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ORIGINAL INVESTIGATION

Set-shifting abilities, central coherence, and handedness in anorexia nervosa patients, their unaffected siblings and healthy controls: Exploring putative endophenotypes

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Abstract

Objective. There is consistent evidence that anorexia nervosa (AN) is associated with an impairment of set-shifting abilities and central coherence. No study to date investigated handedness in AN. Our aim was to study set-shifting abilities, central coherence, and handedness in subjects with lifetime AN, in a sample of unaffected sisters and in healthy controls, in order to explore their suitability as endophenotypes of AN. *Methods.* The Edinburgh Handedness Inventory and several neuropsychological tasks (Wisconsin Card Sorting Test, Trail Making Test, Rey-Osterrieth Complex Figure Test, Overlapping Figures Test, Object Assembly and Block Design) were administered to 153 subjects with lifetime AN, 28 unaffected sisters and 120 healthy controls. *Results.* AN subjects and their healthy sisters showed poorer performances on most tasks investigating set-shifting and central coherence. In addition, we did not find any differences between long-term recovered subjects, weight-restored AN patients and those in an acute phase of their illness. AN subjects were significantly more likely to be left-handed than healthy controls (OR=2.8, 95% C.I. 1.1–7.2). *Conclusions.* Set-shifting and central coherence seem to be promising cognitive endophenotypes that might help in the understanding of the pathogenetic processes involved in AN. Further studies on larger samples are needed to explore the generalizability and implications of our findings concerning handedness.

Key words: *Anorexia nervosa, endophenotype, executive functioning, neuropsychology, handedness*

Introduction

In the last few decades, cognitive functioning in anorexia nervosa (AN) patients has received increased attention in the literature. Neuropsychology is considered to be an effective method to explore the involvement of specific brain areas and functions in psychiatric disorders. Although most studies have found the presence of impairments on a broad spectrum of cognitive functions in acute AN (Szmukler et al. 1992; Green et al. 1996; Kingston et al. 1996), there are also several studies that have failed to find cognitive deficits in these patients (Touyz et al. 1986; Palazidou et al. 1990; Bradley et al. 1997) and others that surprisingly have found cognitive performance to be superior to that of healthy controls (Pieters et al. 2003, 2004). In short, the current literature is inconclusive concerning the characteristics, underlying mechanisms and reversibility of cognitive abnormalities in AN (Katzman et al. 2001; Pieters et al. 2005). The first studies suggested that cognitive deficits observed in acute AN were a consequence of starvation and may be improved once adequate nutritional status is regained (Szmukler et al. 1992; Lauer et al. 1999). However, studies concerning higher-level executive functioning failed to find an improvement after weight gain, refeeding, or other types of treatment (Green et al. 1996; Kingston et al. 1996; Tchanturia et al. 2004). This is why an impairment in specific tasks of executive functioning appears to be a good candidate endophenotype in eating disorders.

For all psychiatric disorders there is an ongoing search for intermediate cognitive phenotypes that may help clarify the relative contributions of genetic

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and environmental risk factors. Some specific impairments of executive functions, such as inflexibility, set-shifting difficulties, and low central coherence, are considered putative endophenotypes of AN because of their stability throughout the illness (Tchanturia et al. 2004, 2005; Steinglass et al. 2006) and their heritability (Holliday et al. 2005). In addition, these impairments might play a role in the development and maintenance of AN (Bulik et al. 2007) and seem to have a negative influence on outcome (Hamsher et al. 1981; Szmukler et al. 1992; Holliday et al. 2005; Roberts et al. 2007). Notwithstanding this, few studies (Holliday et al. 2005) to date have examined the cognitive performance of unaffected sisters (or other first degree relatives) of AN patients which is considered to be an essential step in the identification of putative endophenotypes (Gottesman and Gould 2003).

Executive functions are the abilities that enable a person to engage successfully in independent, purposive and self-serving behaviour (Lezak et al. 2004). In particular, they are involved in the supervision of those cognitive processes, located primarily in the prefrontal cortex, which include restraining and delaying actions, inhibiting responses, setting goals, planning and organizing complex human behavioural output. One example of executive functioning is set-shifting ability that involves the ability to move back and forth between tasks, operations or mental sets (Miyake et al. 2000). There is consistent evidence of an impairment of set-shifting abilities in AN (Roberts et al. 2007). In addition, AN patients seem to have a better ability for the processing of details, but show worse performance on global strategies (Lopez et al. 2008a,b). This characteristic is called weak central coherence (Frith 1989) and is referred to as a cognitive style in which there is a bias towards local or analytical, detailed-focus processing of information and person is unable to integrate incoming information into meaningful context or gestalt (global integration). Global integration of perceptual stimuli involves perceptual and attentional abilities which are specifically impaired in people with lesions of the right hemisphere (temporal and frontoparietal networks) (Lezak et al. 2004). To date, the data available about central coherence in anorexia nervosa allows us to say that there is some evidence of weak global processing in anorexic patients, but there are still few data to demonstrate a superiority in local processing (Lopez et al. 2008c).

Although handedness has been considered as a putative endophenotype in other psychiatric disorders (Savitz et al. 2007) and seems to be consistently associated with schizophrenia and other neurodevelopmental disorders (Dragovic et al. 2005; Ramadhani et al. 2006), no study to date has explored the distribution of handedness in AN. Handedness is in part due to genetic factors, and in part can be conditioned by early environmental insults (prenatal or perinatal). Recent studies have hypothesized that eating disorders may have a neurodevelopmental origin (Connan et al. 2003; Strober et al. 2007) and their risk seems to be increased by the occurrence of perinatal complication (Favaro et al. 2006). For this reason, we included neuropsychological characteristics and handedness among the putative endophenotypes of AN.

The aim of the present investigation was to study handedness and performance on some specific neuropsychological tasks which explore set-shifting abilities and central coherence in women with lifetime AN, their unaffected sisters, and a control group, in order to explore their suitability as putative endophenotypes.

Methods

Subjects

The subjects of the study were 153 female patients with a lifetime diagnosis of anorexia nervosa (AN) referred to the Eating Disorders Outpatient Unit of Padua Hospital. According to the diagnostic status at the time of neuropsychological assessment the subjects were classified into three groups: (1) acute AN according to DSM-IV criteria (APA 1994) in 60 cases (39%), (2) weight-restored AN in 63 cases (41%), and (3) no eating disorder in the other 30 cases (20%). The second group consisted in subjects with previous AN, who were weight-restored, but who were still symptomatic at the time of neuropsychological assessment (binge eating or purging, hyperactivity, fasting). This sample included 14 subjects with bulimia nervosa, 10 subjects with EDNOS with binge eating or purging behaviour, and 39 subjects with EDNOS without binge eating or purging behaviour. The third group was composed of subjects with complete recovery from AN (at least 3 years of normal weight, regular menses, no eating symptoms, and good social and interpersonal outcome). An adapted version of the Morgan–Russell criteria have been used for definition of recovery (Morgan and Hayward 1988). The age of the AN sample ranged from 14 to 47 years with a mean of 26.2 years (SD=6.9) and the mean level of education was 14.2 years (SD=2.8). The mean age of onset for anorexia nervosa was 17.8 years (SD=4.1). The mean body mass index was 16.2 (SD=1.5; range 9.9–17.5) in the acute AN group, 20.5 (SD=3.1; range 18.0–37.0) in the weight-restored group, and 20.6 (SD=1.5; range 19.0–24.4) in the remitted group.

Criteria for participation in the study were: a lifetime diagnosis of anorexia nervosa according to the DSM-IV criteria (APA 1994); more than 14 years of age; written informed consent from patients and, in the case of patients younger than 18, from one parent. Exclusion criteria were: traumatic brain injury, lifetime presence of any neurologic or systemic illness independent from the eating disorder; lifetime presence of Axis I comorbidity (except for depressive and anxious disorders), presence of alcohol or substance abuse, psychoactive medication, except for the use of antidepressants.

After permission was obtained from the patient, we invited the sisters of the patients to participate in the study. We were able to contact 56 out of 72 sisters. Seven sisters were excluded because of the lifetime presence of an eating disorder, another six because their age was below 14, and in 15 cases either the patient or the sister refused. The final sample consisted of 28 healthy sisters, with a mean age of 27.5 years (SD = 8.7), a mean BMI of 22.0 (SD = 2.2) and mean level of education of 13.8 years (SD = 3.4).

The healthy control group consisted of 120 subjects with no history of eating disorder, with a mean age at assessment of 27.4 (SD = 4.5), a mean BMI of 21.8 (SD = 3.0) and mean level of education of 16.4 years (SD = 2.3). Criteria of exclusion were: BMI below 18, presence of a first degree relative with a lifetime eating disorder, traumatic brain injury, presence of any neurologic, psychiatric or systemic illness; presence of alcohol or substance abuse; psychoactive medication. All subjects gave informed written consent for the use of data in an anonymous form and institutional approval for the study was obtained.

Clinical and cognitive assessment

In all subjects (patients, their sisters, and controls), clinical interviews were performed using the eating disorders section of the Structured Clinical Interview for DSM-IV (First et al. 1995) and a semistructured interview to gather socio-demographic and clinical variables, such as family psychiatric morbidity, history of weight, and history of treatments. In addition, they were asked to complete the Hopkins Symptoms Checklist (Derogatis et al., 1974), the State Trait Anxiety Inventory (STAI; Spielberger et al. 1970), and the Tridimensional Personality Questionnaire (TPQ; Cloninger 1987).

Handedness was assessed through the Edinburgh Handedness Inventory (Oldfield 1971), which yields scores ranging from –100, denoting consistent left-handedness, to +100, denoting consistent right-handedness. As in previous studies (Christman et al. 2007), we considered mixed-handedness a score between –80 to +80. One AN subject and three controls did not complete this measure.

A neuropsychological test battery was used to assess some executive functions.

Set-shifting abilities: (1) the *Wisconsin Card Sorting Test* (WCST; Bergh 1948) investigates the ability of abstraction and cognitive flexibility. Particularly, the execution of the WCST presupposes the involvement of manifold cognitive operations, such as the process of initial abstraction, the appeal to functional strategies of problem solving, the ability to modify the strategy when the situation requires a change of rule, the ability to learn and to memorize functional rules (Laiacona et al. 2000). In addition to the indices usually considered in previous studies (number of completed categories, number of perseverative errors and responses, number of non perseverative errors), we used a measure of global efficiency, called the global score (Global score = [no. of trials – (no. of achieved categories × 10)]; Laiacona et al. 2000). The global index, the number of perseverative responses, and the number of non perseverative errors were adjusted for age, sex and educational level as reported in Laiacona et al. (2000). (2) the *Trail Making Test* (TMT; Reitan 1958) to measure attention and mental tracking. The first part of the task (TMT-A) evaluates selective attention and visuospatial ability, whereas the second (TMT-B) is a set-switching task that appraises selective and alternate attention.

Global versus local processing style (central coherence): (1) The *Rey–Osterrieth Complex Figure Test* (ROFT; Osterrieth 1944) appraises different cognitive functions such as perception, visuospatial ability, planning and visuospatial memory. The subject must copy and recall, after an interval of 3 minutes, a complex geometric figure. We used the standard scoring system developed by L. Taylor (Lezak et al. 2004) to assess the drawing accuracy of the Rey figure. The performance score is valued from the accuracy and placement of the reproduction of the 18 details of the figure. Using the Rey Figure Test, it is possible to calculate a central coherence index (ICC), that results from the order of construction index (number of global and local elements drawn in the initial stage of copying the figure) and the style index (the degree of continuity in the drawing process; Booth's method described by Lopez et al. (2008a)). A global approach during the copying task (high index of central coherence) seems to improve the performance on the recall task (Lopez et al. 2008a). In the present study, the copy and recall accuracy scores were adjusted for sex, age and educational level, as reported in Caffarra et al. (2002). (2) The *Unsegmented/Segmented Block*

Design and *Object Assembly* subtests of the revised version of the Wechsler Adult Intelligence Scale (WAIS-R; Wechsler 1981) were used as measures of visuospatial ability, problem solving and central coherence. In the Block Design test, subjects are asked to reproduce complex geometric figures by putting together some cubes. The difference between the time spent in the segmented and unsegmented trials is called benefit from segmentation. It has been hypothesized that subjects with a weak central coherence would gain less advantage from segmentation. In the Object Assembly test the subjects must recompose some jigsaw-type puzzle pieces into a whole figure (mannequin, head, hand, elephant), with no final example given to the subject. A shorter time suggests a better ability to create an integrated global representation from its parts. (3) The *Overlapping Figures Test* (Della Sala et al. 1995) appraises the ability to discriminate figures from the background (visual interference), spatial exploration, and denomination. An entangled sketch composed of many overlapping and segmented figures of animals, fruits, persons, numbers, and various other objects is given to the participant who must recognize and denominate the greatest number of figures in 4 minutes of time. Excessive local processing or weak global processing is associated with impaired performance.

Each subject was assessed individually in a quiet and well-illuminated room by a trained neuropsychologist and the examination took about 90 minutes.

Statistical analysis

All variables were tested for normality. Only the performance indices of the WCST were not normally distributed. We used a natural log transformation for normalization of these variables. After normalization, we used parametric tests to compare independent groups. An exception was the number of completed categories at the WCST which is an ordinal variable and required nonparametric statistical tests. When adjusted scores were not available, an analysis of variance with educational level and age as covariates (ANCOVA) was used to examine groups differences when significant differences in age or education were present between groups. Analyses for paired subjects were performed to compare AN patients and their healthy sisters. These procedures were implemented with Statistical Product and Service Solutions software (SPSS, Inc, Chicago, IL).

Results

Neuropsychological tasks: AN subjects versus controls

Table I shows the scores obtained by AN subjects and control subjects on the neuropsychological assessment. As regards the WCST, AN subjects had an overall worse performance in comparison to controls, reporting a higher global score, a lower number of categories, and a higher number of both perseverative and non perseverative errors (Table I).

Concerning the other neuropsychological tests, AN subjects reported a poorer performance on the Trail Making Test part B, the accuracy of ROFT recall, the central coherence index, the Object Assembly test, the Block Design Test Unsegmented/Segmented and the Overlapping Figures Test. Regarding the Block Design Test, we found no difference between groups across the two conditions of the tasks (benefit score). The inclusion of the Edinburgh score (handedness) among the covariates did not change any of the findings.

In AN, no significant correlation was found between neuropsychological performance and age of onset, BMI at the time of assessment, and lowest lifetime BMI. No differences have been found between subjects with a restricting phenotype and those with binge eating or purging behaviour. State anxiety (STAI) showed a moderate correlation with Trail Making Test part A ($r=0.23$; $P=0.007$), Overlapping Figure Test ($r=-0.37$; $P=0.001$), and Object Assembly test ($r=-0.36$; $P=0.008$). The inclusion of anxiety scores as a covariate in the comparison between AN patients and controls did not change the findings reported in Table I. No significant correlation has been found between neuropsychological performance and SCL depression/SCL obsessionality. Exploring correlations with temperamental variables, we found moderate correlations between the Reward Dependence subscale and ROFT Central Coherence Index ($r=-0.23$; $P=0.007$), ROFT Order Index Copy ($r=-0.26$; $P=0.002$), and ROFT Style Index Copy ($r=-0.17$; $P=0.045$).

No difference was found between medicated ($n=32$) and unmedicated ($n=120$) AN subjects, with the exception of ROFT Accuracy Copy (28.9 ± 4.2 vs. 30.4 ± 3.2; $t=2.18$; $P<0.04$) and the segmented Block Design (41.8 ± 9.4 vs. 48.2 ± 4.2; $t=2.68$; $P<0.02$). The exclusion of medicated subjects from the case–control comparison did not change the results of Table I, with the exception of the segmented Block Design (no significant difference between cases and controls).

Neuropsychological tasks: disease status

We divided the clinical sample according to the diagnostic status at the time of assessment (acute AN, weight-recovered but still symptomatic AN, long-term fully recovered AN) in order to compare the three groups (Table II). The three groups differ as regards education (13.7 ± 2.7; 14.0 ± 2.6; 15.3 ± 2.9;

Table I. Neuropsychological performance in anorexia nervosa patients and healthy controls.

	Raw scores			
WCST[2]	Anorexia nervosa Mean (SD) n=152	Controls Mean (SD) n=117	[1] $F(1,268)$	Effect size
Global score	48.6 (34.2)	32.3 (25.5)	33.37**	0.54
Number of categories[3]	5.2 (1.5)	5.7 (0.9)	–3.64**	0.40
Perseverative errors	14.5 (10.9)	10.5 (8.6)	5.12*	0.41
Non-perseverative errors	15.4 (12.8)	9.7 (8.1)	27.32**	0.53
Perseverative responses	16.2 (13.3)	11.7 (10.5)	28.31**	0.38
	n=152	n=120	$F(1,271)$	
Trail Making Test A	30.7 (11.0)	28.0 (8.1)	2.67	0.28
Trail Making Test B	67.5 (25.3)	55.4 (14.6)	13.26**	0.59
Rey Figure	n=152	n=118	$F(1,264)$	
Copy accuracy	30.1 (3.5)	30.9 (3.1)	1.53	0.24
Copy order	1.94 (0.72)	2.26 (0.70)	6.14*	0.45
Copy style	1.23 (0.46)	1.41 (0.36)	6.09*	0.44
Central coherence Index	1.20 (0.42)	1.38 (0.35)	6.14*	0.47
Recall accuracy	18.6 (5.4)	20.6 (5.0)	7.18**	0.38
	n=98	n=114	$F(1,211)$	
Overlapping Figures Test	35.2 (6.6)	39.2 (6.4)	11.55**	0.61
	n=59	n=84	$F(1,142)$	
Block design unsegm.	34.8 (8.6)	40.5 (6.1)	8.86**	0.76
Block design segm.	46.2 (6.8)	48.4 (3.4)	4.57*	0.41
Benefit from segm.	11.4 (9.3)	8.0 (7.0)	0.88	0.41
Object assembly	27.7 (6.1)	32.7 (4.3)	21.40**	0.95

[1]An analysis of variance was used. Educational level was included as a covariate when adjusted scores were not available (see Methods).
[2]Data about WCST were analysed after logarithmic transformation.
[3]Ordinal variable (Mann–Whitney U-test, z not adjusted for educational level).
*P<0.05; **P<0.005.

$F(2,150)=3.65$; $P=0.028$) and age (25.7 ± 7.7; 24.5 ± 6.1; 30.8 ± 4.6; $F(2,150)=9.58$; $P<0.001$). For this reason, both variables have been used as covariate in Table II. The comparison did not reveal any significant differences between the three groups on any of the neuropsychological measures, with the exception of the accuracy score of the ROFT copy on which the recovered group performed significantly worse.

Neuropsychological tasks: healthy sisters

Table III shows the scores reported by those AN subjects whose sisters participated in the study, the scores reported by their healthy sisters, and those of controls. The performance of healthy sisters is generally in an intermediate position between the other two groups. The performance of AN subjects and their healthy sisters did not differ significantly on any of the neuropsychological tasks, with the exception of the ROFT Central Coherence Index and Copy Order Index. AN patients and their sisters did not differ in a significant way as regards age and education ($P>0.3$). On the contrary, healthy sisters of AN patients differed from controls as regards education ($t=4.87$; $P<0.001$), but not age ($P>0.9$). Compared with controls, the healthy sisters of AN patients reported a poorer performance as regards the number of categories, the global score, the number of perseverative responses and non perseverative errors of the WCST, the Trail Making Test part B, the Overlapping Figures Test, Block Design and Object Assembly. There was no difference between sisters and controls on the ROFT scores, and benefit from segmentation at the Block Design Task.

Handedness

Subjects with AN (13 vs. 5%; $\chi^2=4.88$; df=1; $P<0.03$; OR=2.8, 95% C.I. 1.1–7.2) were significantly more left-handed than controls. A similar percentage of left-handedness was present in the healthy sisters of AN patients (14 vs. 5%; $\chi^2=2.95$; df=1; $P<0.09$; OR=3.1, 95% C.I. 0.8–11.8), but the difference was not statistically significant. No differences emerged as regards the rate of mixed-handedness or

Table II. Neuropsychological performance according to disease status.

WCST[2]	Acute anorexia nervosa Mean (SD) $n=60$	Weight recovered eating disorder Mean (SD) $n=63$	Full remission Mean (SD) $n=29$	[1] $F(2,151)$
Global score	47.4 (34.4)	48.5 (35.2)	51.1 (32.7)	0.17
Number of categories[3]	5.2 (1.6)	5.1 (1.5)	5.2 (1.4)	0.40
Perseverative errors	14.6 (11.1)	14.5 (11.1)	14.4 (10.2)	0.01
Non perseverative errors	15.7 (13.0)	14.8 (13.6)	15.8 (10.6)	0.50
Perseverative responses	16.1 (13.4)	16.1 (13.4)	16.9 (13.6)	0.06
TMT	$n=59$	$n=63$	$n=30$	$F(2, 151)$
Trail Making Test A	30.1 (9.8)	30.7 (10.2)	31.9 (14.5)	0.20
Trail Making Test B	73.3 (27.6)	64.9 (20.9)	61.8 (27.6)	2.48
ROFT	$n=59$	$n=63$	$n=30$	$F(2, 151)$
Copy accuracy	31.2 (3.0)	29.7 (3.6)	28.9 (3.7)	5.05*
Copy order index	1.97 (0.76)	1.92 (0.71)	1.93 (0.68)	0.19
Copy style index	1.24 (0.60)	1.19 (0.44)	1.28 (0.44)	0.30
Central coherence index	1.22 (0.45)	1.18 (0.40)	1.22 (0.40)	0.21
Rey Figure recall	19.1 (5.5)	18.1 (5.6)	18.5 (5.1)	1.16
	$n=29$	$n=41$	$n=28$	$F(2, 97)$
Overlapping Figures Test	33.9 (6.5)	35.4 (6.0)	36.1 (7.7)	1.14
	$n=21$	$n=30$	$n=6$	$F(2, 56)$
Block design unsegmented	35.1 (8.9)	35.2 (7.0)	31.7 (15.1)	0.09
Block design segmented	47.2 (4.2)	45.6 (8.3)	46.2 (6.5)	0.50
Benefit from segmentation	12.1 (8.5)	10.2 (9.6)	14.5 (10.8)	0.31
Object assembly	27.4 (6.4)	27.8 (5.1)	28.3 (10.4)	0.13

[1]An analysis of variance was used. Educational level and age were included as covariates when adjusted scores were not available (see Methods).
[2]Data about WCST were analysed after logarithmic transformation.
[3]Ordinal variable (Kruskal–Wallis test, χ^2 not adjusted for age and educational level).
*$P<0.05$; **$P<0.005$.

in the degree of lateralization. In both AN and controls, handedness or degree of lateralization did not correlate with cognitive performance.

Discussion

Physical, biological or psychological traits may represent endophenotypes or partial phenotypes of a specific disorder when they are measurable, heritable, associated with the illness, independent of the clinical state, and more frequent in first-degree relatives of affected subjects than in the general population. Of a series of putative AN endophenotypes, the present study provides data about three characteristics: association with the illness, independency of the clinical state, and frequency in a sample of unaffected sisters. The traits considered by our study are set-shifting abilities, central coherence, and handedness.

Set-shifting abilities

Our study represents the largest dataset using the WCST in anorexia nervosa (Roberts et al. 2007). Analysing the performance of AN patients on this test, we found a significant impairment both in perseverative and nonperseverative errors. While the first type of errors are indicative of an impairment of set-shifting abilities, the presence of a high rate of both types of errors can be caused by low motivation or an impairment of abstraction, working memory, learning abilities, problem solving, or poor inhibition (Lezak et al. 2004). Both perseverative and nonperseverative errors significantly distinguished healthy sisters of AN patients and controls and did not show differences according to disease status. So, our data indicate that AN patients and their sisters seem to share not only an impairment of set-shifting abilities, but also a more global impairment of executive functions (Laiacona et al. 2000; Lezak et al. 2004). The performance on the TMT confirmed the impairment of flexibility and set-shifting abilities in AN patients and their sisters, but also showed that AN patients were not impaired in their attentive functions, in visual tracking and motor speed (Lezak et al. 2004). The literature provides evidence that set-shifting is a promising cognitive endophenotype for AN. An

Table III. Neuropsychological performance in AN subjects, their healthy siblings and controls.

WCST[3]	Anorexia nervosa Mean (SD) n=28	Healthy sisters Mean (SD) n=28	Controls Mean (SD) n=117	Sisters vs. AN[1] t	Sisters vs. controls[2] F (1, 144)
Global score	48.5 (39.3)	51.1 (34.5)	32.3 (25.5)	–0.36	14.30**
Number of categories[4]	4.9 (1.8)	5.2 (1.1)	5.7 (0.9)	–0.68	–3.52*
Perseverative errors	15.0 (12.2)	16.3 (10.7)	10.5 (8.6)	–0.42	4.85*
Non perseverative errors	16.2 (14.6)	14.9 (11.1)	9.7 (8.1)	0.24	10.48**
Perseverative responses	16.8 (14.8)	18.2 (12.7)	11.7 (10.5)	–0.53	15.90**
TMT	n=28	n=28	n=12		F(1, 147)
Trail Making Test A	31.1 (12.9)	30.5 (9.6)	028.0 (8.1)	0.24	0.75
Trail Making Test B	71.3 (28.2)	63.5 (15.8)	55.4 (14.6)	1.56	4.10*
ROFT	n=28	n=28	n=118		F(1, 145)
Copy accuracy	29.8 (3.0)	29.7 (3.9)	30.9 (3.1)	0.16	1.27
Copy order index	1.73 (0.66)	2.19 (0.61)	2.26 (0.70)	–3.71**	0.32
Copy style index	1.13 (0.51)	1.27 (0.37)	1.41 (0.36)	–1.21	0.50
Central coherence index	1.09 (0.43)	1.30 (0.34)	1.38 (0.35)	–2.40*	0.03
Rey Figure recall	17.8 (5.4)	18.7 (4.6)	20.6 (5.0)	–1.02	1.37
	n=17	n=19	n=114		F(1, 132)
Overlapping Figures Test	35.5 (7.4)	33.5 (8.2)	39.2 (6.4)	0.68	5.41*
	n=11	n=13	n=84		F(1, 96)
Block design unsegm.	35.3 (8.9)	30.8 (8.0)	40.5 (6.1)	2.03	13.13**
Block design segm.	47.3 (5.2)	45.1 (7.0)	48.4 (3.4)	–0.05	12.97**
Benefit from segm.	12.0 (8.4)	14.3 (11.2)	8.0 (7.0)	–1.86	0.71
Object assembly	27.4 (5.8)	26.0 (6.4)	32.7 (4.3)	0.79	13.26**

[1]t-test for dependent samples.
[2]An analysis of variance was used. Educational level was included as a covariate when adjusted scores were not available (see Methods).
[3]Data about WCST were analysed after logarithmic transformation.
[4]Ordinal variable (Mann–Whitney U-test and Wilcoxon test for paired samples).
*P<0.05; **P<0.005.

impairment of set-shifting abilities seems to be heritable (Anokhin et al. 2003; Friedman et al. 2006), to be consistently associated with AN (Tchanturia et al. 2005; Roberts et al. 2007), to be still present after weight recovery (Green et al. 1996; Kingston et al. 1996; Steinlass et al. 2006) and in long-term recovered subjects (Tchanturia et al. 2004), and more frequent in healthy siblings of AN patients than in healthy controls (Holliday et al. 2005). Our study confirmed that poor set-shifting abilities and inflexibility have the characteristics required for being considered among the putative endophenotypes of AN. However, our data also suggest that a wider impairment of executive functioning seems to be present in both AN patients and their healthy sisters, and to be independent of disease status.

Central coherence

There is less literature regarding central coherence as a possible endophenotype for AN. In a recent review, Lopez et al. (2008b) confirmed the presence of a weak central coherence in AN patients. However, they also concluded that studies are consistent in finding an impairment in global processing associated with eating disorders, but there is still little evidence about the presence of superior local processing in these patients (Lopez et al. 2008b). A weakness in central coherence is postulated to reflect an impairment of those functions that are normally responsible for integrating individual pieces of perceptual information to ascertain a global meaning (Frith 1989). Abilities in perception, visuo-spatial organization, abstraction, perceptual flexibility, planning and integration are all involved, in different measures, in the performance of the tests that we used in our study. However, as previously described (Lopez et al. 2008c), the performance on some of these tasks seems to benefit more from global processing (ROFT, Object Assembly, Overlapping Figures) while others benefit more from local processing (Segmented/Unsegmented Block Design). In our study, the performance of AN patients on all the tests investigating central coherence provided support for the presence of weak central coherence in AN, similarly to what has been found in subjects with autism spectrum disorders (Losh et al. 2009). However, AN patients did not report any difference in the benefit

from segmentation on the Block Design test in comparison to control subjects. So, they seem to differentiate from patients with autism spectrum disorders, because their performance is indicative of poor global processing, but not of superior local processing. In addition, while in autism spectrum disorder both social sensitivity and central coherence are impaired (Frith 1989; Soderstrom et al. 2002), in AN patients we found a significant correlation between a weak central coherence and high reward dependence. To our knowledge, this is the first study exploring the relationship between temperament and cognitive functioning in AN. The correlation between these two variables might be due to the fact that some of the brain regions involved in social cognition (orbitofrontal cortex and temporal lobes) are the same involved in central coherence and visuo-spatial abilities. However, while in autism spectrum disorders there is a severe impairment of both central coherence and social functioning (Frith, 1989), in our AN sample an impairment of central coherence seemed to be associated with high sentimentality and dependence. A further exploration of this point in future studies is important, because some authors have found an impairment of social cognition in acute AN (Oldershaw et al. 2009) and severe AN is often associated with social isolation.

Confirming previous studies (Lopez et al. 2008c), a weak central coherence is present in AN patients independently of disease status. Our study is, on the contrary, the first to explore central coherence in healthy sisters of AN patients. Sisters seemed to share with AN patients the presence of weak central coherence and in particular the presence of poor global processing, as shown by performance on the Object Assembly, Block Design and Overlapping Figure tests. The only exception was the performance on the ROFT, that seemed to significantly differentiate AN patients and their sisters as regards the central coherence index and the style used to copy the complex figure. We are uncertain as to why this difference emerged only on the ROFT and not on the other tests. Compared to the other tests, ROFT seems to involve more abstraction abilities (Lezak et al. 2004); in particular, it requires more integration of strategic organizational processes, spatial skills, and nonverbal memory for successful performance. This kind of nonverbal memory might to be more susceptible than other spatial processing tasks (such as Object Assembly, Block Design and Overlapping Figures Test) to executive impairment because of its more abstract nature and greater reliance on organizational capacity. However, the complexity of these tasks makes it difficult to formulate reliable hypotheses about the component of the performance which can explain this difference. When a trait is associated with the illness, independent from the disease status, but not shared with first degree relatives, the possible hypotheses are: (1) the trait is a consequence of the illness (scar hypothesis); (2) the trait is linked to individual environmental risk factors; or (3) the trait is linked to non-shared genetic factors. Although the independence of the central coherence index from disease status makes the first hypothesis improbable, our data did not allow us to choose one of these hypotheses to explain our findings. In any case, this finding is the only that contradicts the hypothesis that weak central coherence represents a good candidate as a putative endophenotype of AN. For this reason, this finding suggests the need for replication in other samples of first degree relatives.

Handedness

Our study is the first, to our knowledge, to explore the characteristics of hand lateralization in AN. Hand preference is believed to be determined in part by genetic factors, that account for about 25% of variance (Medland et al. 2009) and in part by prenatal or very early environmental factors (Ramadhani et al. 2006; Vuoksimaa et al. 2009). Most studies report a higher prevalence of left-handedness in males (rates around 9–10%) than in females (6–8%) (Vuoksimaa et al. 2009). The rate of left-handedness in our sample of AN subjects is significantly higher than the rate of healthy controls and seems higher than the rates reported in female healthy subjects described in other studies (Vuoksimaa et al. 2009). If replicated in larger samples, our finding might have important implications for the understanding of the pathogenesis of AN. It would confirm a neurodevelopmental hypothesis for AN (Connan et al. 2003; Favaro et al. 2006; Strober et al., 2007). An alteration of neurodevelopmental trajectories could be the cause for both the higher frequency of left-handedness and an abnormal development or lateralization of brain functions that could be involved in the development of the illness (Smeets and Kosslyn 2001; Uher et al. 2005). In the literature, there seems to be a tendency for right-handers to perform better than left-handers on visuospatial tasks (Lezak et al. 2004). This is in line with the hypothesis of a dysfunction in lateralized somatosensory functions that are implicated in the visual representation of body image (Smeets and Kosslyn 2001; Grunwald et al. 2001). In a nonclinical sample, Christman et al. (2006) found that strong degrees of handedness, but not type of handedness, are associated with deficits in accurate representation of body image. According to these two hypotheses, we would expect a greater impairment on visuo-spatial tasks (Rey–Osterreth Figure Test, Overlapping Figures Test, Object Assembly, Block Design) according to

type or degree of handedness in anorexia nervosa and control subjects. However, we found no correlation between these tasks and handedness. Studies about brain lesions found that lesions of the left hemisphere (parietal and temporal areas) are associated to deficits in the detail processing, whereas right lesions are associated to an impairment in the global visuo-spatial processing (Lezak et al. 2004). It is possible that abnormal lateralization of brain functions in AN patients is at the origin of both the observed excess of left-handers and weak central coherence.

The excess of left-handers in unaffected sisters of AN patients confirmed that there may be some overlap between the genetic factors that increase the risk for developing AN and those that influence hand lateralization. This means that left-handedness could be included among the putative endophenotypes of AN.

Strengths and limitations

The present study has several strengths, as well as important limitations that should be taken into consideration. It is the first study, to our knowledge, to provide data about handedness in a sample of subjects with lifetime AN and one of the few to explore executive functioning in a large sample of AN patients and in a sample of healthy sisters of AN cases. However, some caution is required and replication in other samples is needed because AN subjects referred for outpatient treatment cannot be considered to be completely representative of all cases existing in the general population and the sample of healthy sisters was not large. In this study, we did not assess psychiatric comorbidity using a Structured Diagnostic Interview. For this reason, we cannot be conclusive about whether our findings are specific to AN or are due to the presence of a comorbid disorder, such as depression (Austin et al. 2001) or obsessive-compulsive disorder (Savage et al. 1999; Henry 2006). However, the lack of significant correlations between obsessive-compulsive and depression symptoms, as measured by the Hopkins Symptoms Checklist, and cognitive performance made this hypothesis unlikely. We found, on the contrary, that state anxiety correlated with the performance of Trail Making Test A, Object Assembly, and Overlapping Figures Test. It is well known that anxiety symptoms can impair cognitive functioning, because of an impaired efficiency of attentional control (Eysenck et al. 2007). The inclusion of anxiety scores among the covariates of analysis of variance did not change any of the findings of the present study.

Although all sisters were assessed after the mean age of onset for anorexia nervosa (Favaro et al. 2009), we cannot rule out that some sisters might develop an eating disorder after our assessment. In addition, given the relative low frequency of left-handers, our study did not have the power to analyse the relationship between handedness and cognitive functioning reliably.

Conclusions

In conclusion, the present study lends support to the hypothesis that impaired set-shifting and low central coherence might be considered good candidate as endophenotypes of AN. Moreover, it explored and provided the first evidence concerning the possibility that handedness could be included among the putative endophenotypes of this illness. Our findings need to be replicated in other samples and the nature of the cognitive impairment measured by the single tasks to be clarified. These findings not only have important implications for future studies addressing the etiopathogenesis of AN, but also could have some clinical utility. Poor abstract thought, visuo-spatial impairment and relative difficulty in integrative processing may not only represent important predisposing and/or maintenance factors to AN, but they may also interfere with treatment course and outcome of illness. In particular, a reduced ability in problem solving, and poor conceptual thinking may explain in part the low consciousness of illness, the neglect of long-term secondary health problems and the lack of full engagement in therapeutic work.

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Statement of interest

None.

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