



**GYRIFICATION BRAIN ABNORMALITIES AS PREDICTORS OF
OUTCOME IN ANOREXIA NERVOSA**

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Keywords:	anorexia nervosa, cortical folding, cortical thickness, outcome

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4 **GYRIFICATION BRAIN ABNORMALITIES AS PREDICTORS OF OUTCOME IN**
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6 **ANOREXIA NERVOSA**
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42 **Short title:** Brain gyrification in anorexia nervosa

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44 **Key words:** anorexia nervosa, cortical folding, outcome, MRI, brain gyrification
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ABSTRACT

Gyrification brain abnormalities are considered a marker of early deviations from normal developmental trajectories and a putative predictor of poor outcome in psychiatric disorders. The aim of this study was to explore cortical folding morphology in patients with anorexia nervosa (AN). A MRI brain study was conducted on 38 patients with AN, 20 fully recovered patients, and 38 healthy women. Local gyrification was measured with procedures implemented in FreeSurfer. Vertex-wise comparisons were carried out to compare: 1) AN patients and healthy women; 2) patients with a full remission at a 3-year longitudinal follow-up assessment and patients who did not recover.

AN patients have significantly lower gyrification when compared with healthy controls. Patients with a poor 3-year outcome had significantly lower baseline gyrification when compared to both healthy women and patients with full recovery at follow-up, even after controlling for the effects of duration of illness and grey matter volume. No significant correlation has been found between gyrification, body mass index, amount of weight loss, onset age, and duration of illness. Brain gyrification significantly predicts outcome at follow-up even after controlling for the effects of duration of illness and other clinical prognostic factors. Although the role of starvation in determining our findings cannot be excluded, our study showed that brain gyrification might be a predictor of outcome in AN. Further studies are needed to understand if brain gyrification abnormalities are indices of early neurodevelopmental alterations, the consequence of starvation, or the interaction between both factors.

INTRODUCTION

Anorexia nervosa (AN) is a severe psychiatric disorder characterized by a high female/male ratio, onset during adolescence (Favaro et al. 2009), and high levels of chronicity and mortality.

Individuals suffering from AN reduce their food intake or increase their energy expenditure, have a distorted body image and often display low levels of insight about their condition. Although several studies have been conducted to explore the effects of having a diagnosis of anorexia nervosa (AN) on brain volumes, no study to date has been carried out to investigate the presence of cortical morphological abnormalities in this group of patients. With few exceptions (Brooks et al. 2011; Frank et al. 2013), AN has been associated with a reduction of both gray and white matter (Fonville et al. 2014; King et al. 2015; Seitz et al. 2014; Titova et al. 2014; Van den Eynde et al. 2012) which is usually considered a side effect of weight loss and malnutrition, given that an improvement of brain volumes has been observed in longitudinal studies (Seitz et al. 2014; Van den Eynde et al. 2012). Whether any scarring effect might persist after full recovery is still a matter of debate, since some studies found a persistent reduction of gray matter volume in the anterior cingulate cortex of fully recovered AN patients (Muhlau et al. 2007), while others found no differences between recovered patients and healthy women (Wagner et al. 2006).

Since the effects of weight loss and malnutrition on brain volumes are known, although not completely characterized, and since malnutrition often begins a considerable amount of time before the onset of the disorder, only long-term longitudinal studies of large cohorts of healthy adolescents would allow to infer the role of brain morphological aberrations in the risk of developing AN using volumetric studies. This question is of some importance since evidence about AN having a possible neurodevelopmental origin is increasing: the disorder has its onset during adolescence (Favaro et al. 2009), is associated with an excess of left-handedness (Tenconi et al. 2010), specific

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4 neuropsychological impairments (Lopez et al. 2008; Roberts et al. 2007; Tenconi et al. 2010), and
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6 subtle neurological abnormalities (Gillberg et al. 1994). In addition, prenatal and perinatal risk
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8 factors that have been implicated in other neurodevelopmental psychiatric disorders, such as autism
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10 and schizophrenia, seem to increase the risk of developing AN (Favaro et al. 2006; 2014; Tenconi
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12 et al. 2014). For this reasons, it is important to look for measures of brain morphology and function
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14 that are potentially not affected by malnutrition and other illness-related factors.

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17 In this study, we explored whether the investigation of brain gyrification can provide useful
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19 information about neurodevelopment outcome in AN. Cortical folding is known to reflect a
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21 person's prenatal development (Dubois et al. 2008) and change only minimally after birth (White et
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23 al. 2010): it is the result of a substantial expansion of cortical surface area despite a relatively minor
24
25 gain in cortical thickness during evolutionary development (Sun and Hevner, 2014). The processes
26
27 leading to cortical gyrification are not fully understood, but recent theories consider cortical folding
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29 to be the result of underlying patterns of connectivity (Van Essen, 1997), thus emphasizing the
30
31 possible functional significance of gyrification alterations (Sun and Hevner, 2014). The gyrification
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33 index, which is the ratio between the inner folded contour and the length of the coronal outline,
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35 excluding the sulcal regions, has been found to increase dramatically during the third trimester of
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37 pregnancy, and then to remain relatively constant throughout development (Armstrong et al. 1995):
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39 this means that the process of gyrification continues through the postnatal developmental period,
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41 maintaining this constant ratio throughout the process (White et al. 2010). For this reason, the
42
43 degree of folding is considered to be a crucial valid marker to our understanding of the timing and
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45 the nature of brain alterations during neurodevelopment (Dubois et al. 2008; White et al. 2010;
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47 Schaer et al. 2013). Gyrification alterations have been found to be associated with prematurity
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49 (Gimenez et al. 2006; Kesler et al. 2006) and exposure to obstetric complications (Haukvik et al.
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51 2012), and to be frequent in neurodevelopmental psychiatric disorders such as autism and
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53 schizophrenia (Nanda et al. 2014; Nesvag et al. 2014; White and Hilgetag, 2011).
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4 Furthermore in first episode psychosis, cortical folding in specific brain areas seems to significantly
5 predict response to antipsychotic treatment (Palaniyappan et al. 2013). Despite the importance of
6 having reliable predictors of poor response in AN, to our knowledge, no attempt to date has been
7 made to explore the relationship between brain characteristics and outcome. The aims of this study
8 were twofold: 1) to investigate the pattern of brain gyrification in a sample of patients with AN and
9 study the relationship between gyrification and relevant clinical variables, such as body mass index,
10 the amount of weight loss, duration of illness, age of onset; 2) to explore the relationship between
11 brain gyrification and the outcome at a 3-year follow-up.
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24 **METHODS**

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28 A total of 38 patients with acute AN and 38 healthy controls were included in this study. A further
29 group of 20 patients in full remission from AN were included to test the state/trait nature of any
30 MRI finding. Women who had recovered from AN were subjects who had had full AN in their
31 lifetime, but were asymptomatic from at least 6 months at the time of scanning (mean remission
32 time: 38.5 months (standard deviation=33.2); range 6-96). All recovered subjects were asked to
33 participate during follow-up visits carried out in our ED Unit after recovery. None of the subjects of
34 this group relapsed in the year following the study. Table 1 describes the main characteristics of the
35 sample.
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46 Exclusion criteria for all subjects were male gender, history of head trauma or injury with loss of
47 consciousness, history of any serious neurological or medical illness, active use of systemic
48 steroids, pregnancy, active suicidality or major depression, history of substance/alcohol abuse or
49 dependence, bipolar disorder or schizophrenia spectrum disorder, moderate mental impairment
50 (IQ<60) or learning disabilities, use of medications other than antidepressants, and known
51 contraindications to conventional MRI. History of any psychiatric disorder and any first-degree
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4 relatives with an eating disorder were additional exclusion criteria for healthy women. Amenorrhea,
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6 food restriction, bingeing, excessive exercise, fasting and purging in the last 6-months were
7
8 additional exclusion criteria for the recovered AN group.
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10 Ethical permission was obtained from the ethics committee of the Padova Hospital. After
11
12 completely describing the study to the subjects, informed written informed consent was obtained.
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15 16 17 Clinical Assessment and Follow-up 18

19 In all subjects, diagnostic interviews were performed according to the eating disorders section of the
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21 Structured Clinical Interview for DSM-IV (First et al. 1995) and a semi-structured interview to
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23 gather socio-demographic and clinical variables, as previously described (Favaro et al. 2012; 2013).
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25 Subjects were also asked to complete the Hopkins Symptoms Checklist (Derogatis et al. 1974) to
26
27 assess depressive and obsessive-compulsive symptoms and the Eating Disorders Inventory (Garner
28
29 et al. 1983) to assess eating psychopathology. Handedness was assessed by the Edinburgh
30
31 Handedness Inventory (Oldfield, 1971).
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34 All subjects were medically stable at the time of scanning and all were recruited at the Padova
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36 Hospital Eating Disorders Unit and all fulfilled all the diagnostic criteria for AN according to DSM-
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38 IV at the time of scanning. The diagnostic subtype at the time of scanning was restrictive in 32 AN
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40 patients (84%) and binge eating/purging type in 6 patients, but 7 patients who were restrictive at the
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42 time of the present study reported previous recurrent binge eating and/or purging. Concerning the
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44 use of medications, 14 AN patients and 4 recovered women were under treatment with
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46 antidepressants at the time the study was conducted.
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49 Follow-up was performed 3 years later (on average 3.4 years, range 1.7-3.9) in acute AN patients.
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51 Both face-to-face interviews and reports from informants were used to gather diagnostic
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53 information. Patients were assessed using the eating disorders section of the Structured Clinical
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55 Interview for DSM-IV (First et al. 1995). Full recovery was defined as weight being in the normal
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4 range, regular menses, absence of binge eating, purging, food avoidance or restraint, excessive
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6 exercise, undue body dissatisfaction, or drive for thinness in the past 3 months.
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10 11 MRI Data Acquisition

12 Data were collected on a Philips Achieva 1.5 Tesla scanner equipped for echo-planar imaging. A
13 high-resolution 3D T1-weighted anatomical image was also acquired, in a gradient-echo sequence
14 (repetition-time=20 sec, echo time=3.78 msec, flip angle= 20°, 160 sagittal slices, acquisition voxel
15 size=1×0.66×0.66 mm, field of view 21-22 cm).
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24 Data Processing and Statistics

25 Surface extraction was completed using the FreeSurfer package (Martinos Center for Biomedical
26 Imaging, Massachusetts General Hospital, Boston) version 5.3.0. Preprocessing, cortical
27 reconstruction and segmentation, and cortical thickness estimation were performed according to
28 standard protocols (Desikan et al. 2006; Fischl et al. 1999; Fischl and Dale, 2000). The local
29 Gyrification Index (IGI) was measured at thousands of points of the reconstructed cortical surface
30 using previously validated algorithms (Schaer et al. 2008). LGI is a measurement of the degree of
31 cortical folding that quantifies the amount of cortex buried with in the sulcal folds in the
32 surrounding circular region. A general linear model controlling for the effects of age and
33 intracranial volume to estimate differences among AN patients and healthy women at each vertex of
34 the right and left hemispheric surfaces. We also compared patients with full recovery to those not
35 making a full recovery over the subsequent three years (and both of these groups were compared to
36 healthy women) controlling for the effects of age, duration of illness, and intracranial volume. In
37 order to reduce the possibility of biased findings due to the reduced cortical volume in AN patients,
38 all vertex-wise analyses were repeated including cortical thickness as a vertex-wise covariate.
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4 The Monte-Carlo permutation approach (10,000 simulations) implemented in the FreeSurfer
5 software was used for statistical correction of multiple comparisons with an additional Bonferroni
6 correction to account for the two hemispheres. Clusterwise probability values of $p < 0.01$ were
7 considered statistically significant in the present study.
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10 11 12 Statistics

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14 General linear models were used to test differences in the overall gyrification index between groups
15 using age and total intracranial volume as covariates. Nonparametric statistical tests were conducted
16 in correlations and group comparisons for the other variables. These procedures were implemented
17 with Statistical Product and Service Solutions software (SPSS, Inc, Chicago, Ill).
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24 25 26 **RESULTS**

27 28 29 30 Diagnostic Group Comparisons

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32 The overall IGI of both hemispheres was significantly lower in AN patients than in healthy women
33 (left: 2.85 ± 0.09 vs. 2.90 ± 0.11 ; $F(3,72) = 4.93$; $p = 0.03$; right: 2.85 ± 0.10 vs. 2.90 ± 0.12 ;
34 $F(3,72) = 4.37$; $p = 0.04$). AN patients who had recovered from the disorder showed no differences
35 in comparison to healthy women in overall hemispheric IGI (left: 2.90 ± 0.09 ; $F(3,54) = 0.11$; $p =$
36 0.745 ; right: 2.90 ± 0.09 ; $F(3,54) = 0.12$; $p = 0.730$). Figure 1 shows the results of the vertex-wise
37 comparison between AN patients and healthy women: both in the left and in the right hemisphere
38 an area in the parietal cortex showed significantly lower gyrification in AN patients. These areas
39 mainly encompassed: in the left hemisphere: precentral, postcentral, superior parietal,
40 supramarginal, and rostral-middle-frontal gyri; in the right hemisphere: precentral and superior-
41 frontal gyri. Performing the analysis including cortical thickness as a vertex-wise covariate changed
42 only marginally the brain areas of significant differences (Supplementary Figure 1). The
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4 comparison between recovered AN patients and healthy women revealed no cluster of significant
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6 difference after the multiple comparison correction.
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9 Neither overall IGIs, nor vertex-wise analyses, led to a significant correlation between gyrification
10 and body mass index, amount of weight loss, age of onset, or duration of illness (Table 2). No
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12 significant differences emerged between patients who were taking antidepressants and those who
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14 were not (left overall IGI: 2.84 ± 0.06 vs. 2.85 ± 0.11 ; $F(3,34) = 0.28$; $p = 0.60$; right overall IGI:
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16 2.83 ± 0.06 vs. 2.86 ± 0.12 ; $F(3,34) = 0.03$; $p = 0.87$). In the 20 AN patients where bioimpedance
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18 analysis was performed, no significant correlation between gyrification and hydration index was
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20 found (left cluster: $\rho=0.03$; $p=0.91$; right cluster: $\rho=0.11$; $p=0.65$). Significant negative age
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22 correlations emerged in both the AN and healthy control groups, but no correlation \times group
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24 interaction was found (Supplementary Figure 2). AN patients also revealed several areas of
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26 significantly reduced cortical thickness (Supplementary Table 1), that only partially overlapped
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28 with cortical areas displaying a reduced gyrification index (Supplementary Figure 3).
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35 Outcome Analysis

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37 Out of the patients who performed the 3 year follow-up assessment ($n=37$), 13 (35%) were
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39 completely recovered. Figure 2 and Table 2 shows the baseline differences between patients with
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41 full recovery and those not making a full recover over the subsequent 3 years. Performing the
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43 analysis including cortical thickness as a vertex-wise covariate changed only marginally the brain
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45 areas of significant differences (Supplementary Figure 4). Areas of between-group significant
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47 differences were located in bilateral superior parietal cortex and, in the left hemisphere, overlap
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49 with brain areas that showed significant difference in the comparison between the whole group of
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51 AN patients and healthy women. The group with poor outcome displayed significantly lower
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53 baseline overall gyrification both in comparison to healthy women (left: 2.82 ± 0.10 vs. 2.90 ± 0.11 ;
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55 $F(3,58) = 6.98$; $p = 0.011$; right: 2.82 ± 0.10 vs. 2.90 ± 0.12 ; $F(3,58) = 6.60$; $p = 0.013$) and in
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4 comparison to those AN patients who recovered (left: 2.82 ± 0.10 vs. 2.90 ± 0.06 ; $F(3,33) = 4.75$; p
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6 = 0.04; right 2.82 ± 0.10 vs. 2.90 ± 0.07 ; $F(3,33) = 5.15$; $p = 0.03$). No differences in gyrification
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8 emerged between good outcome AN patients and healthy women. At vertex-wise analysis, the AN
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10 group with poor outcome showed brain areas of significantly decreased gyrification in comparison
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12 to healthy women (Supplementary Figure 5).

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14 Finally, we tested outcome predictive ability for both the overall hemispheric gyrification indices
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16 and the average gyrification index of clusters significantly differentiating patients with full recovery
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18 and those not making a full recover. Both overall gyrification indices and those specific to
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20 significant clusters showed a significant predictive ability in identifying good outcome patients
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22 (Table 3). No relevant changes in the models were observed after including other possible
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24 prognostic variables, such as SSRI therapy, depressive/anxiety symptoms, diagnostic subtype, and
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26 severity of eating psychopathology.
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32 DISCUSSION

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37 This study was the first to explore the presence of cortical folding aberrations in AN and the
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39 relationship between cortical morphology and outcome. In both hemispheres, AN patients showed
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41 decreased gyrification in comparison to healthy women in brain areas (superior parietal and frontal
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43 cortex) which are considered crucial for integration and elaboration of somatosensory perceptions,
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45 visuo-spatial abilities, and executive functions. These cognitive functions may be related to body
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47 image disturbance, which is considered one of the 'core' characteristics of this disorder (Favaro et
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49 al. 2012). Functional neuroimaging studies relying on different measurement techniques have
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51 consistently implicated aberrations in the bilateral parietal cortex (Kaye et al. 2013; Van Kuyck et
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53 al. 2009) as possible markers of AN, given its role in body image elaboration. However, AN
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55 patients often also display problems in cognitive style, such as poor set-shifting (Roberts et al.
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4 2007; Tenconi et al. 2010) and decision making abilities (Bodell et al. 2014), these being
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6 considered to mainly rely on prefrontal cortex functioning.
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9 Although the mechanisms behind developmental aspects of cortical folds are still unclear, it is
10 hypothesized that the adult pattern of gyrification somewhat reflects the integrity of the process of
11 connectivity development during prenatal life (Dubois et al. 2008; White et al. 2010). In this
12 context, our findings would confirm a neurodevelopmental hypothesis for AN (Favaro, 2013),
13 supported by evidence of similar patterns of hypogyria in other neurodevelopmental psychiatric
14 disorders, such as schizophrenia (Palaniyappan and Liddle, 2012) and autism (Liberio et al. 2014).
15 However, starvation in AN is associated with anatomical brain alterations that potentially could
16 account for our findings. The local gyrification index is not able to distinguish between a decrease
17 in number or in development of sulci, from one hand, and reduced sulcal depth or increased sulcal
18 width on the other (Palaniyappan et al. 2013). In other words, a reduced gyrification index could
19 imply either hypogyria or cortical flattening due to a decrease in cortical volume and thickness. To
20 date, histological cortical changes associated with weight loss and malnutrition in AN have received
21 little attention in literature (Neumarker et al. 1997). The decrease in both gray and white matter
22 volumes and their potential (at least partial) reversibility lead to the hypothesis that rather than
23 neuronal death or other types of neurodegeneration, it is the reduced dendritic ramification and
24 spine density, as well as the reduced number/volume of glia cells, that must be held accountable for
25 these changes (Neumarker et al. 1997; Seitz et al. 2014). Moreover, it is worth noting that the
26 adolescent brain is characterized by developmental changes that physiologically imply reduced gray
27 matter volume (due to cortical thinning) and increased white matter volume associated with the
28 continuing process of myelination in the neuropil and deep intracortical layers (Aleman-Gomez et
29 al. 2013; Klein et al. 2014). The impact of AN on brain developmental trajectories is not known and
30 longitudinal studies would be of great importance for understanding the specific brain changes in
31 this type of patients. In our cross-sectional MRI study, we found both evidence in favor of as well
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4 as evidence against the hypothesis of an effect of weight loss in the determination of gyrification
5 alterations. Our finding of an absence of gyrification alterations in the sample of recovered AN
6 patients would support a weight loss effect hypothesis lacking long-term consequences. This would
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8 be in line with previous studies about cortical thinning in AN (King et al. 2015) and many
9
10 preceding voxel-based morphometry studies (Van den Eynde et al. 2012; Seitz et al. 2014).

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12 According to this hypothesis, decreased gyrification in our sample of acute AN patients could
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14 simply be the result of reduced cortical thickness. In contrast with this hypothesis, however, we
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16 found that maps of reduced cortical thickness and of reduced gyrification only show a marginal
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18 overlapping in our sample and including maps of cortical thickness as a vertex-wise covariate did
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20 not affect our findings. In addition, we observed a decrease of brain gyrification along with age in
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22 large brain areas of both samples (as reported in previous studies on healthy individuals (Aleman-
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24 Gomez et al. 2013; Klein et al. 2014)), with no evidence of differences between groups in the
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26 pattern of gyrification changes.
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30 While analyzing our second objective, namely the impact of brain gyrification in predicting
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32 outcome at follow-up, an alternative hypothesis emerged: in our analyses, we found that low levels
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34 of gyrification significantly predicted poor outcome at a 3-year follow-up, whereas the ‘good
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36 outcome’ group showed no differences in gyrification index when compared to healthy women
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38 even though they were, on average, severely underweight.
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42 The pattern of our findings could thus fit the hypothesis that abnormal brain gyrification is more
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44 evident in a subgroup of ‘poor outcome’ AN patients, probably as the consequence of a more severe
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46 disruption of neurodevelopmental processes. Since the recovered AN group is ‘per definition’ a
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48 group with a good prognosis, this hypothesis would explain why gyrification was not impaired in
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50 this group. Moreover, such result is in line with previous papers dealing with other psychiatric
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52 disorders which found that gyrification is not only a marker of integrity of normal cortical
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54 development (Palaniyappan and Liddle, 2012; Schaer et al. 2008), but also characterizes a subgroup
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4 of patients with low response to treatments (Palaniyappan et al. 2013). Furthermore, in our sample,
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6 gyrification indices were able to predict outcome even after controlling for the effects of well
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8 known prognostic factors such as weight loss, body mass index, severity of psychopathology, and
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10 duration of illness. If confirmed by future studies, this finding would be of great importance for the
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12 identification of patients with poor response to standard treatments as well as for the provision, in
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14 these cases, of more intensive or alternative biological (Lipsman et al. 2013) or non-biological
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16 (Tchanturia et al. 2014) treatments in order to obtain symptomatic relief. Since AN is an illness
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18 with relatively low levels of recovery and high levels of chronicization (Treasure et al. 2010), our
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20 findings might be taken as a warning against the tendency to generalize brain studies based on
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22 recovered patients. Indeed, in these studies although the effects of the presence of malnutrition on
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24 the brain are not present, it is very difficult to keep track of the effects of those favorable prognostic
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26 factors that made recovery possible.
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30 This study has several strengths, as well as important limitations, which should be taken into
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32 consideration. It is the first to explore brain gyrification in terms of the possible relationships
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34 between brain characteristics and subsequent outcomes in a sample of AN patients. However, a
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36 particular word of caution must apply in interpreting brain findings in AN samples for which it is
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38 often difficult to disentangle the effects of early developmental factors on the brain and the
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40 consequences of starvation. In particular, although in our study no linear correlation has emerged
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42 between gyrification and duration of illness, we cannot exclude prolonged starvation as a possible
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44 cause of our findings as the poor outcome group had on average a duration of more than 8 years of
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46 illness. This is the reason why duration of illness was included as a covariate in the comparison
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48 between AN groups. Furthermore, according to a sort of ‘two-hit’ model similar to that
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50 hypothesized for schizophrenia, our findings could be the result of an interaction between early
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52 developmental factors and later weight loss (Favaro, 2013; Schmitt et al. 2014). Although in this
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54 study AN patients were assessed after their medical conditions had stabilized, hydration is another
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4 factor that could account for variations in the shape and volume of the brain cortex. However, we
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6 tested this possible correlation in a subsample of severely underweight patients and found no
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8 significant effects.
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10 In conclusion, the present study provides evidence of cortical gyrification alterations in the parietal
11
12 and frontal cortex of patients with AN. These alterations did not show a linear relationship with
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14 body mass index, cortical thickness or dehydration and these changes were not present in patients
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16 with a good outcome, regardless of their body weight and recovery status. Longitudinal studies
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18 carried out on large cohorts of patients suffering from AN are needed to explore the effects of
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20 malnutrition and weight loss on cortical morphology and to understand how these interact with the
21
22 duration of the illness, the response to treatment and aging. Moreover, to explore the possible
23
24 involvement of these cortical aberrations in the psychopathology of AN and their clinical and
25
26 scientific implications, it would be interesting to study at least two further aspects. One is the
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28 replicability of our findings in patients suffering from the illness for a short period of time or in
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30 high-risk individuals who do not have AN. The other is the exploration of possible
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32 structural/functional connectivity alterations that, according to the Van Essen's hypothesis, underly
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34 aberrations of cortical folding (Van Essen, 1997). Any possible hypothesis about a possible
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36 neurodevelopmental origin of these cortical aberrations requires a careful examination and
37
38 exclusion of alternative hypotheses. However, if our findings will be replicated and supported by
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40 future studies, cortical folding alterations in AN patients, regardless of their origin, could represent
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42 a useful method for identifying patients who are resistant to conventional treatments at an early
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44 stage.
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6 Figure 1 - Vertex-wise comparisons between anorexia nervosa patients and healthy women. General
7
8 linear models with age and total intracranial volume were used, applying the Monte Carlo method
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10 to control for multiple comparison and using a cluster-wise threshold for inclusion of $p < 0.01$. Left
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12 hemisphere: a cluster of 6.761 mm² with a vertex of maximum difference ($p=0.0002$) in the
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14 postcentral gyrus (-36, -36, 54). Right hemisphere: a cluster of 1.419 mm² with a vertex of
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16 maximum difference ($p=0.002$) in the superior frontal gyrus (21, 9, 53). No cluster showed
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18 significant results in the opposite direction.
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7 Figure 2 - Vertex-wise comparisons between anorexia nervosa patients who recovered at 3-year
8 follow-up and those who still had an eating disorder. General linear models with age, duration of
9 illness and total intracranial volume were used, applying the Monte Carlo method to control for
10 multiple comparison and using a cluster-wise threshold for inclusion of $p < 0.05$. Left hemisphere: a
11 cluster of 2.892 mm² with a vertex of maximum difference ($p=0.0018$) in the superior parietal
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Table 1 - Baseline characteristics of the 3 groups

	AN patients (n=38)	Recovered AN patients (n=20)	Healthy women (n=38)	AN vs. HW	recAN vs. HW
	mean (SD)	mean (SD)	mean (SD)	t (p)	t (p)
Age	26.1 (7.2)	26.3 (7.1)	25.3 (6.3)	0.54 (0.59)	0.59 (0.56)
Age at onset	18.3 (5.1)	17.7 (3.2)	=	=	=
Duration of illness (months)	78.6 (81.3)	45.7 (65.0)	=	=	=
Duration of recovery (months)	=	45.4 (46.8)	=	=	=
Baseline BMI	15.8 (1.8)	19.6 (1.6)	21.7 (2.9)	10.51 (<0.001)	2.91 (0.005)
Weight loss*	7.1 (2.8)	5.2 (3.1)	3.4 (1.7)	7.01 (<0.001)	2.95 (0.005)
Lowest BMI	14.0 (1.8)	15.7 (1.4)	19.8 (2.5)	11.56 (<0.001)	6.71 (<0.001)
Education	14.2 (2.2)	14.2 (2.7)	15.5 (2.3)	2.44 (0.02)	1.97 (0.05)
Edinburgh laterality index	57.2 (37.6)	60.6 (35.2)	55.1 (42.0)	0.23 (0.82)	0.50 (0.62)
Drive for thinness	9.9 (6.1)	=	2.3 (4.2)	6.22 (<0.001)	=
Depression	1.4 (0.8)	=	0.7 (0.6)	4.06 (<0.001)	=
Trait anxiety	56.6 (9.7)	=	39.3 (9.6)	7.82 (<0.001)	=

* weight loss is defined as the difference between highest and lowest lifetime body mass index

Table 2 - Correlations between hemispheric gyrification index and clinical variables, and differences in clinical characteristics in anorexia nervosa patients according to outcome at 3-year follow-up

	Correlation with left IGI	Correlation with right IGI	AN patients with recovery at follow-up (n=13)	AN patients without recovery (n=24)	
	rho (p)	rho (p)	mean (SD)	mean (SD)	z (p)
Age	-0.11 (0.51)	-0.16 (0.33)	25.5 (6.8)	26.7 (7.5)	0.33 (0.74)
Age at onset	0.20 (0.23)	0.01 (0.94)	20.8 (6.5)	17.1 (3.8)	2.26 (0.02)**
Duration of illness (months)	-0.36 (0.02)**	-0.30 (0.07)	40.0 (46.2)	101.2 (89.8)	2.10 (0.04)
Baseline BMI	0.03 (0.87)	0.01 (0.80)	14.9 (1.75)	16.2 (1.6)	2.23 (0.03)
Weight loss*	-0.10 (0.54)	0.01 (0.94)	7.0 (2.4)	7.2 (3.1)	0.19 (0.85)
Lowest BMI	0.31 (0.06)	0.17 (0.31)	14.4 (2.0)	13.7 (1.7)	1.13 (0.26)
Drive for thinness	-0.02 (0.91)	-0.07 (0.70)	12.2 (6.1)	8.3 (5.6)	1.82 (0.07)
Depression	0.02 (0.92)	-0.02 (0.89)	1.38 (0.68)	1.39 (0.84)	0.03 (0.98)
Trait anxiety	-0.26 (0.12)	-0.14 (0.40)	55.6 (10.9)	57.0 (9.3)	0.40 (0.69)
Duration follow- up (ys)	=	=	3.2 (0.6)	3.5 (0.5)	1.48 (0.14)

	Correlation with left IGI	Correlation with right IGI	AN patients with recovery at follow-up (n=13)	AN patients without recovery (n=24)	
Final BMI	0.20 (0.24)	0.20 (0.23)	19.6 (2.1)	17.7 (4.3)	3.66 (<0.001)**

AN: anorexia nervosa; IGI: local gyrification index; BMI: body mass index

* weight loss is defined as the difference between highest and lowest lifetime body mass index

** according to false discovery rate method, differences are significant at $p < 0.027$ and correlations at $p < 0.026$

Table 3 - Outcome predictive ability of gyrification indices (logistic regression analyses)

Local gyrification indices*	OR (95% CI)		OR (95% CI) adjusted for age, age at onset, body mass index and duration of illness	
	OR (95% CI)	% individuals correctly classified	OR (95% CI)	% individuals correctly classified
Overall lh LGI	3.4 (1.1-10.3) p = 0.032	67.6%	5.2 (1.1-23.9) p = 0.033	81.1%
Overall rh LGI	2.9 (1.1-7.7) p = 0.033	73.0%	3.8 (1.1-13.0) p = 0.031	83.8%
Left superior parietal cluster LGI	2.4 (1.2-4.7) p = 0.014	67.6%	5.4 (1.4-20.1) p = 0.012	81.1%
Right postcentral cluster LGI	2.3 (1.2-4.5) p = 0.016	70.3%	4.1 (1.4-12.5) p = 0.012	81.1%

* all LGI indices were multiplied by a factor of 10

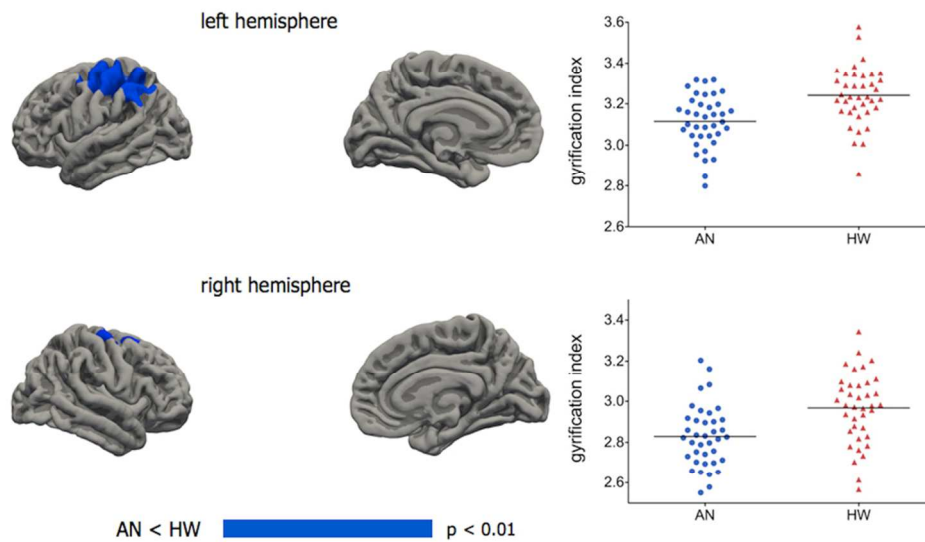
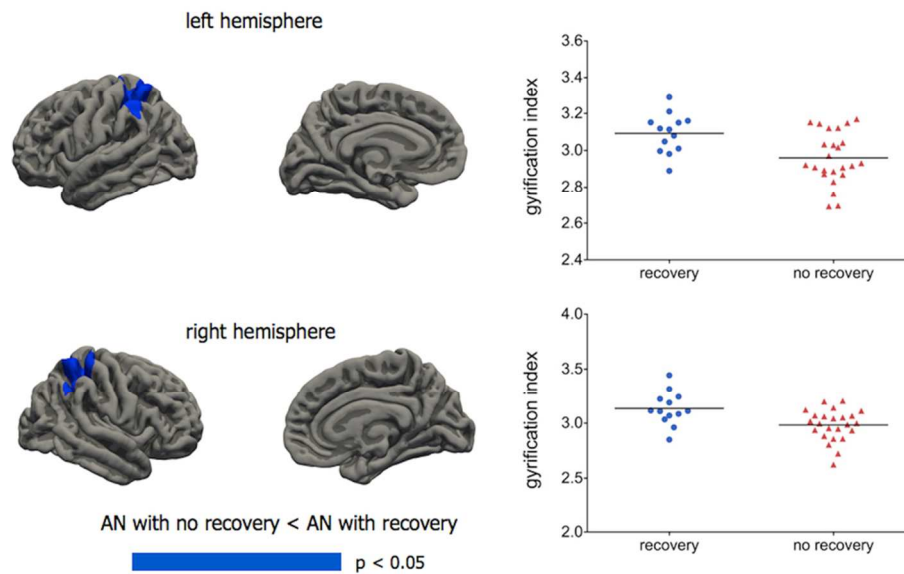


Figure 1 - Vertex-wise comparisons between anorexia nervosa patients and healthy women. General linear models with age and total intracranial volume were used, applying the Monte Carlo method to control for multiple comparison and using a cluster-wise threshold for inclusion of $p < 0.01$. Left hemisphere: a cluster of 6.761 mm² with a vertex of maximum difference ($p=0.0002$) in the postcentral gyrus (-36, -36, 54). Right hemisphere: a cluster of 1.419 mm² with a vertex of maximum difference ($p=0.002$) in the superior frontal gyrus (21, 9, 53). No cluster showed significant results in the opposite direction.

91x54mm (300 x 300 DPI)



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Figure 2 - Vertex-wise comparisons between anorexia nervosa patients who recovered at 3-year follow-up and those who still had an eating disorder. General linear models with age, duration of illness and total intracranial volume were used, applying the Monte Carlo method to control for multiple comparison and using a cluster-wise threshold for inclusion of $p < 0.05$. Left hemisphere: a cluster of 2.892 mm² with a vertex of maximum difference ($p=0.0018$) in the superior parietal cortex (-17, -49, 62). Right hemisphere: a cluster of 3.504 mm² with a vertex of maximum difference ($p=0.0004$) in the postcentral gyrus (27, -38, 51). No cluster showed significant results in the opposite direction.

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