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RESEARCH ARTICLE

Intra-individual cortical networks in Anorexia Nervosa: Evidence from a longitudinal dataset

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Abstract

Objective: This work investigates cortical thickness (CT) and gyrification patterns in Anorexia Nervosa (AN) before and after short-term weight restoration using graph theory tools.

Methods: 38 female adolescents with AN underwent structural magnetic resonance imaging scans at baseline and after - on average - 3.5 months following short-term weight restoration while 53 age-matched healthy controls (HCs) were scanned once. Graph measures were compared between groups and longitudinally within the AN group. Associations with clinical measures such as age of onset, duration of illness, BMI standard deviation score (BMI-SDS), and longitudinal weight changes were tested via stepwise regression.

Results: Cortical thickness graphs of patients with acute AN displayed lower modularity and small-world index (SWI) than HCs. Modularity recovered after weight gain. Reduced global efficiency and SWI were observed in patients at baseline compared to HCs based on gyrification networks. Significant associations between local clustering of CT at admission and BMI-SDS, and clustering/global efficiency of gyrification and duration of illness emerged.

Conclusions: Our results indicate a shift towards less organised CT networks in patients with acute AN. After weight recovery, the disarrangement seems to be partially reduced. However, longer-term follow-ups are needed to determine whether cortical organizational patterns fully return to normal.

KEYWORDS

Anorexia Nervosa, cortical thickness, eating disorders, graph theory, gyrification, neuroimaging

Enrico Collantoni and Francesco Alberti contributed equally to this work.

Highlights

- Patients with acute Anorexia Nervosa (AN) displayed a shift towards less organised cortical networks.
- After a short-term weight restoration, alterations in cortical architecture seems to partially recover, suggesting the beneficial consequences of adequate nutritional programs on the brain structure.
- The associations between the organization of morphological patterns and clinical indices such as BMI standard deviation score (BMI-SDS) and duration of the disorder support and emphasise the importance of an early and thorough weight rehabilitation in the treatment of AN.

1 | INTRODUCTION

Anorexia Nervosa is a severe and often relapsing psychiatric disorder that usually emerges during adolescence and is characterised by low body weight, fear of weight gain, and body image disturbances (American Psychiatric Association, 2013). To date, many studies aimed to investigate the neurobiological basis of AN by exploring the brain structure using different indices and imaging techniques (Collantoni, Madan, et al., 2021; King et al., 2018; Meneguzzo et al., 2019). The analysis of cortical morphology has sparked particular interest in this context, as its modifications appear to occur in close relation with the acute state of starvation of the disorder and to improve after successful nutritional rehabilitation (Seitz et al., 2016). Additionally, examining the structural changes in the cortex of AN patients provides an intriguing opportunity to explore the intricate connections between neurodevelopmental aspects and the disorder itself. Indeed, AN is located at a complicated intersection between the neurodevelopmental factors that contribute to its origin and the impact that the disorder has on the trajectories of brain maturation (Favaro, 2013; Marzola et al., 2021). Normally, the different cortical indices were shown to change differentially during developmental phases, cortical thickness (CT) being less stable and more influenced by environmental and contextual factors than local gyrification index (LGI), which generally maintains a more constant configuration with age (White et al., 2010). At present, different studies have investigated cortical indices such as CT, LGI, and cortical complexity in patients with AN, with the overall aim of characterising both commonalities and divergences in the biological meanings of these non-redundant measures (Meregalli et al., 2022). Taken together, these studies revealed significant alterations of CT and LGI in the most acute stages of the disorder, when patients are most severely malnourished (Collantoni et al., 2020; Favaro et al., 2015). As the nutritional status improves, however, these parameters tend to normalise quite rapidly, regardless of their different stability during neurodevelopment (Bernardoni et al., 2018; King et al., 2015), showing them to be mostly state- and not trait- or developmentally dependent.

In recent years, graph-theory tools have been widely used to model the covariance patterns of functional connectivity changes in AN (Lotter et al., 2021). However, they have recently also been applied to structural indices, improving our neurobiological understanding of various psychiatric disorders (Fornito et al., 2017). This approach helps us describe the relationship between the morphological features of different parts of the cortex by modelling them as a network (i.e., graph). Small cortical (sub-)regions are modelled as nodes and the degree of similarity of their structure with other regions is modelled as their connection (edges). Some examples of topological metrics that can be used to analyse these graphs are: local and global efficiency (indices of the closeness (=cortex structure similarity) of a node with the rest of the graph or within its neighbourhood); clustering (the nodes' tendency to form small groups of connected regions); modularity (how clearly a network can be divided in distinct modular sub-communities); and small-worldness (a proxy of the network balance between being highly segregated and efficiently routed). Conditions such as schizophrenia, depression, and obsessive-compulsive disorder have been associated with topological alterations of structural covariance graphs proposed to reflect atypical functional connectivity patterns that could contribute to the onset of these disorders. Functional interactions, in fact, seem to affect regional morphology due to mutual activity-dependent trophic influences and common neural plasticity mechanisms (Alexander-Bloch et al., 2013).

A distinctive element that characterises AN compared to other neurological and psychiatric disorders is malnutrition. From a connectomic perspective, the consequences of malnutrition can influence functional

network configurations directly – by altering the metabolic support to brain cells and synaptic activity – or indirectly – affecting developmental trajectories – fostering an imbalance between segregation and integration properties (Collantoni et al., 2022; Collantoni, Meneguzzo, et al., 2021). To date, only one study examined the morphological relationships between cortical regions in patients with acute AN, finding increased local efficiency, modularity, and clustering coefficient (CC) in CT networks in adult patients compared to controls (Collantoni, Meneguzzo, Tenconi, et al., 2019). In gyrification graphs, instead, differences emerged only in patients who responded poorly to treatment, who showed increased segregation properties and lower small-worldness in covariance patterns compared to the control group. The discrepancy between the results obtained with the CT and gyrification networks could potentially be explained by the differences in their stability during development, which could be reflected in their covariance patterns. However, the possibility of inferring meaningful hypotheses regarding the neurobiological value of these data is hampered by two factors. First, the absence of longitudinal data, which prevents the possibility of understanding how graph indices vary along with nutritional status during weight gain. Secondly, the infeasibility of performing individual-level analyses on traditional structural covariance graphs, which are usually computed at group level. As for the first factor, the importance of investigating longitudinal recovery trajectories of structural patterns has been highlighted by previous literature that revealed a disruption of the morphological organization of the cortex in individuals with acute AN (Collantoni, Meneguzzo, Tenconi, et al., 2019). Since such alterations constitute stable characterising features of other psychiatric conditions that persist across time (Heinze et al., 2020; Spreng et al., 2019; Subirà et al., 2016), it is crucial to understand if in AN they are secondary to nutritional deficits or persist after weight restoration.

Regarding the second factor recent studies have proposed new algorithms that rely on a measure of within-subject structural similarity between cortical regions – that is, *joint variation* – rather than on across-subject correlation indices, allowing to compute individualised graphs (Nelson et al., 2018; Wee et al., 2013; Yun et al., 2015, 2020). This approach enables to investigate the impact of meaningful clinical individual variables such as body mass index (BMI), age of onset, and duration of illness on the cortical network organization at the single-subject level.

Therefore, the aim of the present study is to overcome the limitations of previous research by (a) investigating structural covariance graphs in a sample of acutely ill adolescent patients as measured by graph theoretical indices and networks, (b) identifying longitudinal changes in a follow-up after short-term weight restoration to study partial or complete normalisation in comparison with healthy controls (HCs), (b) exploring the presence of any relationship between structural covariance data and specific clinical characteristics, especially body weight and eating disorder symptoms.

2 | METHODS

2.1 | Participants

Structural magnetic resonance imaging (MRI), behavioural, and demographic data was collected from a sample of 38 female adolescents with AN and 52 age-matched HCs. Anorexia Nervosa patients were recruited after admission to the eating disorders unit of the Department of Child and Adolescent Psychiatry of Aachen RWTH University Hospital. Ethical permission was obtained from the ethics committee of the Aachen University Hospital. After completely explaining the study details to the participants and parents/legal guardians, informed written consent was obtained from both patients/HCs and their parents/legal guardians. The study was conducted in accordance with the Helsinki Declaration. Exclusion criteria for patients included a history of psychosis, a history of substance abuse and an IQ below 80 as assessed by the "Hamburg Wechsler Intelligence.

Test (HAWIK-IV) or screened by the German "Mehrfach Wortschatz Intelligenz-Test B" (MWT-B). The diagnosis of AN was based on the diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV) criteria (American Psychiatric Association, 1994). The severity of ED symptomatology was assessed using the Eating Disorder Inventory II (EDI-II; Thiel et al., 1997) in a sub-sample of 28 patients. All patients underwent an MRI scan shortly after admission and then received inpatient treatment with a short-term weight recovery of on average 3.5 months to a target weight of reaching the 20th BMI-percentile adjusted for age. Treatment took place in stepped care inpatient and day patient settings and included psychoeducation, graded nutritional refeeding and multimodal socio- and psychotherapy in single and group settings, as well as intensive coaching of parents as co-therapists. After this period, a second MRI and up-to-date clinical data were collected from all AN participants. General cortical volume data of patients at admission and HC only have been presented before as a part of 56 acutely ill patients with AN, showing wide-spread grey matter deficits and their association to low BMI-SDS (Seitz et al., 2015).

The age-adjusted standardized Body Mass Index (BMI-SDS) of all patients was calculated at baseline (t1) and follow-up (t2) using the Kromeyer-Hausschild normative dataset of German youth (Kromeyer-Hausschild et al., 2001). We also measured weight loss between the onset of the disorder and the time of the admission and weight gain between admission and after weight recovery in terms of BMI-SDS. Additional clinical information collected included the age of onset and the duration of the illness at baseline.

The HC group was recruited via flyers and newspaper advertisements and exclusion criteria for the HCs were any psychiatric diagnoses or an IQ that was below 80. Individuals of this group underwent a single structural MR.

The main characteristics of the sample are reported in Table 1.

Ethical permission was obtained from the ethics committee of the Aachen University Hospital. After completely explaining the study details to the participants and parents/legal guardians, informed written consent was obtained from both patients/HCs and their parents/legal guardians. The study was conducted in accordance with the Helsinki Declaration.

2.2 | MRI data acquisition and preprocessing

T1-weighted MRI images were acquired at two different sites (Aachen University Hospital and Julich Research Centre) with 3 T Siemens TrioTim whole body MRI using gradient echo sequence (repetition-time = 2.25 ms, echo time = 3.03 ms, inversion time = 900 ms, flip angle = 9°, 176 sagittal slices, voxel size = 1 × 1 × 1μL, field of view *256* × *256* mm). Image preprocessing, cortical reconstruction, and segmentation were performed using FreeSurfer version 7.1.1 (Martinos Centre for Biomedical Imaging, Massachusetts General Hospital, Boston), following standard protocols and software guidelines (Fischl, 2012). Preprocessing steps included skull-stripping, intensity correction, the definition of the white-grey matter boundary of both hemispheres, and tessellation of the resulting boundary. The cortical reconstructions were visually inspected and minor manual interventions were performed with respect to the FreeSurfer instructions. The cortical surface was parcellated in 148 regions (74 per hemisphere) using the Destrieux atlas (Destrieux et al., 2010; Fischl, 2004). For each parcel, we extracted the average CT and LGI. A vertex-wise analysis of CT and gyrification was conducted and is reported in the Supplementary Materials.

2.3 | Construction of structural joint-variation graphs

To control for possible confounding effects, we build multiple within-region across-participants linear models using age and site of acquisition as predictors and the morphological indices as dependent variables. Then, raw CT and LGI values were replaced with the models' residuals normalised by region using the local mean and standard deviation of the HC sample (Yun et al., 2020).

$$w_{ij} = \frac{1}{e\left(z_i - z_j\right)^2} \quad (1)$$

Joint-variation of a morphological measure between nodes *i* and *j*, where *zi* and *zj* are their respective z-transformed structural indices.

These data were then used to build one CT- and one LGI-based graph for each participant, in which each node represented a parcel, and the edge-weights were assigned based on the similarity of morphological measures between regions. We calculated two 148×148 matrices per subject populated with the joint-variation (Equation 1) of CT, and LGI residuals of each pair of regions (Wee et al., 2013; Yun et al., 2015, 2020). The weighted graphs were then binarised using proportional thresholding converting to 1 the strongest *k*% of all weights and setting all others to 0 (*k* goes from 5% to 55% by steps of 2). To ensure that this procedure did not lead to fragmentation of the graph, we first identified the minimum spanning tree (MST) of the weighted matrix and converted it to binary, then we progressively added other edges in order of descending weight until the desired density had been achieved. Finally, five global topological metrics were calculated from all graphs at every level of *k*: global efficiency, local efficiency, CC, modularity, and small-world index (SWI). Graph measures were extracted using the Brain Connectivity Toolbox (brain-connectivity-toolbox.net; Rubinov & Sporns, 2010).

In addition to the main methodological approach described above, we also re-ran the group comparisons using three more binarisation procedures in order to have a more complete picture of the data and its susceptibility to this step of the analyses (Fornito et al., 2016). The first alternative method used is simple proportional thresholding with the same levels of *k* as the main analyses, but without preserving the MST backbone. The other two algorithms, instead, consist of absolute thresholding with the preserved MST and without it. In this procedure, only edges above an *a-priori* threshold value are maintained, while all others are removed. To be able to use the same comparison method for all analyses, we decided to use

TABLE 1 Demographic and clinical data of the participants.

	AN ($N = 38$)			ANOVA		
	t1 Mean (SD)	t2 Mean (SD)	HC ($N = 52$) Mean (SD)	AN-t1 versus AN-t2 F(1, 37) (p)	AN-t1 versus HC F(1, 89) (p)	AN-t2 versus HC F(1, 89) (p)
Age (years)	15.25(1.88)	15.54(1.91)	15.74(1.65)	281.88(0.00)***	1.73(0.19)	0.28(0.59)
BMI-SDS	−2.74(1.14)	−1.01(0.49)	0.16(0.87)	116.94(0.00)***	187.86(0.00)***	56.68(0.00)***
Illness duration(months)	12.55(9.49)	16.24(9.88)	n.a.			
Follow-up time (months)	3.45(1.26)		n.a.			
Age at onset (years)	14.12(1.60)		n.a.			
BMI-SDS at onset	0.00(0.88)		n.a.			
BMI-SDS loss(t1 – onset)	−2.77(1.11)		n.a.			
BMI-SDS gain(t2 – t1)	1.77(0.97)		n.a.			

Abbreviations: AN, Anorexia Nervosa; BMI-SDS, BMI standard deviation score; HC, healthy controls.

multiple, progressively increasing thresholds. These binarisation procedures are described in more detail in the Supplementary Materials.

All our main results and their interpretation are centred on the data obtained from the first binarisation method described because we believe it is best fit to represent morphological relationships for three reasons. First, it is unlikely that there is complete independence between the structural properties of certain regions and the rest of the cortex, which is what a fragmented graph with isolated nodes would represent. Second, the path length between nodes belonging to separate, disconnected communities is infinite, which causes several issues because many of the metrics used here are based on this value. Third, applying proportional thresholding based on individual edge weights' percentiles ensures that all graphs have the same number of edges throughout the sample, which is not the case when with absolute thresholding. However, instead of selecting only one and upholding the other information from the reader, we believed it is most useful to display all analyses results including trend-level results so that the informed reader can come to his or her own conclusions.

2.4 | Statistical analyses

To identify relevant differences between groups and across follow-up, we used a non-parametric permutation analysis. The testing procedure involved the following steps: a) computing the groups' mean curve of graph measures across k levels; b) calculating the area comprised between the groups' curves (ΔAUC); c) comparing this value with a null distribution of ΔAUCs of the same measure computed from 10.000 pairs of random groups created by permuting the subjects' group affiliation. The p-value of the differences was calculated as the proportion of data points in the null distribution with a ΔAUC larger than the one calculated on real data. Furthermore, we explored possible associations between morphological graph topology and clinical measures in the AN group using stepwise linear regression. For each graph metric, a constant-only model was built, and clinical variables were progressively added to it as predictors if they significantly improved the fit of the model. The independent variables used for the analyses were age of onset, duration of illness, BMI-SDS, and weight-loss or weight-gain for AN-t1 and AN-t2 respectively. Given that the EDI scores were available for a subset of 28 participants, we performed a distinct regression analysis for these individuals. In this analysis, we included the global score of the scale as an additional predictor variable. The results of the analysis are reported in the supplementary materials. Statistical testing was carried out using MATLAB R2018b, adopting a significance threshold at $p = 0.05$.

3 | RESULTS

3.1 | Sample characteristics

Sample demographics are summarised in Table 1. Repeated measure ANOVAs showed that, as expected, normalised BMI ($F(89) = 116.94$, $p < 0.001$) of the AN group increased significantly between admission and follow-up, indicating that the patients did gain weight during treatment (Figure 1). ANOVAs comparing the values to the control group revealed that the patients did not differ in terms of age from the healthy participants. However, the AN group was found to have a lower normalised BMI than control subjects both at t1 ($F(89) = 187.86$, $p < 0.001$) and also at t2 ($F(89) = 56.68$, $p < 0.001$).

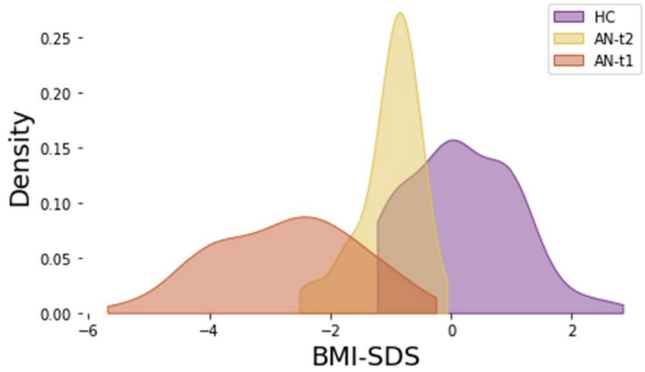

FIGURE 1 Kernel density estimate (KDE) plot of the normalised body mass index (BMI) of the participants. [Colour figure can be viewed at wileyonlinelibrary.com]

Regional CT and LGI differences were evidenced in patients with AN at baseline and after short-term weight gain compared to HCs. Also, significant increases were found in both measures between admission and follow-up; see the Supplementary Materials (section S3 Supplementary Methods) for further details on these measures.

3.2 | Cortical thickness-based networks

At baseline, patients with AN displayed significantly lower modularity ($\Delta AUC = 0.275$, $p = 0.003$) and SWI ($\Delta AUC = 0.355$, $p = 0.028$) compared to HCs. In the longitudinal comparison within the AN group, it emerged that, at follow up, modularity increased significantly after short-term weight gain ($\Delta AUC = 0.152$, $p = 0.015$) (Figure 2, Table 2). In the comparison of network characteristics between short-term weight-recovered patients and HCs no significant difference emerged in the main analyses, indicating that the modular organization of CT rapidly recovers with weight gain. These results were generally corroborated by the additional binarisation methods tested (see Supplementary Table 1). Three out of the four procedures (node-connected proportional thresholding, basic proportional thresholding, and basic absolute thresholding) confirmed an alteration in modularity at baseline, with the remaining approach (node-connected absolute thresholding) capturing only an alteration and a persisting alteration of this measure after weight-gain. All methodologies, however, replicated the significant increase of modularity across follow-up. The loss of SWI at baseline emerged from two of the four procedures (the ones ensuring node-connectedness). This discrepancy is possibly due to the effect that maintaining the MST intact may have on the clustering index used to compute this metric. One additional binarisation method (node-connected absolute thresholding) also evidenced a gain of global and local efficiency across short-term weight gain.

Finally, the stepwise regression, evidenced a significant positive association between patients' BMI-SDS and their CC ($F(28) = 4.79$, $p = 0.0372$) at baseline, which may contribute to the disruption of modularity in CT graphs.

3.3 | Local gyrification index-based networks

At baseline, patients with AN were found to have a reduced global efficiency ($\Delta AUC = 0.003$, $p = 0.048$) and SWI ($\Delta AUC = -0.423$, $p = 0.035$) compared to control participants. In LGI graphs, however, the longitudinal comparison within the AN group did not show any significant difference between baseline and follow-up. After weight gain, patients with AN did not display statistically significant differences in lower global efficiency ($\Delta AUC = -0.027$, $p = 0.074$) and SWI ($\Delta AUC = -0.355$ $p = 0.099$) compared to HC (Figure 3, Table 2). The significant loss of global efficiency at baseline was corroborated by all the secondary binarisation procedures. As for SWI, again, alterations were found only in the graphs binarised using proportional thresholding. Interestingly, all secondary binarisation procedures found the reduction in global efficiency to remain significant also after short-term weight rehabilitation.

Additionally, two secondary binarisation procedures (those using absolute thresholding) found a reduction in modularity. Moreover, the analyses that used classic proportional-thresholding found a statistically significant difference in SWI.

Finally, the regression analyses identified the patients' duration of illness to be significantly positively associated with average clustering ($F(27) = 5.46$, $p = 0.027$) at baseline, and with local efficiency ($F(27) = 5.33$, $p = 0.038$) at follow-up.

4 | DISCUSSION

The present study aimed at addressing three main research questions regarding (a) the presence of structural covariance abnormalities in the acute phase of the disorder in adolescent patients, (b) the presence of alterations persisting after short-term weight-restoration, (c) the association of specific clinical parameters with structural covariance measures, potentially pointing towards underlying mechanisms.

Overall, our results showed a lower modularity and SWI in CT graphs of patients with acute AN compared to

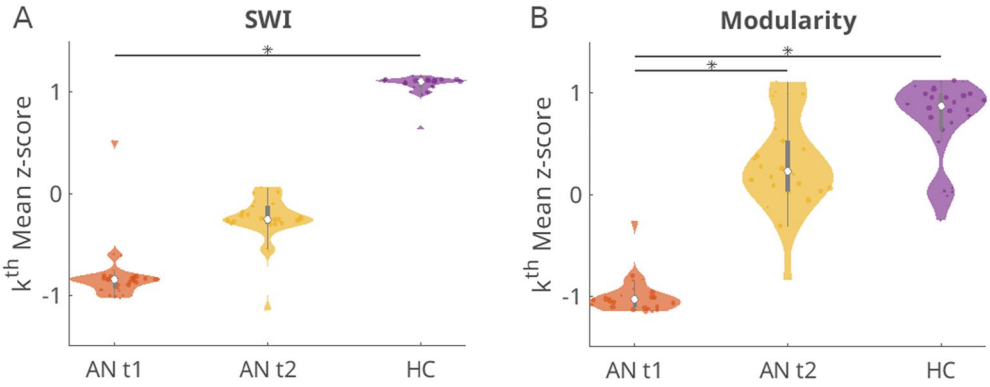

FIGURE 2 Comparisons between Anorexia Nervosa (AN) and healthy control (HC) based on cortical thickness (CT) networks. [Colour figure can be viewed at wileyonlinelibrary.com]

TABLE 2 Group comparisons based on cortical thickness (CT) and gyrification networks.

	Cortical thickness		Gyrification	
	Delta AUC	**p**	**Delta AUC**	**p**
	AN t1 versus HC		**AN t1 versus HC**	
Global efficiency	−0.020	0.120	−0.298	0.048*
Local efficiency	−0.012	0.772	−0.678	0.066
Clustering	−0.029	0.517	−0.047	0.255
Modularity	−0.275	0.003**	−0.156	0.206
Small-world index	−0.355	0.028*	−0.423	0.035*
	AN t2 versus HC		**AN t2 versus HC**	
Global efficiency	−0.019	0.088	−0.027	0.074
Local efficiency	0.011	0.804	−0.030	0.464
Clustering	0.010	0.823	−0.004	0.935
Modularity	−0.116	0.238	−0.148	0.226
Small-world index	−0.246	0.123	−0.355	0.099
	AN t1 versus AN t2		**AN t1 versus AN t2**	
Global efficiency	−0.007	0.457	−0.004	0.818
Local efficiency	−0.018	0.499	−0.021	0.609
Clustering	−0.015	0.655	−0.044	0.335
Modularity	−0.168	0.030*	−0.167	0.186
Small-world index	−0.131	0.161	−0.187	0.397

Note: The asterisk indicate statistical significant values.

Abbreviations: AN, Anorexia Nervosa; BMI-SDS, BMI standard deviation score; HC, healthy controls.

HCs, with an improvement after weight gain. Gyrification graphs exhibited reduced global efficiency and SWI in patients at baseline, maintaining trend-level alterations compared to HCs. Associations emerged between CT clustering and BMI-SDS, and gyrification clustering/global efficiency and duration of illness.

With regard to the first point, our results evidenced that both CT and gyrification networks showed marked alterations in the balance between integration and segregation properties and a less structured organization in the acute phase of the disorder, which is reflected by a decrease in the SWI. The presence of a shift towards more random configurations in the CT covariance architecture is also supported by the presence of a lower modularity in patients with acute AN than in HCs, which means that the CT covariance patterns cannot be clearly divided in structurally similar communities. The gyrification-based network showed a reduced global efficiency in the group of patients at baseline compared to the controls. These results are in line with some previous connectomic investigations in AN, but contrast with those in adults. In particular, similar to the present research, previous studies highlighted a less balanced organization of structural and functional brain connectivity in AN patients compared to controls (Collantoni, Meneguzzo, Tenconi, et al., 2019; Collantoni, Meneguzzo, et al., 2021; Lotter et al., 2021). Conversely, a recent cortical structural analysis showed that adult patients with acute AN showed an increase in SWI in both CT and gyrification graphs (Collantoni, Meneguzzo, Tenconi, et al., 2019). Several factors may account for the discrepancies between the findings in adults and the present research in adolescents, that mainly concern the mean age of the patients and also the duration of the disorder, which is shorter in this investigation than in the one cited. The importance of considering the patients' age and disorder duration in evaluating imaging results in AN is supported by several observations in recent eating disorder research (Frank et al., 2018), as differences in these variables may reflect differences in neurodevelopmental stages and in the disorder's effects on the brain. For instance, while the effect on morphological covariance patterns remains unclear to date, profound changes in cortical structure have been observed during development, encompassing a

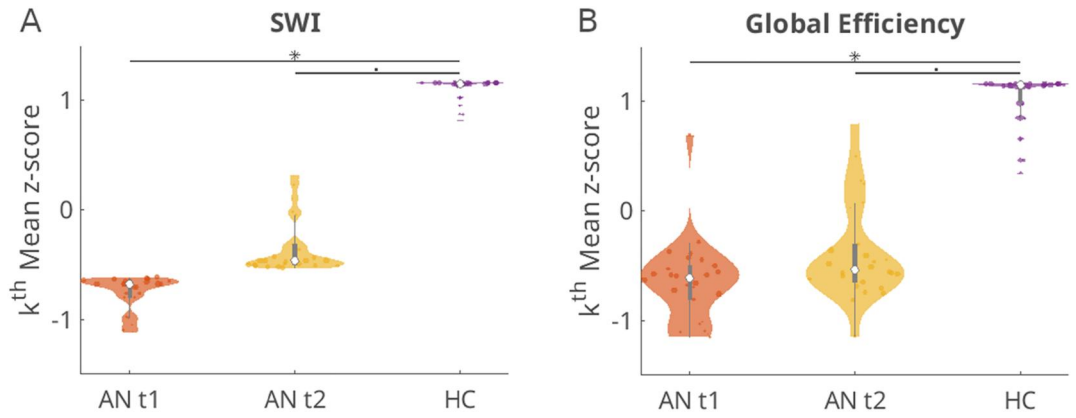

FIGURE 3 Comparisons between Anorexia Nervosa (AN) and healthy control (HC) based on gyrification networks. [Colour figure can be viewed at wileyonlinelibrary.com]

progressive sulcal widening, a reduction in sulcal depth and a progressive cortical thinning (Collantoni, Meneguzzo, et al., 2021). Also, brain volume reductions in grey and white matter are more pronounced in adolescent patients with AN compared to adult ones by an order of twofold (Seitz et al., 2018), affecting technical measurement metrics of at least LGI but also probably stemming from underlying changes in brain substrate. Furthermore, it should be considered that cortical indices have been shown to be elevated in acute AN (Bernardoni et al., 2018; Seitz et al., 2016; Walton et al., 2022), which has been shown to have a negative effect on brain volume, potentially also influencing modifications in the properties of the network. An additional factor that should be taken into account concerns the stage of the disorder at the time of recruitment. In fact, in the present study, all the patients underwent the first scan in the acute phase, that is, at the beginning of inpatient treatment, while in a previous study (Collantoni, Meneguzzo, Tenconi, et al., 2019), although underweight, the adult patients underwent the MRI scan in a phase of greater clinical stabilisation. It is worth noting in this context that a decrease in regularity within cortical networks has been observed in other psychiatric disorders, such as obsessive-compulsive disorder and schizophrenia, as a possible result of an alteration in developmental trajectories (Palaniyappan et al., 2015; Yun et al., 2020). This, along with other observations, underscores the importance of taking into account multiple contributing factors in the neurobiology of AN, and underscores the possibile role of developmental trajectories and comorbidities in the aetiology of this condition.

The longitudinal analysis revealed that, after a short-term weight restoration, the CT covariance patterns partially normalise, as no significant differences were detectable between patients at follow-up and HCs in the main analysis. Especially, modularity increased significantly across this time interval. It is also worth noting that a significant increase in SWI was also detected by all the secondary binarisation procedures (Supplementary Table 1S). However, one secondary binarisation procedure did identify lasting reductions in CT global efficiency and modularity. Generally, gyrification graphs did not show this degree of improvement and still display a lower global efficiency in patients after weight-recovery. Although this difference is only significant at trend level in the main analyses, it is significant in all the supplementary procedures for graph binarisation (Supplementary Table 2S). Unlike CT, sulcal and gyral morphology exhibit little variation in post-natal development (Hensch, 2004; Im & Grant, 2019; Sandu et al., 2014). Thus, the lack of recovery of gyrification patterns may be due to both the brief duration of weight restoration treatment and to the higher stability of this index compared to other cortical parameters. Also, remaining global reductions of grey and white matter must be considered. Nevertheless, in light of previous evidence showing a rapid normalisation of cortical folding after weight gain (Bernardoni et al., 2018), this research point is certainly worthy of further investigation.

These findings are the first longitudinal data on structural covariance patterns in AN. They align with previous longitudinal evaluations on general cortical morphology in the disorder showing improvement with weight gain. A further commonality between these data and the previous literature concerns the evidence that the dramatic impact of AN on the cortical structure is strongly related to malnutrition, with CT changing rapidly even with short-term weight restoration, which includes some patients that do not completely reach target weight during inpatient treatment. The evidence that malnutrition-related cortical changes are reflected not only in specific morphological indices but also in their covariance patterns suggest that these alterations

could be subtended by similar etiopathogenic mechanisms and should be studied also in a system-levels approach taking into account their interdependence. Since the relationship patterns between brain areas are determined based on mechanisms involving the overall balance of the network, the present analysis highlights the importance of proper nutritional rehabilitation programs in restoring the balancing between interconnected rather isolated brain regions.

Since folding patterns are likely to structurally support both white matter structural, as well as functional connectivity (Henderson & Robinson, 2014; Palaniyappan et al., 2015), a decrease in global efficiency and small-worldness of the gyrification-based network could indicate a decreased efficiency in the brain functional connectivity of patients with acute AN. The observation of persistently lower global efficiency values in patients in the partially weight-recovered AN group might suggest a higher stability of folding networks in face of environmentally driven perturbation in general and to re-alimentation-related mechanisms in particular.

The regression analysis' results showed that the nutritional status (reflected by the standardized BMI) has a direct influence on the clustering of CT networks. This metric measures the portion of neighbours of a given node that are also connected to each other. A lower clustering in patients with a low BMI-SDS might undermine the cohesion of the modules and explain the loss of modularity observed in the AN group at baseline. Such results, together, suggest a role of malnutrition in the shift towards a more random configuration of CT patterns in this group.

As regards the gyrification-based connectome, the regression analysis showed that a longer duration of the disorder predicts a higher clustering and local efficiency, that is, the longer the disorder, the more the network tends to segregate. These results suggest that the loss of small-worldness may be due to an increase in the number of edges uniting neighbouring nodes or members of the same module, which grow closer and more segregated as the illness (and malnutrition) persists. These data could be usefully interpreted in light of the previous gyrification-based connectomic assessment in AN, according to which patients who responded worse to treatment have a more segregated graph than HCs (Collantoni, Meneguzzo, Tenconi, et al., 2019). Interestingly, as previously specified, that study was conducted on a group of patients with a longer duration of the disorder and a higher mean age than the present research. Therefore, greater segregation in networks based on gyrification can reflect the triggering of neuroprogressive processes, which lead to a loss in the efficiency of the connectome, and which can represent a neurobiological basis for prognostically unfavourable characteristics.

5 | STRENGTH/LIMITATIONS

This study has several strengths, as well as important limitations, that should be considered when interpreting the results. It is the first study to analyse cortical covariance patterns in AN longitudinally, thus allowing to study the effects of a nutritional rehabilitation programme on the architecture of the cortex. Furthermore, the extraction of individual-based cortical networks allowed us to explore the association between graph measures and specific clinical variables such as standardized BMI, age of onset, and illness duration. Limitations of this research mainly regard the sample size. It is possible that a larger cohort would have revealed clearer deviations after weight recovery. Additionally, the presence of some missing elements in the research could have potentially enhanced the quality of our analyses: the lack of a hemispheric dominance index prevented us to explore whether the lateralisation of cortical networks differs between patients and HC, and the presence of more precise measures of individual weight restoration, such as resumption of menses, could have been helpful in better interpreting the longitudinal results. Other limitations relates to the general brain volume changes, especially of the underlying white matter, that might affect CT and LGI measurements, to the employment of DSM-IV for diagnosing the disorder, and to the use of an outdated version of the EDI (EDI-2 instead of the more current EDI-3). Also, it should be noted that since some of the results present only a modest degree of evidence, they should be approached with caution. Lastly, due to the high comorbidity with depression and obsessive compulsive disorder, also known for alterations of structural cortical networks, potential overlap of findings cannot be excluded. The rapid normalisation of CT based measures withing 3 months of short-term weight rehabilitation, however, points towards an at least partial unique contribution of AN in this process.

6 | CONCLUSIONS

In conclusion, the present research evidenced, in underweight patients with AN, the presence of lower small-worldness in both CT and gyrification networks. In the same group, lower modularity in the CT network and

lower global efficiency in the gyrification one were observed. Although the exact clinical significance of this alterations in the acute phases of AN are not entirely known, the observation that the overall organization of CT patterns seem to partially recover after a short-term weight restoration, is likely to indicate the beneficial consequences of adequate nutritional programs on the brain structure. Moreover, these findings underscore the importance of considering both weight loss and re-alimentation when exploring the neurobiology of AN. The lack of recovery of gyrification graphs suggest that either their alterations are permanent, or their normalisation requires a longer time, as suggested by previous literature. Finally, the finding of a link between the organization of morphological patterns and clinical indices suggests a role of the nutritional status in determining the alterations observed and their recovery and again emphasises the importance of a multidisciplinary approach and an early and thorough weight rehabilitation in the treatment of AN.

DATA AVAILABILITY STATEMENT

Data available upon request.

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