Effects of Obstetric Complications on Volume and Functional Connectivity of Striatum in Anorexia Nervosa Patients

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ABSTRACT
Objective: To investigate the volume and functional connectivity of dorsal and ventral striatal nuclei in anorexia nervosa (AN) and their relationship with early exposure to obstetric complications.
Method: Fifty-one patients with lifetime AN (35 acute, 16 recovered) and 34 healthy controls underwent high-resolution and resting-state functional magnetic resonance imaging.
Results: The AN group showed reduced functional connectivity of the putamen compared with healthy women, and this reduction was more evident in patients with lifetime binge eating/purging. Both acute and recovered AN groups showed larger left accumbens area compared with that of healthy women. The functional connectivity of bilateral nucleus accumbens and putamen showed significant negative correlations with number of obstetric complications in the AN group.
Discussion: This study supports the hypothesis that AN is associated with structural and functional alterations of striatal networks, and reveals the possible role of obstetric complications in the pathogenesis of striatal dysfunction. © 2014 Wiley Periodicals, Inc.
Keywords: fMRI; functional connectivity; striatum; obstetric complications; anorexia nervosa

Introduction

Anorexia nervosa (AN) is described as a condition characterized by intrinsic disturbances of the reward system,1,2 which are hypothesized to be caused by altered striatal dopamine function. Dysfunction of brain reward circuits in AN may be involved in alterations in the drive to eat3 but also in more general functions such as motivation, learning, and habit formation. Besides alterations in eating behavior, patients with AN appear to have dysfunctional sensitivity to reward and punishment,4 poor decision making,5 and altered stimulus-response learning, leading to the transformation of pathological behavior, such as food restriction or compensatory behavior, into consolidated habits.6,7 Habit formation is a complex phenomenon involving both ventral (nucleus accumbens) and dorsal striatal neural circuits (caudate and putamen nuclei). Yin and Knowlton8 hypothesized hierarchical functioning of cortico-basal ganglia networks in habit formation and emphasize the key role of accumbens and the limbic network—implicated in appetitive learning—in influencing the subsequent processing of associative (caudate) and sensorimotor (putamen) networks. In this way, physiologically, a goal-directed action reinforced by rewards may become a habitual response.8 The persistence of AN and its resistance to change has led researchers to hypothesize alterations in the process of habit formation in these patients,6,7 similar to what has been proposed for addictions.9

However, although several pieces of evidence support the hypothesis of striatal dysfunction in AN3: to date, no study has investigated the morphology and functional connectivity of these brain nuclei in AN patients, nor have they explored any possible link between striatal dysfunction and early environmental risk factors implicated in the pathogenesis of several major psychiatric diseases, including AN.11 A method to explore functional

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connectivity of brain areas of interest is the measurement of resting-state spontaneous fluctuations in the blood oxygen level-dependent (BOLD). Recent discoveries concerning brain function have demonstrated that this MRI technique provides unique insights into the organization of intrinsic activity in the human brain. Coherent resting-state networks appear to play a fundamental role in brain functional organization; the physiological functions of resting-state networks and their correlation with psychopathology remain to be explored, but available studies have shown that disturbances in the correlation structure of spontaneous activity is present in many psychiatric diseases.

Recent studies found that various types of obstetric complications may increase the risk of developing AN and have explored possible pathways to explain the role of obstetric complications in the pathogenesis of AN. Many hypotheses attempt to explain the mechanisms by which obstetric complications increase the risk of psychiatric disorders. Early complications during pregnancy, such as anemia, diabetes, or pre-eclampsia, are thought to cause chronic hypoxia or malnutrition, leading to developmental delay and prematurity/dysmaturity at birth; later complications, such as cardiac problems, delivery complications, and respiratory distress may cause subtle damage due to acute hypoxia. However, recent studies hypothesize that the common factor linking pathological hypoxia and other early environmental risk factors, such as prenatal infections or stress exposure, is dysregulation of genes involved in neurodevelopment and the consequent disruption of developmental trajectories of neural structures and circuits. The mechanisms of action of early environmental risk factors have been extensively studied in animal models and evidence has been found that obstetric complications may cause striatal dysfunction. The hippocampus and basal ganglia are particularly vulnerable to hypoxia-ischemia in the neonate. In animals, cesarean section and/or exposure to perinatal anoxia have been linked to greater neuronal spine density in the nucleus accumbens, decreased striatal dopamine turnover and altered dopamine receptor mRNA in the striatum. In humans, few studies have examined the relationship between obstetric complications and striatal dysfunction. Haukvik et al. found a positive relationship between number of obstetric complications and volume of the nucleus accumbens in a sample of patients with schizophrenia, but the correlation was nonsignificant after correction for multiple comparisons.

In this study, we hypothesize that altered function of striatal circuits is one of the mechanisms explaining the role of perinatal factors in increasing the risk of developing AN.

This study therefore aims at exploring the relationship between number of perinatal complications and volumes of dorsal and ventral striatal nuclei, such as caudate, putamen, and accumbens nuclei. It then examines the relationship between number of obstetric complications and resting-state functional connectivity of dorsal and ventral striatal nuclei, in order to identify mechanisms contributing to AN pathogenesis.

Method

Participants

The final sample in this study was 51 patients with lifetime AN (35 acute, 16 recovered) and 34 healthy women (see Table 1 for description of sample). All participants were Caucasian women. All AN patients met DSM-IV criteria for AN in their lifetime. We initially approached 39 patients with acute AN and 20 recovered AN patients: 2 acute AN and 1 recovered patients were then unable to participate, 1 recovered patient refused participation and 2 acute AN and 2 recovered patients were excluded after MRI scanning for the presence of motion artifacts (see below). Participation rate was 90% for acute AN and 80% for recovered AN patients.

The healthy control group consisted of women with no history of eating disorders. All participants gave their informed written consent for use of their data in an anonymous form, and the Local Ethics Committee approved the study.
Women who had recovered from AN were patients who had had full DSM-IV AN in their lifetime, but had been asymptomatic for at least 6 months at the time of scanning (mean remission time: 33.3 months; range, 6–90). All recovered patients were asked if they would participate in this study during follow-up visits in our Eating Disorders (ED) Unit. None of the patients in this group relapsed in the two years following the study. Exclusion criteria for all participants were major medical illnesses, history of neurological problems, head trauma with loss of consciousness, active use of systemic steroids, antipsychotics, mood stabilizers or benzodiazepines, pregnancy, active suicidal ideation or major depression, history of substance/alcohol abuse or dependence, bipolar disorder or schizophrenia spectrum disorder, moderate mental impairment (IQ < 60), or any contraindication for MRI. Amenorrhea, food restriction, bingeing, excessive exercise, fasting, and purging were additional exclusion criteria for the recovered AN group; history of any psychiatric disorder and any first-degree relatives with an eating disorder were additional exclusion criteria for healthy women. None of the healthy women were taking psychoactive medication. Eleven AN patients and three recovered women were currently taking antidepressants (1 case mirtazapine, 10 cases SSRI).

Clinical Assessment
All AN patients were medically stable at the time of testing/scanning and all were recruited at the ED Unit of Padova, Italy. Only five patients had been admitted to a medical ward at the time of participation, but MRI scanning was performed after stabilization of their medical condition and normalization of electrolyte levels. Healthy women within the same age range were recruited from the general population and among volunteers, as described in previous studies. In all participants (cases and controls), diagnostic interviews were performed by the Eating Disorders section of the Structured Clinical Interview for DSM IV. To exclude participants with major psychiatric diagnoses, we administered the MINI International Neuropsychiatric Interview to all participants. To exclude individuals with mental impairment, participants also completed the Brief Intelligence Test (the Italian version of the National Adult Reading Test, a measure of premorbid intellectual ability) when they were 18 years old or more, and the “Information” subscale of the Wechsler Intelligence Scale for Children (age below 16) or Wechsler Adult Intelligence Scale (age between 16 and 18) when age was below 18. None of the participants scored below the 90th percentile of the measure used. Handedness was assessed with the Edinburgh Handedness Inventory. All participants also completed the Hopkins Symptoms Checklist, a self-report measure of depressive, anxiety and obsessive-compulsive symptoms.

Obstetric Complications
Data regarding obstetric complications were available for 28 AN patients, 14 recovered AN patients, and 32 healthy women. Most participants had been born in Padova Hospital (18 AN patients, 11 recovered AN patients, 17 healthy women) and data regarding obstetric complications were available from hospital archives. As in our previous studies, we reviewed obstetric records to collect any important information. In all the other cases, we interviewed the parents of participants, using an adapted version of the Pregnancy History Instrument, an interview covering a wide range of pregnancy, delivery, and neonatal complications. In addition, in all these cases, we were able to obtain copies of birth certificates giving details of major complications, gestational age, birth weight/length, head circumference, and Apgar scores. All interviews were performed face-to-face with mothers or both parents of participants. None of the parents interviewed were suffering from psychiatric disorders.

Recorded information about mothers included age at birth (in completed years at the infant’s birth), marital status at birth, parity (number of births, including birth in question), and weight changes before and during pregnancy. A complete list of the main obstetric complications and their definitions are available in our previous papers. The McNeil-Sjöström Scale was used to define obstetric complications. Only complications scored at level 3 (potentially harmful) or higher (clearly harmful) by the McNeil-Sjöström Scale were considered here.

Neuroimaging Protocol
Data were collected on a Philips Achieva 1.5 Tesla scanner equipped for echo-planar imaging. A resting-state fMRI scan entailed 250 continuous functional volumes (repetition-time = 2,009 ms, echo-time = 50 ms, flip angle = 90°, 21 slices, matrix = 128 × 128, acquisition voxel size = 1.8 × 1.8 × 6 mm³, acquisition-time = 8 min; field of view = 23 cm). Participants were instructed to lie with their eyes closed during the scan. At the end of the procedure, all subjects were asked about their emotions or tendency to fall asleep during the scanning. None of the subjects in the study had moved, fallen asleep, or reported anxiety or other particular emotion during scanning. For spatial normalization and localization, high-resolution 3D T1-weighted anatomical images were also acquired in a gradient-echo sequence (repetition-time = 20 s, echo time = 3.78 ms, flip angle = 20°, 160 slices, acquisition voxel size = 1 × 0.66 × 0.66 mm³, field of view = 21–22 cm). A trained neuroradiologist (R.M.) evaluated all scans as without gross pathology. Subjects with excessive motion (displacements greater than 2.5 mm or 2.5°) or major...
scanner artifacts detected by visual inspection were excluded (2 patients with AN, 2 recovered AN patients, and 3 healthy women). These 7 participants were excluded from all analyses in the present study and their data is not included in the samples described above. Mean and relative displacements during scanning did not differ between groups (mean displacement (mm): AN, 0.147 ± 0.080; recovered AN, 0.189 ± 0.079; controls, 0.154 ± 0.070; relative displacement (mm): AN, 0.078 ± 0.040; recovered AN, 0.109 ± 0.057; controls, 0.074 ± 0.037).

Structural Image Processing

Measurements of total volumes of putamen, nucleus accumbens, and nucleus caudatus, were obtained from T1-weighted MR images with FreeSurfer version 5.0 automated software (http://surfer.nmr.mgh.harvard.edu). With this method, each voxel in the MRI volume was automatically assigned a neuroanatomical label, based on probabilistic information estimated automatically from a manual training set.37 The validity of the volumes of putamen, nucleus caudatus and nucleus accumbens as obtained by FreeSurfer has been tested against manual tracings, and agreement between automated and manual volume measures has been reported to be comparable with that obtained comparing the manual volume measures of several experts.37 Estimations of total intracranial volumes were obtained with the same software.

Functional Image Processing

Resting-state scans were preprocessed with both Analysis of Functional NeuroImages (version AFNI_2010_10_19_1028; http://afni.nimh.nih.gov/afni; NIMH, Bethesda, MD) and FM-RIB Software Library (version FSL 4.1.6; http://www.fmrib.ox.ac.uk; FMRIB, Oxford, UK). Preprocessing was performed as described in Biswal et al.38 and www.nitrc.org/projects/fcon_1000. Details of pre-processing and processing are described elsewhere.29,30 In brief, preprocessing consisted of motion correction by Fourier interpolation, spatial smoothing with a 6-mm full-width at half maximum Gaussian kernel, mean-based intensity normalization of all volumes by the same factor, linear and quadratic detrending, and spatial normalization via estimation of a linear transformation from the individual functional spaces to MNI152 standard brain space, with each individual’s high-resolution anatomic image. A high-pass filter setting of 200 s (<0.005 Hz) was used to reduce very-low frequency artifacts such as scanner draft and a low-pass filter to remove any components in the high-frequency spectrum (>0.1 Hz). Nuisance signals were removed by multiple regression before functional connectivity analyses. Each individual’s four-dimensional (4D) time series was regressed on nine predictors, consisting of white matter, cerebrospinal fluid, the global signal, and six motion parameters (three cardinal directions and rotational movement around three axes). Each participant’s residual 4D time series was transformed into Montreal Neurological Institute space by means of a linear affine transformation implemented in FSL, and the time series was extracted for each seed. Time series were averaged across all voxels in the seed region of interest (ROI) and then, for each participant, the correlations between the time series of the seed ROI and of each voxel in the brain were determined. Lastly, correlation maps were converted to z-value maps.

For this study, we selected three bilateral spherical seeds (diameter = 8 mm) from the previous literature representing: (1) dorsal caudate (DC; MNI coordinates: ±13, 15, 9); (2) dorsal rostral putamen (DRP; ±25, 8, 6); (3) ventral striatum inferior or nucleus accumbens (VSI; ±9, 9, −8). Based on the study of Di Martino et al.,39 we expected the dorsal caudate to connect with the dorsolateral prefrontal cortex, ventral lateral prefrontal cortex, anterior cingulate cortex, and parietal association areas (cognitive control areas); the dorsal rostral putamen with the secondary motor areas and the anterior cingulate cortex (sensori-motor areas), and the ventral striatum with the medial orbitofrontal cortex, parahippocampal gyrus and the posterior cingulate cortex (emotional processing areas).

The resulting standardized maps were then used for testing differences between groups and linear relationships with variables of interest, with age and hand lateralization as nuisance variables. Non-parametric permutation testing (5,000 permutations) was used for statistical analysis of spatial maps, with the TFCE (Threshold-Free Cluster Enhancement)40 method and multiple comparison corrections across space, thresholding at p < 0.05. This study tested: (1) whether the linear relationship between functional connectivity and obstetric complications differed between the two groups; (2) whether linear relationships existed (and were significant) between functional connectivity and obstetric complications in the two groups. Graph data were obtained by extracting the average z-value in the brain area of interest for any individual map, and managing data by Statistical Product and Service Solutions software (SPSS, Inc, Chicago, IL). The validity of findings was checked against the presence of dehydration and brain atrophy, as described in our previous papers.29,30

Statistical Analyses

Statistical Product and Service Solutions software was used (SPSS, Inc, Chicago, IL) to perform comparisons between groups in clinical characteristics and brain
nuclei volumes. Differences between groups in volumes were performed by means of generalized linear models, with total intracranial volume, age and hand lateralization as covariates of no interest. In addition, since in acute AN a linear positive relationship has been observed between gray matter volumes and body mass index, volumetric comparisons were performed both including and nonincluding this variable as a covariate. The false discovery rate method was used to check for the risk of chance finding, with $p = 0.029$ (six contrasts) as the threshold for significance.

### Results

**Volumetric Analysis: Between-Group Comparisons**

Striatal volumes of patients with AN, recovered AN and healthy women are listed in Table 2 (non-standardized volumes). No differences emerged between patients with AN and healthy controls, with the exception of the left accumbens area, which appeared to be greater in patients with AN ($p = 0.014$; FDR threshold for significance = 0.029). This difference increased in significance when body mass index was included as a covariate ($p = 0.002$; FDR threshold for significance = 0.029). Similar average volumes (and standard deviations) were found in the recovered AN group, but no statistical significance emerged compared with healthy women, because of the lower power of the analysis. Controlling for the effects of covariates, patients who were taking antidepressants did not differ from those who were not, and no difference was found between restricting and nonrestricting patients. In the AN group, a significant correlation was found between left accumbens volume and body mass index (raw volume: $r = 0.50; p = 0.002$; correlation adjusted for effects of total intracranial volume: $r = 0.56; p = 0.001$), whereas only a significant trend emerged for right nucleus accumbens ($r = 0.31; p = 0.070$; adjusted correlation: $r = 0.31; p = 0.074$). No significant correlations emerged between body mass index and estimated volumes of caudate and putamen nuclei. No significant relationship emerged between striatal nuclei volume and depressive, anxiety, and obsessive-compulsive symptoms or between striatal nuclei volume and hand lateralization.

**Volumetric Analysis: Correlations with Obstetric Complications**

No significant linear relationship emerged between striatal volumes and number of obstetric complications in any group.

**Functional Connectivity Analysis: Between-Group Comparisons**

No significant differences emerged between acute AN patients and healthy women or between recovered AN patients and healthy women in the functional connectivity of dorsal caudate (DC) and nucleus accumbens (VCI). As regards the functional connectivity of dorsal putamen (DRP), we found significantly decreased coactivation in acute AN patients compared with controls in both left putamen (peak: 30, 0, 12 (6 voxels, right putamen)) and right putamen connectivity (peaks: 3, −6, 42 (180 voxels, left putamen), 30, 0, 9 (97 voxels, right putamen), 3, −6, 42 (94 voxels, cingulate gyrus), −24, −3, −12 (36 voxels, left amygdala), 3, −15, 60 (21 voxels, precentral gyrus)). In the areas with significant differences, average coactivation appeared to be significantly lower in those patients with lifetime binge eating (restricting vs. lifetime binge eating/purging: $0.14 \pm 0.06$ vs. $0.09 \pm 0.06; t = 2.08; p = 0.046$) and significantly correlated with the obsessive-compulsive ($r = −0.34; p = 0.04$), depressive ($r = −0.39; p < 0.02$) and anxiety symptoms ($r = −0.40; p < 0.02$). Patients who were taking antidepressant medication did not differ from patients who were not. No significant relationship emerged between average coactivation and hand lateralization.

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**Table 2.** Striatal volumes (mm$^3$) in three samples: Comparison among groups with general linear models$^a$

<table>
<thead>
<tr>
<th></th>
<th>Underweight AN (n = 35) Mean (SD)</th>
<th>Recovered AN (n = 16) Mean (SD)</th>
<th>Healthy women (n = 34) Mean (SD)</th>
<th>AN vs HW F</th>
<th>AN vs HW$^b$F</th>
<th>REC vs HW F</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left caudate</td>
<td>3423 (333)</td>
<td>3414 (565)</td>
<td>3331 (337)</td>
<td>0.56</td>
<td>1.16</td>
<td>0.08</td>
</tr>
<tr>
<td>Right caudate</td>
<td>3368 (336)</td>
<td>3357 (584)</td>
<td>3328 (328)</td>
<td>0.01</td>
<td>0.00</td>
<td>0.01</td>
</tr>
<tr>
<td>Left putamen</td>
<td>4990 (433)</td>
<td>5100 (564)</td>
<td>4901 (436)</td>
<td>0.42</td>
<td>0.12</td>
<td>1.29</td>
</tr>
<tr>
<td>Right putamen</td>
<td>4704 (423)</td>
<td>4886 (462)</td>
<td>4705 (396)</td>
<td>0.11</td>
<td>0.05</td>
<td>1.35</td>
</tr>
<tr>
<td>Left accumbens</td>
<td>530 (75)</td>
<td>530 (76)</td>
<td>483 (66)</td>
<td>6.42$^a$</td>
<td>10.8$^a$</td>
<td>4.31</td>
</tr>
<tr>
<td>Right accumbens</td>
<td>489 (77)</td>
<td>507 (73)</td>
<td>473 (67)</td>
<td>0.60</td>
<td>1.72</td>
<td>1.84</td>
</tr>
</tbody>
</table>

$^a$With total intracranial volume, age and hand lateralization as covariates of no interest.

$^b$Adjusted for body mass index.

$^p < 0.029$ (FDR threshold for significance).
Functional Connectivity Analysis: Correlation with Obstetric Complications

The number of obstetric complications did not show any significant linear relationship with dorsal caudate connectivity. In contrast, we observed a significant correlation per group interaction (i.e., a significant difference between slopes of correlation) when exploring the linear relationship between nucleus accumbens connectivity and number of obstetric complications in the contralateral accumbens and subcallosal cortex (Fig. 1). Coactivations in these brain areas showed significant negative correlations with number of obstetric complications in the AN group (left accumbens: \( r = -0.72; p < 0.001 \); right accumbens: \( r = -0.72; p < 0.001 \)) and significant positive correlations in
the healthy women group (left accumbens: $r = 0.48; \ p = 0.005$; right accumbens: $r = 0.40; \ p = 0.023$). Post-hoc analyses showed nonsignificant (but positive) correlations in the recovered AN group (left accumbens: $r = 0.49; \ p = 0.07$; right accumbens: $r = 0.21; \ p = 0.47$). As regards putamen functional connectivity, no significant correlation per group interaction emerged. However, significant negative correlations with number of obstetric complications in the AN group (left putamen: $r = -0.78; \ p < 0.001$; right putamen: $r = -0.75; \ p < 0.001$) were found in connectivity with the contralateral putamen (Fig. 2). Among healthy women, correlations were positive but not significant for putamen connectivity (left putamen: $r = 0.007; \ p = 0.97$; right putamen: $r = 0.13; \ p = 0.46$) and in
OBSTETRIC COMPLICATIONS AND STRIATUM CONNECTIVITY IN AN

Discussion

This study found significant alterations in striatal functional connectivity and striatal volumes in patients with AN, confirming previous hypotheses of dysfunction of the striatum in this disorder.\(^3\),\(^7\),\(^10\) Even more interestingly, a significant association was found between number of obstetric complications and the functional connectivity of accumbens and putamen nuclei, allowing interesting hypotheses about the involvement of these brain areas in explaining the pathogenic role of obstetric complications in AN.

In the acute AN group, we found a significant negative correlation between number of obstetric complications and striatal functional connectivity, which was consistently present bilaterally and in both accumbens and putamen. The correlations mainly involved interhemispheric connectivity with the contralateral striatum (Figs. 1 and 2) and, for the accumbens, the subcallosal and medial prefrontal cortex. This suggests that obstetric complications may contribute to reduced interhemispheric coordination in the regulation of behavior and response inhibition, and possible dysfunction in emotional processing. Abnormality of striatal interhemispheric connectivity has been implicated in the pathogenesis of tic disorders,\(^41\) suggesting the role of this type of connectivity in response inhibition and the impulsive/compulsive behavior which are characteristically associated with tic disorders. It was interesting to observe, in this regard, that lower interhemispheric coactivation of both accumbens and putamen was characteristic of the binge eating/purging subgroup.

It is noteworthy that the negative correlation between obstetric complications and functional connectivity was only found in the underweight AN sample. The correlation was of the opposite sign or absent in both recovered AN and healthy women. This observation suggests an interaction between being underweight and obstetric complications, and might explain why compulsive behavior tends to be greatly exacerbated with weight loss in many AN patients. Obstetric complications may be “latent” risk factors which only display their pathogenic effects in particular circumstances, such as those determined by weight loss/malnutrition or stress.

Although previous studies on recovered patients have found significantly increased task-related activation in the dorsal striatum\(^1\) and increased D2/D3 receptor binding in the ventral striatum,\(^42\) we did not find any differences between recovered AN patients and healthy women in striatal functional connectivity. In contrast, patients with acute AN, compared with healthy women, showed significantly decreased functional connectivity of the dorsal rostral putamen with the contralateral putamen, cingulate gyrus, amygdala, and precentral gyrus. Functional connectivity in these areas was significantly lower in patients with lifetime binge eating, compared with restricting patients with AN, suggesting the role of putamen connectivity in the pathogenesis of compulsive behaviors in patients with AN. It must be recalled that this is the first study exploring functional connectivity in the striatum in AN, and replications are needed to confirm our findings and hypotheses.

Voxel-based morphometry studies have usually found a consistent decrease in the volume of brain gray matter in patients with AN,\(^43\),\(^44\) with few exceptions concerning areas in the dorsolateral prefrontal cortex\(^45\) and medial orbitofrontal cortex.\(^46\) However, few studies have specifically analyzed volumes of subcortical nuclei. An exception is the study of Connan et al.,\(^47\) who found decreased hippocampal volumes in AN patients.

Our study found that, on the contrary, the striatal nuclei showed an enlargement of volumes in comparison with those observed in healthy women. The differences reached statistical significance only for the left nucleus accumbens, and were very small for the other nuclei, but they suggest the possible involvement of striatal nuclei in developing or maintaining AN psychopathology. Similar volumes were also observed in recovered AN patients and may indicate a “stable” characteristic, present even before the onset of the disease, or its “scar”. We found no relationships between volumes of striatal nuclei and obstetric complications,
indicating that other factors (weight, psychopathology, genetic factors) are involved in determining this variable. The increased volume of the accumbens has been observed in other psychiatric conditions, such as alcoholism and schizophrenia48,49 and it may originate in excessive activation of the nucleus (due to the involvement of this brain area in a specific psychopathology) or to an alteration in its neurodevelopmental trajectory due to exposure to genetic and/or environmental risk factors.

This study has advantages and limitations which should be taken into account. Although the sample size is not small, replications of our findings are needed before our data can be generalized. Psychiatric comorbidity was not formally assessed in our sample and, although comorbidity with depressive and anxiety disorders may be a secondary effect of AN, we cannot make inferences about the role of comorbidity on our findings. The effects of brain atrophy or dehydration on detection of differences in the BOLD signal are not completely known. To control for any linear effect, we performed the additional analyses described in our previous studies,26 but found no significant effect of brain atrophy, weight loss, dehydration, or body mass index on the functional connectivity of the striatal nuclei. The inclusion in the study of a recovered group is a strength of this study, since it allows a distinction to be made between state and trait characteristics.

In conclusion, our study found evidence of structural and functional alterations of striatum in patients with AN. The fact that acutely ill and recovered patients share structural alterations and that striatal functional connectivity significantly correlates with obstetric complications, may lead to the hypothesis of a disruption of developmental trajectories of striatum in patients with AN. Since striatal network dysfunctions appear to only be present in the ill state, this study also shows that, although obstetric complications and other risk factors may contribute to create a vulnerability status for the development of AN, a further potentially reversible factor that may model neurocircuit development in AN is represented by weight loss and malnutrition.18

These findings are of potential interest, due to their important scientific implications, but they need replication in view of the absence of similar studies, not only in patients with AN but also in healthy individuals and other patient samples. The pathogenetic pathways explaining the role of obstetric complications as risk factors for specific psychiatric disorders, such as AN and schizophrenia, need further exploration in future studies. Functional MRI is a promising tool in this field, since it seems to be less influenced by weight loss and dehydration26,27 than structural brain measures and also has the potential to indicate which neurocircuits are implicated, partly in order to provide suitable treatment.20

In conclusion, this study supports the hypothesis that AN is associated with structural and functional alterations of striatal networks, and also shows the possible role of obstetric complications in the pathogenesis of striatal dysfunction. There is potential for functional neuroimaging to produce further insights on this topic, especially with larger samples and combined with knowledge of molecular/genetic factors.

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