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Adolescent Anorexia Nervosa: Cognitive performance after weight recovery

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ABSTRACT

Objective: Although there is no definitive consensus on the impairment of neuropsychological functions, most studies of adults with Anorexia Nervosa (AN) find impaired functioning in cognitive domains such as visual–spatial abilities. The objective of this study is to assess the cognitive functions in adolescents with AN before and after weight recovery and to explore the relationship between cognitive performance and menstruation.
Methods: Twenty-five female adolescents with AN were assessed by a neuropsychological battery while underweight and then following six months of treatment and weight recovery. Twenty-six healthy female subjects of a similar age were also evaluated at both time points.
Results: Underweight patients with AN showed worse cognitive performance than control subjects in immediate recall, organization and time taken to copy the Rey's Complex Figure Test (RCFT). After weight recovery, AN patients presented significant improvements in all tests, and differences between patients and controls disappeared. Patients with AN and persistence of amenorrhea at follow-up ($n = 8$) performed worse on Block Design, delayed recall of Visual Reproduction and Stroop Test than patients with resumed menstruation ($n = 14$) and the control group, though the two AN groups were similar in body mass index, age and psychopathological scale scores.
Conclusion: Weight recovery improves cognitive functioning in adolescents with AN. The normalization of neuropsychological performance is better in patients who have recovered at least one menstrual cycle. The normalization of hormonal function seems to be essential for the normalization of cognitive performance, even in adolescents with a very short recovery time.

Introduction

Many studies have found cognitive inefficiencies in patients with Anorexia Nervosa (AN) [1,2]. Although there is no definitive consensus on the impairment of neuropsychological functions, general studies suggest that patients with AN present alterations in cognitive domains such as visual–spatial abilities [2,5] and executive functions [6]. Patients with AN show weakness in central coherence, resulting in superior detail processing and a weakness in global integration [7]. Several authors have found difficulties in cognitive flexibility [8–10] and set-shifting abilities that lead to rigidity [7]. Some studies have compared cognitive performance before and after weight recovery in AN patients. When AN patients achieve weight restoration, improvements in tasks of attention [2,3] and psychomotor speed [4,6] tasks have been observed. Nevertheless, almost all follow-up studies have found that alterations persist after refeeding, especially in immediate memory [3,4], delayed memory [11], motor tasks [3], visual–spatial abilities [2] and executive functions such as cognitive flexibility [12,13] and problem-solving abilities [6]. These characteristics are also found in some relatives of patients with AN [14,15]. In the light of these findings, some authors have proposed that impairment in functions such as set-shifting or central coherence may be a stable trait of the illness rather than a state, conforming an endophenotype of the disorder [7–10,16].

The majority of these studies have been conducted in adult patients with a long duration of the disorder. Little is known about cognition in adolescent patients, in whom time of evolution of AN and time of starvation are shorter, although some studies in this population have also recorded difficulties in visual–spatial abilities [17–19]. To our knowledge, few follow-up studies have assessed cognitive performance exclusively in adolescent patients with AN before and after weight

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restoration. Schmidt et al. [20] evaluated reaction time and concentration in 52 adolescent inpatients with AN, finding improvement in all cognitive measures over the course of inpatient treatment. Grunwald et al. [21] found that the haptic abilities of 10 adolescents with AN improved with refeeding. Pieters et al. [22] compared drawing and copying tasks in 17 patients versus 17 healthy controls, and reported that the AN group had shorter reaction times on tasks after weight restoration. Hatch et al. [23] found that the AN group (n = 37) was significantly faster on attention and executive function tasks, exhibited superior verbal fluency and working memory and a superior ability to inhibit well-learnt responses than controls (n = 45). However, Sarrar et al. [24] found subtle deficits in cognitive flexibility in 30 AN patients compared with 28 control subjects. After weight gain, adolescents with AN improved relative to their baseline values but did not reach control values. Finally, Bühren et al. [25] compared set-shifting abilities in 28 female adolescents with AN before and after weight rehabilitation and 27 healthy controls. They found no set-shifting inefficiencies in adolescent patients with AN and proposed that the shorter duration of illness and the incomplete maturation of the prefrontal cortices compared to adult patients with AN contributed to the explanation of these findings.

Neuropsychological follow-up studies with AN patients have been carried out after weight restoration. Although weight is one indicator of biological recovery from the condition [26], menstrual function may remain abnormal in some weight-recovered patients [27,28]. Some authors have studied the relation between hormones and cognitive functioning across the female life span, in moments such as pregnancy, post-partum or menopause, and report relationships between estrogens and impairment in some cognitive functions such as verbal memory [29]. To our knowledge, only two studies have studied the relationship between menstrual function and cognitive performance in AN, and their results are conflicting. Chui et al. [30] found that adult subjects with a history of adolescent-onset AN and persistent amenorrhea or irregular menses had lower scores on a variety of domains: verbal ability, thinking ability, cognitive efficiency, working memory, oral language, broad reading, written language and math than participants with regular menses or using oral contraceptives. Also, Bühren et al. [31] found subtle memory impairments in AN adolescents before and after weight recovery and a positive correlation between verbal learning inefficiency and starvation-induced estrogen deficits after weight recovery.

In summary, in comparison with studies with adult AN patients, not all studies with adolescents with AN show impairment in cognitive performance after refeeding. In fact the results are conflicting: while some studies find persistence of cognitive inefficiencies after refeeding [24], the majority show no differences between patients and controls [22,23,25]. The main aim of this study is to describe the cognitive performance of adolescents with AN at the moment of diagnosis and after six months of treatment and refeeding. Our second objective is to study the influence of menstruation on the neuropsychological functioning in these patients. We hypothesized that adolescents with AN will show more cognitive impairments similar to those reported in adult patients – visual memory, visual–spatial ability and executive function – while they are underweight than healthy controls. We expected that functions such as velocity would improve after refeeding, but that functions related to visual–spatial abilities would remain below control group levels in the second assessment. We also expected to find subtle cognitive inefficiencies in relation to persistent amenorrhea after six months of treatment.

Method

Participants

Twenty-five patients who met the DSM-IV-TR diagnostic criteria for AN were recruited consecutively at the Department of Child and Adolescent Psychiatry and Psychology at the Hospital Clinic in Barcelona. The patients were adolescents aged between 11 and 18 years. All were in an acute phase of the disorder with a body mass index (BMI) lower than 17.5 kg/m^2 in the first assessment. Length of illness ranged between 4 and 20 months (mean = 12.26, SD = 8.1). Patients and their parents were interviewed with a semi-structured interview following DSM-IV-TR criteria used in clinical practice at our department to investigate current psychopathology and developmental history. The control group comprised 26 female volunteers of similar age recruited from several secondary schools in Barcelona. Control subjects and their parents were interviewed using the Kiddie-Schedule for Affective Disorders and Schizophrenia (K-SADS-PL) to assess current and past psychopathology [32]. Exclusion criteria in both groups were the presence of psychiatric disorder (other than AN in the patient group), history of neurological impairment or estimated low intellectual level (Standard Score below 5 on the Vocabulary subtest of the WISC-R).

Patients and control subjects were evaluated by two trained psychologists (EL and SA) using a comprehensive neuropsychological battery with pen and paper tests. A second complete evaluation was carried out in both groups after six months. During this time, AN patients followed our department's treatment program. Treatment at our unit is based on a multidisciplinary approach combining biological management, nutritional rehabilitation, a standardized behavioral program which aims to improve eating patterns and weight, individual and group cognitive treatment, and individual and group parent counseling. Only patients who respond well to treatment are seen as outpatients: when physical risk is high, psychopathology intense or cooperation in the outpatient setting very poor, inpatient treatment is indicated. During hospitalization all patients receive a complete diet of about 1250 calories per day during the first days which is increased progressively to 2500 calories per day, but they do not receive vitamin supplements or any hormonal replacement therapy. After discharge, the vast majority of patients follow a Day Hospital program which includes weight and eating control, nutritional counseling, and body image and social skills group therapy for an average of three months. After the Day Hospital program, outpatient follow-up is indicated to control weight maintenance and general outcome. In the first assessment all patients were receiving treatment in hospitalization or Day Hospital because outpatient treatment was not possible due to the severity of disorder. In this program, patients usually regain near normal weight within six months. This is one of the first objectives of the treatment, even if patients are not totally recovered.

All patients, controls and parents gave written informed consent to participate in the study. The procedures were approved by our hospital's Ethical Committee.

Psychopathological assessment

Validated Spanish versions of the following psychopathological scales were administered: the Eating Attitudes Test (EAT-40) [33], a questionnaire for evaluating eating attitudes and symptoms, the Children's Depression Inventory (CDI) [34], used to assess severity of depressive symptoms, and the Leyton Obsessional Inventory—Child Version (LOI-CV) [35] to assess the severity and interference of obsessive–compulsive symptoms.

The State and Trait Anxiety Inventory for Children (STAIC) [36] evaluates the level of anxiety at the moment of evaluation (STAIC State) and anxiety as a general trait (STAIC Trait).

Neuropsychological tests

Neuropsychological assessment in children and adolescents is difficult because these patients present different developmental levels. A battery with internationally validated tests [37] was designed by our team (S.A) on the basis of the literature available on cognitive performance in AN. The tests with the best psychometric properties for assessing each cognitive function were selected, but some of them

were not validated at all ages (for example, the WISC-R in subjects over 16). To minimize the risk of error we worked with raw scores in the data analyses.

Wechsler Intelligence Scale for Children—Revised (WISC-R) [38]; the Vocabulary subtest was used to estimate level of intelligence and to control this confounding variable. Block Design, considered as a measure of central coherence [10], was used as a visual organization measure. WISC-R was used because the WISC-IV had not been validated in our country at the time the battery was designed.

Wechsler Memory Scale III (WMS-III) [39]; the Visual Reproduction (VR) test measures the number of details from five geometric figures that patients remember in immediate (VR1) and delayed (VR2) recall.

Rey's Complex Figure Test (RCFT) [40]; this test evaluates perceptual organization and visual memory. The organizational strategy used to copy the RCFT is considered a measure of central coherence [10]. It was assessed following Savage's criteria [41]: subjects can obtain six points for different structural elements (central square, vertical and horizontal lines, central cross and final angle) drawn during the copying task (RCFT Org). We assessed accuracy of copy (RCFT Copy) and immediate recall (RCFT Recall) of the figure using the assessment criteria of the test manual [40]: in copying and recall, 18 elements of the figure were assessed and scored following localization and accuracy criteria: right, well-located (2 points), correct and misplaced (1 point), incomplete but recognizable and well-located (1 point), incomplete but poorly located (0.5 points) and unrecognizable or absent (0 points). Time taken to copy RCFT was recorded (RCFT Time). To avoid a learning effect, Taylor's Complex Figure Test (TCFT) was used for retesting [42]. This form is a valid alternative to RCFT to avoid implicit learning which may occur when the same version of the RCFT is used for repeated testing sessions [43]. The organizational strategy of Taylor's Complex Figure Test was scored similarly to the Rey's Complex Figure Test, following Savage's criteria, but the central cross was substituted by the other horizontal line.

Trail Making Tests A and B (TMT) [44]; these tests assess speed in processing information, attention, and cognitive flexibility.

Wisconsin Card Sorting Test (WCST) [45]; this test measures sorting and set-shifting ability. It was used to assess categories obtained (number of correct runs of ten sorts) (WCST-cat), number of sorting errors (WCST-err) and perseverative errors (WCST-per).

Stroop Test (Stroop) [46]; this test is based on the finding that it takes longer to name colors than to read words, and even longer to read the name of a color printed in some other color. Patients who fail this test tend to have difficulty in concentrating and in warding off distractions.

Statistical analyses

The normality of the sample distribution was tested with the Kolmogorov–Smirnov test and the equality of variances with Levene's test. As the application conditions were satisfied, parametric tests were used to analyze differences between patients and controls. Demographic and psychopathological variables were compared by the Student's *t* test. The results obtained on all neuropsychological tests in the patient and control groups were compared by a Multiple Analyses of Variance (MANOVA) in the first assessment and in the follow-up. Changes between the two assessments were analyzed using a MANOVA for repeated measures with time of testing (basal assessment vs. follow-up) as the within-subject factor and diagnostic group (AN vs. control group) as the between-subject factor. In all the MANOVA, Bonferroni correction for multiple comparisons was applied in order to avoid the presence of false positives.

For the second objective, the AN group was divided into two subgroups: patients with restored menstruation in the follow-up assessment (at least one menstrual cycle) and patients who remained amenorrheic. Because one of the groups was very small (AN with amenorrhea = 8) comparisons of clinical and neuropsychological variables between patient and control groups were made with non-parametrical tests (Kruskal–Wallis and Mann–Whitney tests).

All analyses were performed using the statistical package SPSS 15.0. A *P* value of 0.05 or less was considered significant in all analyses.

Results

Demographic and clinical characteristics

As shown in Table 1, at baseline assessment there were no significant differences in age or estimated intellectual level between patient and control groups. In the psychopathological questionnaires, the AN group showed higher scores on all scales, with significant differences in depression, state anxiety and eating symptomatology, but in the DSM-IV-TR interview none of the patients fulfilled criteria for diagnoses of depression, anxiety or obsessive disorders.

After six months of treatment, AN patients showed significant increases in weight and BMI. Again, there were no significant differences in estimated intellectual level between the groups. AN patients showed statistically significant improvements in eating and state anxiety symptomatology, but continued to score higher than control subjects in eating and in depressive and obsessive symptoms (Table 1).

Neuropsychological differences at first assessment between AN and control groups

The comparison of neuropsychological performance at baseline using MANOVA showed significant overall differences between AN and control groups ($F = 2.407$; $P = 0.018$). Differences between the groups were found in immediate recall, time to copy and organization of RCFT (Table 2). In all cases the control group obtained better scores. None of the other tests showed differences between the groups.

Evolution of cognition after six months of treatment

Differences between the groups in scores of all neuropsychological tests were compared at both times of assessment. A MANOVA calculated with all neuropsychological tests found significant differences in the results of the AN and control groups between baseline and follow-up assessments (MANOVA, $F = 2.266$, $P = 0.026$). In the second assessment there were no differences in the cognitive performance of the two groups (MANOVA, $F = 0.954$, $P = 0.511$).

Neuropsychological differences in relation to menstrual status in AN patients and controls

Among the post-pubertal patients, fourteen had recovered menstruation (63%) and eight remained amenorrheic after six months of treatment. Patients who had had at least one menstrual cycle were considered to have recovered menstruation. Three patients in whom these data were not adequately recorded were excluded from this analysis. Comparing AN subgroups with and without recovery of menstruation, no differences in BMI, age or psychopathological scores were found (Table 3).

As Table 4 shows, differences in Block Design, recall of Visual Reproduction and Stroop Test were found between the three groups. AN with amenorrhea showed lower scores in all cases than AN with menstruation and controls. The results of the control group and patients who had recovered menstruation were very similar.

Discussion

The main finding of this study is that cognitive inefficiencies present in adolescents with AN at the time of diagnosis improved significantly after refeeding. Certain functions such as speed of processing visual information, visual memory and organization reached levels similar to those of healthy controls, and the differences recorded in the underweight state disappeared. But not all patients showed the same neuropsychological performance; patients with persistent amenorrhea after six months of treatment had worse cognitive performance on some tests related with visual abilities and executive functions than patients who had recovered at least one menstrual cycle.

In the acute phase of the illness, adolescents with AN showed poorer cognitive performance on certain tests of visual memory, visual–spatial organization, central coherence and speed processing visual information. These results corroborate those of studies with adult patients [1,8,16,47,48] which reported impaired visual–spatial abilities. Difficulties in the global integration of complex visual stimuli and a tendency toward detail processing may be related to worse fixation of information and worse later recall [41]. This style of cognitive processing has been related with rigidity and with the difficulties in cognitive flexibility common in AN patients [8–10].

Table 1
Comparison of demographics and psychopathological questionnaires between AN (n = 25) and control (n = 26) groups

	Baseline assessment				Follow-up assessment				Difference AN	
	AN Mean (SD)	Control Mean (SD)	*t*	*P*	AN Mean (SD)	Control Mean (SD)	*t*	*P*	*t*	*P*
Age	15.1 (1.2)	15.5 (1.6)	−1.094	0.279						
Vocabulary	10.6 (2.6)	11.2 (2.0)	−0.965	0.339	10.1 (2.6)	10.1 (1.8)	−0.051	0.960		
Weight	40.3 (6.4)				49.2 (5.1)				−12.292	<0.001
BMI	15.4 (1.6)				19 (0.8)				−11.651	<0.001
EAT-40	41.9 (25.5)	8.8 (6.8)	6.028	<0.001	24.1 (14.1)	9 (6.2)	3.232	0.004	3.498	0.002
STAIC-S	72.9 (27.9)	53.1 (32.8)	2.305	0.026	51 (40.1)	55.7 (32.6)	−0.435	0.666	2.143	0.044
STAIC-T	48.0 (33.4)	35.9 (29.0)	1.373	0.176	42.5 (32.9)	36.4 (27.4)	0.682	0.499	0.830	0.416
CDI	14.0 (7.9)	9.2 (4.1)	2.705	0.010	12.4 (10.8)	7.1 (5.4)	2.072	0.046	1.053	0.304
LOI-S	8.7 (3.4)	7.8 (2.5)	1.022	0.312	9.3 (4.1)	7.5 (2.2)	1.890	0.068	−0.530	0.602
LOI-I	7.6 (7.1)	5.4 (4.3)	1.337	0.189	10.1 (11.5)	4 (5.2)	2.335	0.024	−0.883	0.388

Vocabulary = vocabulary subtest of Wechsler Intelligence Scale for Children—Revised; BMI = body mass index; STAIC-S = STAIC State; STAIC-T = STAIC Trait; LOI-S = LOI Severity; LOI-I = LOI Interference.

After refeeding, studies with adults find that not all functions show the same response: some functions improve quickly and completely, while others show no change or may deteriorate over time. In adolescent patients as well, the results of the few longitudinal studies published to date are conflicting; some report changes in all dysfunctions after refeeding [20–23,25] but others find a wide range or responses, as in the adult studies [24]. In our study, after six months of treatment and renutrition the impairments in velocity and visual–spatial functions disappeared. Other authors [4,6] also observed improvement on tests measuring psychomotor speed in adults after refeeding. These results suggest that the dysfunction in velocity may be directly related to the patients' nutritional state, and that renutrition may be enough to reestablish this function. But in visual–spatial functions the results range widely. Poor visual organization and central coherence have been reported to form a very stable processing style in adults with AN [2,13,49], but they were not found either in our study or in other studies with adolescents [23,25]. Adult patients with AN show a longer time of disorder, with more years of malnutrition and other symptoms of the disease. Adolescent patients with AN have a shorter length of illness (a mean of 12 months in the present study), shorter time of starvation and a higher rate of seeking treatment (because their parents seek medical help on their behalf, even if they are not in agreement). These clinical characteristics can explain the differences between adults and adolescents.

Differences in brain functioning between adults and adolescents have also been found in neuroimaging studies. Several studies have found alterations in brain structure and function during starvation in adolescent and adult patients, describing enlarged sulci and ventricles and decreased brain mass [50,51] especially in gray matter [52]. But some studies have shown that these brain alterations may be reversed if the adolescent patient recovers weight [53,54]. In adult patients, these abnormalities tend to improve with weight restoration, but it is still not clear whether they normalize completely. Some studies have found complete reversibility of cerebral changes with weight restoration [55,56], but others have not [2]. It may be that years of malnutrition and illness in patients who do not recover their weight alter the brain structure and functioning and cause the permanent cognitive deficits found in patients with long evolution.

Another possibility is that a biological variable such as hormonal functioning may be related to cognitive alterations in some patients, and is a factor of poor prognosis and persistence of illness until adult age. The relationship between menstrual and cognitive functions in the female population has been widely studied and the importance of this relation in moments as pregnancy, post-partum or menopause has been clearly established [29]. Studying the relationship between cognition and menstruation in adults with a history of adolescent onset illness, Chui et al. [30] reported poorer cognitive functioning in women with irregular menstruation or amenorrhea. In the present study, some of the patients who presented normalized weight during follow-up had not recovered menstruation. Patients with menstruation and patients with amenorrhea during follow-up presented similar clinical characteristics according to psychopathology questionnaires, BMI and age, but patients with amenorrhea presented worse cognitive performance on tests of visual memory, visuo-constructive abilities and central coherence, and also resistance to interference. These are all areas in which adult patients continue to present alterations after treatment, and in fact they have been proposed as stable traits of the illness [49]. Our results suggest that cognitive impairments may also be related to hormonal alterations in patients with weight restoration. As Lauer et al. [6] suggest, hormonal or metabolic factors may be mediating factors in cognitive performance. Other authors hold that cognitive inabilities are a cause of disorder [49,57], and that, for instance, alterations in

Table 2
Differences in neuropsychological tests between AN (n = 25) and control (n = 26) groups in the basal assessment

	AN	Control	F	*P*
VR1	92.1 (11.7)	95.9 (5.9)	2.132	0.151
VR2	73.8 (14.9)	71.2 (21.2)	0.247	0.622
RCFT Immed	20.3 (6.8)	24.3 (6.1)	4.863	0.032
RCFT Time	176.7 (75.7)	118 (35.5)	12.642	0.001
Blocks	47.2 (10.7)	51.7 (9.6)	2.494	0.121
RCFT Org	3.4 (1.7)	4.6 (1.9)	5.620	0.022
RCFT Copy	34.8 (1.5)	35.1 (1.3)	0.840	0.364
TMT A	35.6 (12)	35.4 (11)	0.002	0.962
TMT B	74.1 (25.9)	61.9 (18.6)	3.760	0.058
Stroop	52 (10.3)	55.2 (6.5)	1.843	0.181
WCST-cat	5.7 (0.9)	5.7 (1.0)	0.007	0.934
WCST-err	21 (16.6)	15.2 (10.1)	2.330	0.133
WCST-per	8.2 (13.2)	4.7 (7.2)	1.404	0.242

VR1 = Visual Reproduction, immediate recall; VR2 = VR, delayed recall; RCFT Immed = Rey's Complex Figure Test immediate recall; RCFT Time = seconds for copy of RCFT; RCFT Org = Organization of copy of RCFT; TMT A = Trail Making Test A; TMT B = Trail Making Test B; WCST: cat = categories, err = errors, per = perseverative errors.

Table 3
Comparison of demographic, clinical and psychopathological questionnaires between AN with amenorrhea (n = 8) and AN with menstruation (n = 14) in follow-up assessment

	AN with amenorrhea Mean (SD)	AN with menstruation Mean (SD)	U	*P*
Age	14.5 (1.6)	15.5 (0.9)	36.5	0.188
Vocabulary	10.1 (2.6)	10.1 (1.8)	36	0.188
BMI	18.8 (0.9)	19.1 (0.8)	40	0.414
EAT-40	24.2 (23.4)	27.8 (21.7)	32	0.579
STAIC-S	40 (38.9)	52.9 (42.9)	40	0.699
STAIC-T	32.4 (36.9)	45.8 (32.2)	28	0.183
CDI	12.3 (12.1)	11.7 (10)	43.5	0.877
LOI-S	7.8 (3.4)	10.8 (4)	26	0.196
LOI-I	5.7 (7.6)	12.9 (12.6)	28.5	0.261

BMI = body mass index; STAIC-S = STAIC State; STAIC-T = STAIC Trait; LOI-S = LOI Severity; LOI-I = LOI Interference.

Table 4
Differences on neuropsychological tests between AN with amenorrhea (n = 8), AN with menstruation (n = 14) and control (n = 26) groups in the follow-up assessment

	AN with amenorrhea Mean (SD)	AN with menstruation Mean (SD)	Control group Mean (SD)	X^2	*P*
VR1	93.5 (7.8)	94.9 (9.6)	97.9 (5)	2.599	0.273
VR2	63.4 (20.6)	84.9 (13.1)	80.7 (22.1)	6.179	0.045
TCFT Immed	23.3 (8.5)	28.1 (4)	29.1 (4.3)	3.547	0.170
TCFT Time	90.5 (17.3)	92 (28.1)	82.9 (18.8)	0.602	0.740
Blocks	44.9 (7.8)	54.4 (6)	53.5 (9.2)	6.923	0.031
TCFT Org	4.5 (1.9)	5.1 (1.3)	5 (1.2)	0.410	0.815
TCFT Copy	35.1 (1.1)	34.9 (1.2)	35.4 (1.2)	2.923	0.232
TMT A	30.8 (5)	27.6 (5.2)	28.8 (7.9)	1.715	0.424
TMT B	54.8 (10.3)	57.6 (15.6)	51.5 (13.1)	1.494	0.474
Stroop	48.4 (3.5)	53.7 (10.9)	56.2 (8.6)	6.882	0.032
WCST-cat	5.9 (0.4)	5.6 (1.6)	6 (0.2)	0.780	0.677
WCST-err	18.1 (13.3)	12.9 (15.4)	12.5 (8.7)	3.939	0.140
WCST-per	5.5 (7.9)	2.2 (6.1)	2.3 (4.2)	4.793	0.091

VR1 = Visual Reproduction, immediate recall; VR2 = VR, delayed recall; TCFT Immed = Taylor's Complex Figure Test immediate recall; TCFT Time = seconds for copy of TCFT; TCFT Org. = Organization of copy of RCFT; TMT A = Trail Making Test A; TMT B = Trail Making Test B; WCST: cat = categories, err = errors, per = perseverative errors.

visual abilities may raise the risk of developing eating disorders [58]. Patients with these neuropsychological alterations may have more difficulty in following treatment, achieving weight restoration and recovering menstruation, and may be vulnerable to chronic illness [59]. More studies are needed to explore the complex relationship between hormonal and cognitive functioning in patients with AN, but the idea of a link between the two may have very important clinical implications. If cognitive functions improve with the recovery of regular menstruation, then their reestablishment becomes an important objective of treatment, in addition to weight recovery.

This study presents some limitations. The main limitation is the small sample size, which makes it difficult to study subgroups of patients with different clinical characteristics. Controls were not weighed and detailed data concerning their hormonal function were not recorded, although all of them presented a healthy appearance and regular menstruation. Patients were assessed clinically with the semi-structured interview based on DSM-IV-TR criteria used in clinical practice at our department, but no standardized interviews such as K-SADS-PL were used. The battery designed for this study also has some limitations. For instance, the use of parallel forms of the memory tests such as Rey's Complex Figure Test is controversial. Taylor's Complex Figure Test was chosen to avoid the learning effect, and Savage's organizational criteria for Rey's Complex Figure Test were adapted to this parallel form. This solution is debatable, but it was chosen in order to avoid the problem of learning effect.

The strengths of the study include its longitudinal design, assessing the cognitive changes in a group of adolescents with AN after six months of refeeding, and the inclusion of a control group of similar characteristics. The study shows that weight restoration and regular menstruation are very important for recovery of the cognitive function. More longitudinal studies with longer follow-up periods are necessary to determine the implications of these variables for the course and prognosis of the illness.

Conflict of interest

The authors have no competing interests to report.

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