0.14$	0.08 $p = 1.00$	−0.03 $p = 1.00$	−0.00 $p = 1.00$	−0.07 $p = 1.00$	−0.13 $p = 1.00$	0.16 $p = 1.00$
Haemoglobin $n = 65$	0.18 $p = 1.00$	0.23 $p = 0.98$	−0.01 $p = 1.00$	−0.08 $p = 1.00$	−0.26 $p = 0.60$	0.18 $p = 1.00$	−0.04 $p = 1.00$	0.24 $p = 0.65$
EVF $n = 54$	0.14 $p = 1.00$	0.21 $p = 1.00$	−0.06 $p = 1.00$	−0.07 $p = 1.00$	−0.24 $p = 1.00$	0.23 $p = 1.00$	−0.08 $p = 1.00$	0.29 $p = 0.56$
LD $n = 55$	−0.10 $p = 1.00$	−0.16 $p = 1.00$	0.05 $p = 1.00$	−0.29 $p = 0.45$	0.00 $p = 1.00$	−0.03 $p = 1.00$	−0.14 $p = 1.00$	0.02 $p = 1.00$
pH $n = 28$	0.11 $p = 1.00$	0.13 $p = 1.00$	0.03 $p = 1.00$	−0.12 $p = 1.00$	−0.30 $p = 1.00$	0.11 $p = 1.00$	−0.09 $p = 1.00$	0.13 $p = 1.00$
pCO_2 $n = 28$	−0.18 $p = 1.00$	−0.17 $p = 1.00$	0.11 $p = 1.00$	−0.16 $p = 1.00$	0.22 $p = 1.00$	0.07 $p = 1.00$	0.18 $p = 1.00$	−0.38 $p = 0.65$
Bicarbonate $n = 29$	−0.13 $p = 1.00$	−0.12 $p = 1.00$	−0.10 $p = 1.00$	−0.25 $p = 1.00$	0.08 $p = 1.00$	0.16 $p = 1.00$	0.17 $p = 1.00$	−0.34 $p = 0.77$
Base excess $n = 30$	−0.17 $p = 1.00$	−0.11 $p = 1.00$	−0.15 $p = 1.00$	−0.30 $p = 1.00$	0.01 $p = 1.00$	0.23 $p = 1.00$	0.16 $p = 1.00$	−0.30 $p = 1.00$

Note: *p*-values are adjusted according to a Bonferroni–Holm correction, and all correlations are non-significant.

Abbreviations: CRP, C-reactive protein; EVF, erythrocyte volume fraction; GM, grey matter; LD, lactate dehydrogenase; pCO_2, partial pressure of carbon dioxide; WM, white matter.

[a]Calcium corrected for albumin levels.

2018) and another reporting decreased surface area (Leppanen et al., 2019) as compared to healthy individuals. As cortical volume is defined by both cortical thickness and surface area, our findings suggest that the association between BMI and cortical volume is primarily due to thinning of the cortex and not decreased cortical surface area.

While our findings highlight independent associations of both age and BMI with brain morphology, no significant interaction effect was evident. Thus, there was no evidence of a moderating role of age on the association between BMI and brain morphology. Some have noted that younger individuals with AN may have particularly smaller brain volumes (Seitz et al., 2016), raising the possibility that malnutrition and low body weight influences adolescents more than adults. The current study showed no such relation. As only a quarter of patients in our sample were below 18 years of age, it is possible we had insufficient statistical power to reveal such effects.

We attempted to elucidate the mechanisms underlying the covariation between BMI and brain morphology by examining potential associations between various biochemical parameters and brain morphology. Despite several of the parameters were outside reference intervals for many patients (indicative of acid-base imbalance), none of the correlations with brain morphometry measures were significant, and the magnitudes of the correlations were generally small. This indicates that the mechanisms underlying reductions in brain mass may be unrelated to the biochemical parameters we considered. Few studies have examined similar relationships between biochemical parameters and brain morphology in patients with AN. One study (Bernardoni et al., 2016) considered serum albumin and specific gravity of urine, but found that these were within normal range and thus unlikely to contribute to observed changes to brain morphology. We similarly failed to detect an association between albumin and brain morphology, despite albumin levels being high for many patients. This may suggest that dehydration and fluid shifts are unlikely causes of the brain mass reductions. However, our null findings may be due to insufficient statistical power, as information on biochemical parameters was unavailable for many patients. It is also possible that brain morphology alterations in AN are influenced by other biochemical and hormonal parameters not considered in our study. For example, previous studies have found an association between brain morphology and cortisol (Castro-Fornieles et al., 2009; Mainz et al., 2012) and follicle-stimulating hormone (Mainz et al., 2012). Future highly powered studies are needed for continued investigation of the underlying mechanisms of brain mass reductions and normalization in AN.

Our study had several limitations, most of which are related to the clinical nature of our data. We had limited diagnostic and clinical information regarding patients, and no data on AN subtypes, comorbidities or AN duration, which precluded us from exploring the impact of such characteristics on brain morphology. Collection of neuroimaging data had not been performed in a systematic manner and was attained on several different scanners. For this reason, we focussed on global brain morphology, which precluded us from investigating local morphology measures. For many patients, information regarding BMI and biochemical parameters had not been collected on the same day as the MRI examination. Patients were also in different stages of treatment and weight restoration, but rate of weight gain was slow and most were still considerably underweight at the time of the MRI examination. This natural variability in BMI also constitutes a strength of the study, as we were able to sample patients with varying degrees of emaciation. Moreover, as our study was without a comparison group, we cannot determine the extent to which our patients were characterized by brain mass reductions relative to healthy individuals. However, such reductions are well documented in previous studies, and our findings highlight the influence of BMI on brain morphology. Finally, the cross-sectional study design is an indirect way of investigating maturation and development, and we therefore cannot exclude the possibility that age and brain morphology related findings reflect factors other than neurodevelopment (e.g., AN duration).

In conclusion, our study highlights that both age and BMI are independently associated with variations in brain morphology in AN. However, there was no evidence of an interaction effect between age and BMI, and thus no indication that age moderates the relationship between BMI and brain morphology. These results suggest the presence of at least partial normal neurodevelopmental patterns among individuals with AN. Importantly, our findings also showed that severity of emaciation is related to brain morphology reductions, underscoring the importance of weight restoration. We did not detect associations between biochemical parameters and brain morphology, and further studies are needed to shed light on potential mechanisms underlying the brain alterations. Our findings align with prior work highlighting the positive message that weight gain leads to normalization of brain morphology. Communicating this to patients and their families may provide hope and reassurance.

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CONFLICT OF INTEREST

The authors have no conflict to declare.

DATA AVAILABILITY STATEMENT

Due to issues regarding confidentiality and ethics, data cannot be shared.

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SUPPORTING INFORMATION

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

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