Psychological Medicine (2011), **41**, 839–848. © Cambridge University Press 2010
doi:10.1017/S0033291710001303

ORIGINAL ARTICLE

Neurocognitive functioning in bulimia nervosa: the role of neuroendocrine, personality and clinical aspects

S. Galderisi[1]*, P. Bucci[1], A. Mucci[1], L. Bellodi[2], G. B. Cassano[3], P. Santonastaso[4], S. Erzegovesi[2], A. Favaro[4], M. Mauri[3], P. Monteleone[1] and M. Maj[1]

[1] *Department of Psychiatry, University of Naples SUN, Italy*
[2] *Department of Neuropsychiatric Sciences, Vita-Salute University, Istituto Scientifico HS Raffaele, Milan, Italy*
[3] *Department of Psychiatry, Neurobiology, Pharmacology, and Biotechnology, University of Pisa, Italy*
[4] *Department of Neurosciences, University of Padua, Italy*

Background. Studies investigating neurocognitive impairment in subjects with eating disorders (EDs) have reported heterogeneous patterns of impairment and, in some instances, no dysfunction. The present study aimed to define the pattern of neurocognitive impairment in a large sample of bulimia nervosa (BN) patients and to demonstrate that neuroendocrine, personality and clinical characteristics influence neurocognitive performance in BN.

Method. Attention/immediate memory, set shifting, perseveration, conditional and implicit learning were evaluated in 83 untreated female patients with BN and 77 healthy controls (HC). Cortisol and 17β-estradiol plasma levels were assessed. Cloninger's Temperament and Character Inventory – Revised (TCI-R), the Bulimic Investigation Test Edinburgh (BITE) and the Montgomery–Asberg Depression Rating Scale (MADRS) were administered.

Results. No impairment of cognitive performance was found in subjects with BN compared with HC. Cortisol and 'Self-directedness' were associated with better performance on conditional learning whereas 17β-estradiol had a negative influence on this domain; 'Reward dependence' was associated with worse performance on implicit learning; and depressive symptomatology influenced performance on the Wisconsin Card Sorting Test (WCST) negatively.

Conclusions. No cognitive impairment was found in untreated patients with BN. Neuroendocrine, personality and clinical variables do influence neurocognitive functioning and might explain discrepancies in literature findings.

Received 17 June 2009; Revised 15 May 2010; Accepted 20 May 2010; First published online 1 July 2010

Key words: Co-morbidity, cognitive functions, eating disorders, neuroendocrine indices, reward dependence.

Introduction

Cognitive impairment in patients with eating disorders (EDs) has been reported by the majority of studies addressing this issue. However, heterogeneous patterns of cognitive dysfunctions have been found and, in a minority of studies, no dysfunction was observed [see Zakzanis *et al*. (2010) for a meta-analysis and Appendix 1 (available online) for a detailed description of literature data]. The heterogeneity of findings might be due to the use of different neuropsychological tests, exploring different subdomains of complex cognitive functions. This is particularly true for memory and executive functions, the two most investigated cognitive domains in the literature on EDs.

Studies investigating memory dysfunction in EDs have reported either no impairment or deficits in different memory subdomains, such as short-term verbal or visuospatial memory, secondary verbal and/or visuospatial memory and verbal learning (see Appendix 1). In particular, of eight studies exploring memory in patients with bulimia nervosa (BN), three found no impairment, one found impaired short-term and working memory only in subjects with co-morbidity, and four investigated verbal memory and reported impaired learning, secondary memory or short-term memory (see Appendix 1); three out of these four also included a test for secondary visuospatial memory, but only two reported a deficit in this subdomain. None of the studies carried out in BN patients explored recognition *versus* free recall to rule out the possibility that the observed memory impairment is due to an executive dysfunction, that is a deficit in the ability to initiate a suitable strategy for successful recall.

* Address for correspondence: Professor S. Galderisi, Department of Psychiatry, University of Naples SUN, Largo Madonna delle Grazie, 80138 Naples, Italy.
(Email: sgalderi@tin.it)

Findings relevant to executive functions in EDs were also heterogeneous, showing an impaired set shifting, deficits of problem solving or working memory, and also no impairment of the same subdomains (see Appendix 1). Set shifting was most often explored by means of the Wisconsin Card Sorting Test (WCST) and the Trail Making Test Part B (TMT-B). An impairment on these tests might result from visuospatial deficit, a factor not always controlled for. Furthermore, the TMT-B index (time to complete the test) can be affected by slowness on test execution. In patients with BN impaired processing speed has been reported (Ferraro *et al*. 1997; Lauer *et al*. 1999), which makes it difficult to rule out the possibility that the impaired set shifting reported by all studies using TMT-B, but not by those using the WCST (Appendix 1), is simply due to slowness. Apart from the confounding role of visuospatial deficits and psychomotor speed, it is also worth noting that different mechanisms may underlie the impairment of set shifting. Indeed, perseveration may be due to either a deficit in the ability to shift from a previously attended perceptual category to a new one (i.e. attentional set shifting deficit due to perseveration), as observed in patients with frontal lobe lesions, or an inability to focus on the new stimulus dimension because it was previously learned as irrelevant (deficit in inhibiting a reinforced action), as observed in patients with Parkinson's disease (Owen *et al*. 1993). Investigations aimed to disentangle these mechanisms were not carried out in patients with BN.

Other methodological factors may account for discrepancies in neuropsychological findings in EDs: (1) small sample sizes; (2) insufficient clinical characterization of experimental samples; (3) use of different control groups (healthy subjects, patients with other psychiatric diagnosis, or normative data); and (4) lack of control for confounding variables, such as education, general cognitive abilities, drug status and starvation, in addition to the presence of depressive, anxious or obsessive–compulsive symptomatology, which might have an impact on task performance, especially when speed and accuracy are not evaluated separately. In addition, personality traits, such as perfectionism and harm avoidance, are often reported in these patients (Halmi *et al*. 2000; Fassino *et al*. 2004) and might influence neuropsychological performance (Strupp *et al*. 1986; Tchanturia *et al*. 2002), and are not generally controlled for. Moreover, other than malnutrition with metabolic imbalance and structural brain abnormalities, it has been hypothesized that neuroendocrine dysfunctions may influence cognitive deficits observed in patients with EDs. It is well known that cognitive functions are influenced by steroid hormones (Squire, 1992; Lupien *et al*. 1994, 1998; van Niekerk *et al*. 2001; Blair *et al*. 2005; Alhaj *et al*. 2006; Li *et al*. 2006), and indeed steroid abnormalities have been reported in subjects with EDs (Zumoff *et al*. 1983; Winterer *et al*. 1985; Hotta *et al*. 1986; Fichter *et al*. 1990; Monteleone *et al*. 2001, 2006; Klein *et al*. 2007). Studies investigating the influence of steroid hormones on neurocognitive performance in patients with ED have reported conflicting results (Laessle *et al*. 1992; Seed *et al*. 2000; Galderisi *et al*. 2003), probably because of the diagnostic heterogeneity of experimental samples among different studies (patients with BN or with anorexia nervosa, AN).

The present study aimed to define the pattern of neurocognitive impairment in a large group of untreated patients with BN, by tapping several domains of cognition previously investigated in these patients with conflicting results. To disentangle the relative contribution of the verbal *versus* the visuospatial domain and of processing speed *versus* accuracy, we chose a comprehensive neuropsychological battery, in which each test has subtests for visuospatial and verbal materials, matched for task difficulties and providing separate indices for speed and accuracy. The battery assesses (*a*) attention/immediate memory (Block Span and Digit Span), (*b*) implicit learning of supraspan sequences [learning tests independent of executive functions; the Corsi Block Tapping Task (CBTT) and Hebb's Digit Recurring Sequences (HDRS)], (*c*) conditional learning, a form of learning dependent on executive functions, assessing the ability to learn, by using an external reinforcing feedback, correct associations between pairs of stimuli [the Spatial (SCAL) and Non-Spatial Conditional Associative Learning Tasks (NSCAL)], and (*d*) perseveration independent of inhibition of a previously reinforced action [the Self-Ordered Pointing Tasks for Words (SOPT-W) and for Drawings (SOPT-D)].

The WCST was included to assess set shifting, independently of speed, and it was therefore preferred to the TMT-B. It involves the ability to focus on a new stimulus category previously learned as irrelevant, by inhibiting a previously reinforced action. The Wechsler Adult Intelligence Scale – Revised (WAIS-R) was used to assess cognitive general abilities.

The study was also designed to demonstrate that neuroendocrine, personality and clinical characteristics influence neurocognitive performance in BN.

Method

Subjects

Patients were recruited among those attending the out-patient and in-patient units of the Eating Disorder Centers of the University Psychiatric Departments of Naples, Milan, Padua and Pisa. Before entering the

https://doi.org/10.1017/S0033291710001303 Published online by Cambridge University Press

study, patients participated in a 1-h clinical interview to verify their conformity to the following inclusion criteria: (*a*) DSM-IV diagnosis of BN, confirmed by the Structured Clinical Interview for DSM-IV (SCID-I; First *et al*. 2002); (*b*) female sex; (*c*) age >16 years; (*d*) informed consent to participate in all the experimental procedures; (*e*) absence of drug treatment for ⩾4 weeks (6 weeks in the case of fluoxetine treatment); and (*f*) absence of both cerebral or somatic diseases not related to the aberrant eating pattern.

Healthy controls (HC), matched with patients for age (±3 years), were selected on the basis of the above criteria from (*b*) to (*e*) plus the absence of both previous or current physical and mental disorders, as assessed by means of the Mini-International Neuropsychiatric Interview (MINI; Sheehan *et al*. 1994) and physical examination.

Psychopathological evaluation

Patients' psychopathological state was evaluated by using the following instruments: the Bulimic Investigation Test Edinburgh (BITE; Henderson & Freeman, 1987) to assess eating-related psychopathology, and the MADRS (Montgomery & Asberg, 1979) to evaluate depressive symptoms.

The presence of co-morbidity for other psychiatric disorders was assessed by using SCID-I. For all these instruments, the inter-rater reliability was formally evaluated: the κ value for the principal diagnosis of SCID-I was 0.89, whereas for co-morbid diagnoses it was between 0.86 and 0.89; the κ value for the MADRS total score was 0.88. The inter-rater reliability was not evaluated for the BITE, which is a self-rating scale.

Personality characteristics were assessed by means of Cloninger's Temperament and Character Inventory – Revised (TCI-R; Cloninger, 1999). Height and body weight were measured and the body mass index (BMI) was calculated for each subject.

Neuropsychological assessment

Each test included in the battery provides separate indices for accuracy and speed of execution and includes a verbal and a non-verbal version matched for task requirements, thus enabling an accurate evaluation of both verbal and visuospatial abilities. The only exception is the WCST, widely used to investigate set shifting, which was added mainly for comparison with previous literature findings. Finally, cognitive general abilities were assessed so as to control for their influence on neuropsychological performance.

The following neurocognitive domains were assessed: (*a*) attention/immediate memory, (*b*) implicit learning, (*c*) conditional learning, (*d*) perseveration, (*e*) set shifting and (*f*) cognitive general abilities.

Attention/immediate memory was assessed by the Block Span and the Digit Span. Implicit learning was evaluated by the CBTT and the HDRS, which assess the ability to learn a supraspan spatial or non-spatial sequence that, unknown to the subject, recurs every third sequence, and whose memory trace is expected to be reinforced more than those of the non-recurring sequences (Milner, 1978).

Conditional learning, dependent on executive control, was assessed by the SCAL and the NSCAL, which evaluate the ability to learn, by trial and error, the correct association between pairs of stimuli (Petrides, 1985).

Perseveration was evaluated by the SOPT-W and SOPT-D, which explore the ability to initiate, organize and monitor a sequence of self-generated responses, and to carry them out while constantly monitoring their execution (Petrides & Milner, 1982); no external feedback is provided to subjects during task execution, thus preventing establishing reinforced associations and learned irrelevance, so that perseveration on this test is independent of inhibition of previously reinforced associations. All set sizes included in the SOPT (6, 8, 10 and 12 items) were administered and both time and speed indices were calculated as an average across them.

Set shifting was assessed by the WCST. This complex test explores categorization abilities, the presence of perseveration and the ability to maintain the cognitive set, and also set shifting. As a measure of set shifting, it entails the ability to focus on a new stimulus category previously learned as irrelevant, by inhibiting a previously reinforced action.

Cognitive general abilities were evaluated by the WAIS-R, which estimates the Full Scale, Performance and Verbal Intelligence Quotient (FSIQ, PIQ and VIQ). For further details on the test procedures see Galderisi *et al*. (1995, 1999).

To reduce the number of statistical comparisons, we selected two outcome measures for each test. For the WCST, we chose the number of perseverative errors, which is the most commonly used measure and therefore meets our need of comparison with previous literature findings, and the number of correct responses, which was preferred as an accuracy index to the number of categories as it is a continuous measure. For all the other tests two summary indices were chosen, one for speed of execution and one for accuracy, as they were deemed more robust than partial measures (for the SOPT, for instance, the average accuracy was used instead of the accuracy for each set size). The summary indices included: for SOPT-W and SOPT-D, the total mean time to complete the test

and the average number of repeated items; for SCAL and NSCAL, the mean time per trial and the total number of errors; for CBTT and HDRS, the mean time ratio (mean time on recurring sequences/mean time on non-recurring sequences) and the accuracy ratio (ratio between the percentage of correct recurring and non-recurring sequences).

All tests except the WCST and the WAIS-R were administered in a single session lasting 2 h and in the same order (SCAL, NSCAL, SOPT-D, SOPT-W, CBTT, HDRS). The WAIS-R and the WCST were administered in a separate session, starting with the WAIS-R for all subjects. In each centre, all tests were administered by the same examiner, who had received an *ad-hoc* training organized by the coordinating center.

Biochemical analyses

Cortisol and 17β-estradiol plasma levels were assessed according to the following procedure: after an overnight fast, each subject underwent a blood sample collection between 0800 and 0900 hours, when a butterfly needle was inserted into a forearm vein and kept patent by a saline infusion; after 30 min resting, blood was collected in tubes with lithium heparin as anticoagulant; plasma was separated and stored at –20 °C. Menstruating women underwent blood sample collection in the follicular phase of their menstrual cycle (day 5–8 from menses). Plasma cortisol concentrations were determined by a double-antibody radioimmunoassay (RIA) method, using a commercially available kit (Biochem Immunosystems, Milan, Italy); intra- and interassay coefficients of variation (CVs) were $<5\%$ and $<8\%$ respectively. Plasma 17β-estradiol levels were determined by an immunometric method (MAIA clone), using a commercially available kit (Biochem Immunosystems); intra- and interassay CVs were 4.3% and 3.2%, respectively.

Data analysis

To meet the criteria of normality and homogeneity of variance, the speed indices of neuropsychological tests and also the total number of errors on SCAL and NSCAL and plasma levels of 17β-estradiol were log transformed. Outliers (subjects whose scores exceeded the 75th or the 25th percentile by 1.5 times the interquartile range) were excluded from the analysis (Rothamsted *et al*. 1994).

For each neuropsychological index, *z* scores were calculated from the mean value of the HC group. A sign inversion was applied to those neuropsychological indices for which a lower number indicates a worse performance (e.g. the number of correct responses at WCST) so as to homologate for all indices the direction indicating impairment (the higher the index, the greater the impairment).

For all the variables considered, missing data were substituted with the mean value of the group.

Independent one-way analyses of variance (ANOVAs) were used to test for group differences on demographic variables, WAIS-R Full Scale IQ, BMI and neuroendocrine indices. In the case of group differences on these indices, group comparisons on neuropsychological variables were performed by entering them as covariates. To test for group differences on neuropsychological performance, separate multivariate ANOVAs (MANOVAs) were run for accuracy and speed indices using multivariate and repeated-measure designs. Tukey's Honestly Significantly Different (HSD) procedure was used for *post-hoc* comparisons only when a significant main effect or interaction had been found in the multivariate analyses. The statistical power was 0.94 and 0.87 for the MANOVA on accuracy and speed indices respectively, for the interaction between the group factor (with two levels) and the neuropsychological domains factor (with eight and six levels for accuracy and speed indices respectively), considering a mean difference of $\frac{1}{4}$ S.D. between the two groups. All group comparisons were also carried out after the exclusion of patients with co-morbidity for depressive disorders to control for the influence of a significant burden of depression on the results. To check for site differences, this variable was added as a categorical predictor in all group comparisons. To clarify the simultaneous effect of several confounding variables on patients' neuropsychological performance, multiple regression analyses were carried out, in which neuropsychological variables were entered as dependent variables, and independent variables included education, BITE total score, duration of illness, MADRS total score, previous history of AN, neuroendocrine indices (cortisol and 17β-estradiol), and TCI-R dimensions (Novelty seeking, Harm avoidance, Reward dependence, Persistence, Self-directedness, Cooperativeness, Self-transcendence).

Correlation analyses were carried out by means of Pearson's test.

Results

A total of 83 female patients with BN and 77 HC were included in the study. No difference was observed between the two groups on BMI, IQ and demographic variables, with the exception of education, which was significantly lower in the patient group (Table 1). Seventeen BN patients showed co-morbidity for current depressive disorder (11 major depressive

https://doi.org/10.1017/S0033291710001303 Published online by Cambridge University Press

Table 1. *Demographic characteristics, intellectual quotient (IQ) and body mass index (BMI) of the experimental sample*

	Patients with BN ($n=83$)	HC ($n=77$)
Age (years)	24.0 ± 4.3	23.8 ± 3.4
Education (years)	12.6 ± 2.4*	14.8 ± 2.5
WAIS-R Verbal IQ	100.6 ± 18.0	107.8 ± 12.7
WAIS-R Performance IQ	98.1 ± 15.4	103.4 ± 11.9
WAIS-R Full-scale IQ	100.2 ± 17.4	106.7 ± 11.8
BMI	21.5 ± 3.7	21.5 ± 2.6

BN, Bulimia nervosa; HC, healthy controls; WAIS-R, Wechsler Adult Intelligence Scale – Revised.

*Significant difference between the two groups: $p<0.00005$.

disorder, single episode, four major depressive disorder, recurrent, two dysthymic disorder), with a mean total score of 22.8 (S.D. = 11.2) on the MADRS. Twenty-two BN patients had a previous history of AN, remitted for at least 1 year for all of them. These patients did not differ from those without previous history of AN for any neuroendocrine or neuropsychological variable, with the exception of the speed index of the HDRS, which was higher in the latter group. Five patients were amenorrheic, and 18 were oligomenorrheic. None of the subjects included in the study were using hormonal contraceptives.

A significant main effect of site was observed for both neuroendocrine and neuropsychological indices; however, the interaction with diagnosis was not statistically significant. Group comparison on neuroendocrine indices showed significantly higher values of cortisol plasma levels in patients with BN than in HC [mean ± S.D. = 162.7 ± 50.4 and 142.3 ± 45.5 respectively, $F(1,158)=7.20$, $p=0.008$], but no significant group difference on plasma levels of 17β-estradiol was found. Similar results were found when comparing BN patients with HC after the exclusion of patients with co-morbidity for depressive disorder [mean ± S.D. = 164.9 ± 52.6 and 142.3 ± 45.5 respectively, $F(1,141)=7.58$, $p=0.007$ for group comparison on cortisol plasma levels]. In the light of these results, all comparisons between patients and controls were carried out using education and cortisol plasma levels as covariates.

In the whole experimental sample, no significant group difference was found for neurocognitive test accuracy indices. Raw data and the effect size for these variables are shown in Table 2*a*. After excluding patients with co-morbidity for depressive disorders, the MANCOVA for the accuracy indices showed a significant main effect of diagnosis [Hotelling $T^2=0.15$, $F(10,130)=2.01$, $p=0.04$] and a significant diagnosis × neuropsychological index interaction [Hotelling $T^2=0.15$, $F(9,131)=2.13$, $p=0.03$]. Follow-up ANOVAs showed that the effect of diagnosis was due to better performance on the accuracy indices of CBTT and SCAL in BN patients compared to HC ($p=0.04$ and $p=0.02$ respectively).

In the whole experimental sample, the MANCOVA for the speed indices also showed a significant main effect of diagnosis [Hotelling $T^2=0.09$, $F(6,151)=2.32$, $p=0.04$] and a significant diagnosis × neuropsychological index interaction [Hotelling $T^2=0.09$, $F(5,152)=2.67$, $p=0.02$]. *Post-hoc* analyses revealed that the interaction was due to a faster performance on the CBTT in patients with BN compared to HC ($p=0.02$). A significant main effect of the covariate cortisol was also observed [Hotelling $T^2=0.10$, $F(6,151)=2.42$, $p=0.03$], revealing an association between this index and the neuropsychological performance. We explored this association by means of correlation analyses, which showed a weak negative association between cortisol plasma levels and mean time on the SCAL ($r=-0.17$, $p=0.03$) and the NSCAL ($r=-0.18$, $p=0.02$), indicating that the higher the cortisol plasma levels, the faster the performance on tests exploring conditional learning. Raw data and effect size for neuropsychological speed indices are shown in Table 2*b*. After excluding patients with co-morbidity for depressive disorders, no significant group difference was found for the speed indices.

The results of multiple regression analyses are reported in Table 3. The MADRS total score was associated with the number of perseverative errors on the WCST (the worse the depressive symptomatology, the poorer the performance on the WCST). The dimension 'Reward dependence' of the TCI-R was associated with the accuracy index of the HDRS (the higher the score on 'Reward dependence', the worse the performance on the verbal subtest exploring implicit learning). The dimension 'Self-directedness' of the TCI-R was associated negatively with the speed index of the NSCAL (the lower the score on this dimension, the slower the performance on the NSCAL). The 17β-estradiol was associated with both the accuracy and speed indices of the NSCAL (the higher the plasma levels of this neuroendocrine index, the less accurate and the slower the NSCAL performance). The BITE total score was associated negatively with the accuracy index of the NSCAL (the higher the bulimic symptomatology, the better the performance of the non-spatial subtest exploring conditional learning). The duration of illness was associated negatively with the accuracy indices of the CBTT and the SOPT-W (the longer the duration of illness, the better the performance on the two tests).

https://doi.org/10.1017/S0033291710001303 Published online by Cambridge University Press

Table 2. *Raw data for the neuropsychological indices of (a) accuracy and (b) speed*

	Patients with BN (mean ± S.D.)	HC (mean ± S.D.)	Effect size[a]
(*a*) Neuropsychological indices of accuracy			
Block Span	5.5 ± 0.8	5.8 ± 0.7	−0.40
Digit Span	5.8 ± 0.7	5.8 ± 0.8	–
CBTT Accuracy ratio	1.4 ± 0.9	1.2 ± 0.8	0.23
HDRS Accuracy ratio	1.2 ± 0.6	1.1 ± 0.6	0.17
NSCAL Total errors	29.7 ± 22.6	22.8 ± 14.4	−0.36
SCAL Total errors	50.3 ± 30.0	61.6 ± 35.4	0.34
SOPT-D Repetitions	1.0 ± 0.5	0.9 ± 0.4	−0.22
SOPT-W Correct responses	0.7 ± 0.4	0.5 ± 0.4	−0.50
WCST Correct responses	50.0 ± 7.4	49.9 ± 7.0	0.01
WCST Perseverative errors	7.7 ± 4.0	6.7 ± 3.1	−0.28
(*b*) Neuropsychological indices of speed			
CBTT Mean time ratio[b]	0.9 ± 0.1	1.0 ± 0.04	1.30
HDRS Mean time ratio[b]	0.9 ± 0.1	1.0 ± 0.1	1.0
NSCAL Mean time	26.5 ± 18.4	23.0 ± 13.8	−0.21
SCAL Mean time	26.4 ± 14.6	25.3 ± 13.9	−0.08
SOPT-D Mean time	4.4 ± 0.2	4.5 ± 0.3	0.40
SOPT-W Mean time	4.3 ± 0.3	4.4 ± 0.3	0.33

BN, Bulimia nervosa; HC, healthy controls; S.D., standard deviation; CBTT, Corsi's Block Tapping Task; HDRS, Hebb's Digit Recurring Sequences; NSCAL, Non-Spatial Conditional Associative Learning Task; SCAL, Spatial Conditional Associative Learning Task; SOPT-D, Self-Ordered Pointing Tasks for Drawing; SOPT-W, Self-Ordered Pointing Tasks for Words; WCST, Wisconsin Card Sorting Test.

[a] A negative sign indicates a worse performance in BN *v.* HC.

[b] Mean time ratio = mean time on recurring sequences/mean time on non-recurring sequences.

Discussion

According to our findings, patients with BN have no impairment in the domains of attention/immediate memory, implicit learning and different aspects of executive functions, including conditional associative learning, set shifting and perseveration independent of 'learned irrelevance' and inhibition of previously reinforced associations. In particular, group comparison on accuracy indices in the whole experimental sample did not reveal any significant group difference. After excluding patients with co-morbidity for depressive disorders, neurocognitive performance was even better in patients with BN than in HC on the CBTT and SCAL, two tests exploring non-verbal implicit and conditional learning respectively. This suggests a negative influence of depression on these two tests. With regard to the speed indices, the only group difference in the whole experimental sample was a faster performance in patients with BN than in HC on the CBTT, the test exploring non-verbal implicit learning, whereas no difference was observed after excluding patients with co-morbidity for depressive disorders. This might be explained by the smaller size of the sample when excluding patients with depression; however, even though slowness has been widely reported in depression, in a study investigating reaction time in depressed patients and healthy controls during the execution of tasks requiring either effortful information processing or automatic information processing (Hammar, 2003), patients were slower only on tasks requiring effortful information processing.

In a previous study by our group (Galderisi *et al.* 2003), ED patients were slower than controls on implicit learning and more accurate on a spatial executive task, showing a cognitive pattern similar to that observed under conditions of heightened arousal, which impairs implicit learning and enhances effortful processing. The discrepancy between this cognitive profile and that observed in the present study might be due to the difference in the characteristics of the experimental samples (in the previous study patients with AN were included) and to the failure to take into

https://doi.org/10.1017/S0033291710001303 Published online by Cambridge University Press

Table 3. *Results of multiple regression analyses on neuropsychological indices*

	WCST Perseverative errors		HDRS Accuracy ratio		CBTT Accuracy ratio		NSCAL Total errors		NSCAL Mean time		SOPT-W Repetitions	
	$F(1, 65)$	MR	$F(1, 65)$	MR	$F(1, 65)$	MR	$F(1, 65)$	MR	$F(1, 65)$	MR	$F(1, 65)$	MR
History of AN	0.002		0.35		0.03		1.57		0.61		0.27	
Education	0.01		0.18		0.20		1.01		1.36		0.005	
Duration of illness	0.93		0.35		5.08	0.07*−	0.58		0.24		4.95	0.07*−
BITE Total score	0.57		0.17		1.24		7.15	0.10**−	1.99		0.54	
MADRS Total score	5.79	0.08*+	2.11		0.19		2.43		0.36		0.87	
Cortisol	0.65		0.38		0.39		0.0001		0.01		2.25	
Log 17β-estradiol	1.12		0.14		1.30		7.83	0.20**+	6.80	0.09**+	0.55	
Novelty seeking	2.98		0.002		0.12		0.002		0.32		0.03	
Harm avoidance	2.28		0.005		1.94		0.18		2.09		1.20	
Reward dependence	0.39		4.25	0.06*+	0.07		0.83		0.25		0.07	
Self-directedness	1.36		0.29		0.24		1.02		4.04	0.15*−	0.002	
Persistence	3.47		0.34		3.84		1.13		0.07		1.15	
Cooperativeness	3.77		0.08		3.96		0.18		0.002		1.84	
Self-transcendence	0.64		0.75		1.37		0.58		0.93		0.02	

WCST, Wisconsin Card Sorting Test; HDRS, Hebb's Digit Recurring Sequences; CBTT, Corsi's Block Tapping Task; NSCAL, Non-Spatial Conditional Associative Learning Task; SOPT-W, Self-Ordered Pointing Tasks for Words; MR, multiple regression; AN, anorexia nervosa; BITE, Bulimic Investigation Test Edinburgh; MADRS, Montgomery–Asberg Depression Rating Scale.

* $p \leqslant 0.05$, ** $p \leqslant 0.01$; +, positive association; −, negative association.

account confounding variables. In line with our previous findings, no impairment was found in executive functions, including set shifting abilities, whose impairment in EDs has been reported in several studies (Fassino *et al*. 2002; Tchanturia *et al*. 2002, 2004, 2007; Holliday *et al*. 2005; Steinglass *et al*. 2006; Brand & Franke-Sievert, 2007) and has been proposed as a trait marker of AN (Tchanturia *et al*. 2002; Holliday *et al*. 2005). However, in accordance with our findings, no impairment of mental flexibility (explored with WCST) was reported in patients with BN with respect to HC in a recent study (Mobbs *et al*. 2008). Impairment of set shifting might be limited to patients with AN; indeed, among the above-mentioned studies reporting such an impairment, only two included patients with BN (Tchanturia *et al*. 2004; Brand & Franke-Sievert, 2007) and none of them used the WCST.

The absence of cognitive impairment observed in our experimental sample is only partially discrepant with findings reported by the few neuropsychological studies carried out in patients with BN. Jones *et al*. (1991), in a paper investigating several cognitive domains, found a slight impairment of attention and executive functions. Lauer *et al*. (1999) reported, in a group of BN patients during the acute phase of their illness with respect to normative data (no control group), no impairment of memory and an impairment of attention and executive functions that improved after 7 months of treatment. In the paper by Ferraro *et al*. (1997), impairment of attention, executive functions, visuospatial ability and memory was reported in patients with BN with respect to HC, and also a higher variability of the performance on tests exploring attention and executive functions, which suggests that the impairment of some cognitive domains reported in patients with BN might be present in only some of them. Finally, in a study by McKay *et al*. (1986), the only difference observed between BN patients and HC on the Luria–Nebraska Neuropsychological Battery was a slower performance in the group of patients while drawing geometric figures, one of the factors of the Motor scale, whereas the remaining 13 clinical scales were within the normal range. The main causes of the discrepancies between our findings and those reported in the above-mentioned studies include the heterogeneity of tests used to investigate the same neuropsychological domain and the lack of control for confounding variables such as the presence of depressive symptomatology, TCI-R dimensions or neuroendocrine indices in some studies.

With regard to the neuroendocrine indices, in line with previous findings (Monteleone *et al*. 1999, 2001), we found higher plasma levels of cortisol but not of 17β-estradiol in BN patients *versus* HC. Moreover, the MANCOVA for the speed indices in the whole

https://doi.org/10.1017/S0033291710001303 Published online by Cambridge University Press

experimental sample showed a significant main effect of cortisol. Correlation analyses showed that cortisol had a favorable, though weak, effect on the speed of execution of both tests exploring conditional learning, whereas multiple regression analyses showed a negative effect of 17β-estradiol on the accuracy and speed indices of the non-spatial version of the same tests. The finding of a positive effect of cortisol on some neuropsychological indices, also observed in our previous study (Galderisi *et al*. 2003), is in contrast with the hypothesis that stress, through an increase in glucocorticoid levels, induces neurotoxic effects, and with evidence that elevated glucocorticoid levels are associated with memory impairment and hippocampal atrophy (Squire, 1992; Lupien *et al*. 1994, 1998; Sapolsky, 1996; León-Carrión *et al*. 2009). It is our hypothesis that, in patients with EDs, steroid abnormalities, such as the increase in cortisol, might reflect a mild and prolonged stress reaction producing an adaptive facilitation of cognitive processes, instead of a disruptive neurotoxic effect (Galderisi *et al*. 2003). This hypothesis would be in line with the observation that many subjects with EDs, despite malnutrition, metabolic alterations and brain pseudo-atrophy, only present mild cognitive alterations and are often high achievers at school or at work. The finding of a negative association between 17β-estradiol and performance on a test exploring conditional learning falls within the complex picture of the effects of this hormone on cognitive functions. It is possible that estrogens influence only some cognitive domains and that the effects on these domains depend on their plasma levels (according to some studies, an optimal range of estrogens plasma levels may exist for some cognitive domains; Barrett-Connor *et al*. 1999; LeBlanc *et al*. 2001) and/or plasma levels of other hormones, such as progestins, which might attenuate the cognitive effects of estrogens (Duff & Hampson, 2000).

According to our findings, the presence of a previous history of AN has no significant influence on either the neurocognitive profile or the neuroendocrine indices.

Multiple regression analyses in our study showed that not only neuroendocrine indices but also psychopathological and temperamental variables are associated with cognitive functioning. In particular, we observed that depressive symptomatology was associated with a worse performance on the WCST. This finding is in line with other studies reporting an association between depression and poor performance on tests exploring executive functions (Cullen *et al*. 2005; Erberk-Ozen *et al*. 2006; Must *et al*. 2006; Gruber *et al*. 2007). Moreover, the TCI-R dimension 'Reward dependence', which reflects sensitivity to social approval, was associated with a worse performance on the verbal subtest exploring implicit learning. In support of the hypothesis formulated in our previous study (Galderisi *et al*. 2003), this association suggests that, in patients with EDs, personality traits characterized by the tendency to obtain the highest possible standards of behavior and external approval (Halmi *et al*. 2000) might promote a focused style of processing, which enhances executive control and impairs implicit learning (Strupp *et al*. 1986). Finally, the TCI-R dimension 'Self-directedness' was associated negatively with the performance on a test exploring verbal conditional learning, again revealing the importance of personality traits as mediating variables.

Bulimic symptomatology was associated with a better performance on the NSCAL, and duration of illness with a better performance on the CBTT and SOPT-W. These data are in line with the hypothesis that cognitive impairment does not represent a core feature of BN.

In conclusion, according to our findings, patients with BN have no neurocognitive abnormality in the domains of attention/immediate memory, set shifting, perseveration, conditional and implicit learning. An influence of steroid levels, depressive symptomatology and personality traits on neurocognitive performance was found, which underscores the need to control for these variables in studies investigating neurocognitive functioning in patients with EDs.

Note

Supplementary material accompanies this paper on the Journal's website (http://journals.cambridge.org/psm).

Acknowledgments

This work was supported by grant MM06493915 from the Italian Ministry of University and Scientific Research.

Declaration of Interest

None.

References

Alhaj HA, Massey AE, McAllister-Williams RH (2006). Effects of DHEA administration on episodic memory, cortisol and mood in healthy young men: a double-blind, placebo-controlled study. *Psychopharmacology* **188**, 541–551.

Barrett-Connor E, Goodman-Gruen D, Patay B (1999). Endogenous sex hormones and cognitive function in older men. *Journal of Clinical Endocrinology and Metabolism* **84**, 3681–3685.

Blair C, Granger D, Peters Razza R (2005). Cortisol reactivity is positively related to executive function in preschool children attending Head Start. *Child Development* **76**, 554–567.

Brand M, Franke-Sievert C (2007). Neuropsychological correlates of decision making in patients with bulimia nervosa. *Neuropsychology* **21**, 742–750.

Cloninger CR (1999). *The Temperament and Character Inventory – Revised*. Center for Psychobiology of Personality, Washington University: St Louis, MI.

Cullen B, Coen RF, Lynch CA, Cunningham CJ, Coakley D, Robertson IH, Lawlor BA (2005). Repetitive behaviour in Alzheimer's disease: description, correlates and functions. *International Journal of Geriatric Psychiatry* **20**, 686–693.

Duff SJ, Hampson E (2000). A beneficial effect of estrogen on working memory in postmenopausal women taking hormone replacement therapy. *Hormones and Behavior* **38**, 262–276.

Erberk-Ozen N, Birol A, Boratav C, Kocak M (2006). Executive dysfunctions and depression in Behçet's disease without explicit neurological involvement. *Psychiatry and Clinical Neurosciences* **60**, 465–472.

Fassino S, Amianto F, Gramaglia C, Facchini F, Abbate Daga G (2004). Temperament and character in eating disorders: ten years of studies. *Eating and Weight Disorders: EWD* **9**, 81–90.

Fassino S, Pierò A, Daga GA, Leombruni P, Mortara P, Rovera GG (2002). Attentional biases and frontal functioning in anorexia nervosa. *International Journal of Eating Disorders* **31**, 274–283.

Ferraro FR, Wonderlich S, Jocic Z (1997). Performance variability as a new theoretical mechanism regarding eating disorders and cognitive processing. *Journal of Clinical Psychology* **53**, 117–121.

Fichter MM, Pirke KM, Pöllinger J, Wolfram G, Brunner E (1990). Disturbances in the hypothalamo-pituitary-adrenal and other neuroendocrine axes in bulimia. *Biological Psychiatry* **27**, 1021–1037.

First MB, Spitzer RL, Gibbon M, Williams JBW (2002). *Structured Clinical Interview for DSM-IV-TR Axis I Disorders, Research Version, Patient Edition* (*SCID-I/P*). Biometrics Research: New York.

Galderisi S, Mucci A, Catapano F, Colucci D'Amato A, Maj M (1995). Neuropsychological slowness in obsessive compulsive patients: is it confined to tests involving the fronto-subcortical system? *British Journal of Psychiatry* **167**, 394–398.

Galderisi S, Mucci A, Mignone ML, Bucci P, Maj M (1999). Hemispheric asymmetry and psychopathological dimensions in drug-free patients with schizophrenia. *International Journal of Psychophysiology* **34**, 293–301.

Galderisi S, Mucci A, Monteleone P, Sorrentino D, Piegari G, Maj M (2003). Neurocognitive functioning in subjects with eating disorders: the influence of neuroactive steroids. *Biological Psychiatry* **53**, 921–927.

Gruber S, Rathgeber K, Bräunig P, Gauggel S (2007). Stability and course of neuropsychological deficits in manic and depressed bipolar patients compared to patients with major depression. *Journal of Affective Disorders* **104**, 61–71.

Halmi KA, Sunday SR, Strober M, Kaplan A, Woodside DB, Fichter M, Treasure J, Berrettini WH, Kaye WH (2000). Perfectionism in anorexia nervosa: variation by clinical subtype, obsessionality, and pathological eating behavior. *American Journal of Psychiatry* **157**, 1799–1805.

Hammar A (2003). Automatic and effortful information processing in unipolar major depression. *Scandinavian Journal of Psychology* **44**, 409–413.

Henderson M, Freeman CPL (1987). A self-rating scale for bulimia: the BITE. *British Journal of Psychiatry* **15**, 18–24.

Holliday J, Tchanturia K, Landau S, Collier D, Treasure J (2005). Is impaired set shifting an endophenotype of anorexia nervosa? *American Journal of Psychiatry* **162**, 2269–2275.

Hotta M, Shibasaki T, Masuda A, Imaki T, Demura H, Ling N, Shizume K (1986). The responses of plasma adrenocorticotropin and cortisol to corticotropin-releasing hormone (CRH) and cerebrospinal fluid immunoreactive CRH in anorexia nervosa patients. *Journal of Clinical Endocrinology and Metabolism* **62**, 319–324.

Jones BP, Duncan CC, Brouwers P, Mirsky AF (1991). Cognition in eating disorders. *Journal of Clinical and Experimental Neuropsychology* **13**, 711–728.

Klein DA, Mayer LE, Schebendach JE, Walsh BT (2007). Physical activity and cortisol in anorexia nervosa. *Psychoneuroendocrinology* **32**, 539–547.

Laessle RG, Fischer M, Fichter MM, Pirke KM, Krieg JC (1992). Cortisol levels and vigilance in eating disorder patients. *Psychoneuroendocrinology* **17**, 475–484.

Lauer CJ, Gorzewski B, Gerlinghoff M, Backmund H, Zihl J (1999). Neuropsychological assessments before and after treatment in patients with anorexia nervosa and bulimia nervosa. *Journal of Psychiatric Research* **33**, 129–138.

LeBlanc ES, Janowsky J, Chan BK, Nelson HD (2001). Hormone replacement therapy and cognition: systematic review and meta-analysis. *Journal of the American Medical Association* **285**, 1489–1499.

León-Carrión J, Atutxa AM, Mangas MA, Soto-Moreno A, Pumar A, Leon-Justel A, Martín-Rodriguez JF, Venegas E, Domínguez-Morales MR, Leal-Cerro A (2009). A clinical profile of memory impairment in humans due to endogenous glucocorticoid excess. *Clinical Endocrinology* **70**, 192–200.

Li G, Cherrier MM, Tsuang DW, Petrie EC, Colasurdo EA, Craft S, Schellenberg GD, Peskind ER, Raskind MA, Wilkinson CW (2006). Salivary cortisol and memory function in human aging. *Neurobiology of Aging* **27**, 1705–1714.

Lupien S, Lecours AR, Lussier I, Schwartz G, Nair NP, Meaney MJ (1994). Basal cortisol levels and cognitive deficits in human aging. *Journal of Neuroscience* **14**, 2893–2903.

Lupien SJ, de Leon M, de Santi S, Convit A, Tarshish C, Nair NP, Thakur M, McEwen BS, Hauger RL, Meaney MJ (1998). Cortisol levels during human aging predict hippocampal atrophy and memory deficits. *Nature Neuroscience* **1**, 69–73.

McKay SE, Humphries LL, Allen ME, Clawson DR (1986). Neuropsychological test performance of bulimic patients. *International Journal of Neuroscience* **30**, 73–80.

Milner B (1978). Clues to the cerebral organization of memory. In *Cerebral Correlates of Conscious Experience* (ed. P. Buser and A. Rougeul-Buser), pp. 139–153. Elsevier: Amsterdam.

Mobbs O, Van der Linden M, d'Acremont M, Perroud A (2008). Cognitive deficits and biases for food and body in bulimia: investigation using an affective shifting task. *Eating Behaviors* **9**, 455–461.

Monteleone P, Luisi M, Colurcio B, Casarosa E, Monteleone P, Ioime R, Genazzani AR, Maj M (2001). Plasma levels of neuroactive steroids are increased in untreated women with anorexia nervosa or bulimia nervosa. *Psychosomatic Medicine* **63**, 62–68.

Monteleone P, Luisi M, Martiadis V, Serritella C, Longobardi N, Casarosa E, Genazzani AR, Maj M (2006). Impaired reduction of enhanced levels of dehydroepiandrosterone by oral dexamethasone in anorexia nervosa. *Psychoneuroendocrinology* **31**, 537–542.

Monteleone P, Maes M, Fabrazzo M, Tortorella A, Lin A, Bosmans E, Kenis G, Maj M (1999). Immunoendocrine findings in patients with eating disorders. *Neuropsychobiology* **40**, 115–120.

Montgomery SA, Asberg M (1979). A new depression scale designed to be sensitive to change. *British Journal of Psychiatry* **134**, 382–389.

Must A, Szabó Z, Bódi N, Szász A, Janka Z, Kéri S (2006). Sensitivity to reward and punishment and the prefrontal cortex in major depression. *Journal of Affective Disorders* **90**, 209–215.

Owen AM, Roberts AC, Hodges JR, Summers BA, Polkey CE, Robbins TW (1993). Contrasting mechanisms of impaired attentional set-shifting in patients with frontal lobe damage or Parkinson's disease. *Brain* **116**, 1159–1175.

Petrides M (1985). Deficits on conditional associative-learning tasks after frontal- and temporal-lobe lesions in man. *Neuropsychologia* **23**, 601–614.

Petrides M, Milner B (1982). Deficits on subject-ordered tasks after frontal- and temporal-lobe lesions in man. *Neuropsychologia* **20**, 249–262.

Rothamsted V, Barnett V, Lewis T (1994). *Outliers in Statistical Data*. Wiley: Chichester.

Sapolsky RM (1996). Why stress is bad for your brain. *Science* **273**, 749–750.

Seed JA, Dixon RA, McCluskey SE, Young AH (2000). Basal activity of the hypothalamic-pituitary-adrenal axis and cognitive function in anorexia nervosa. *European Archives of Psychiatry and Clinical Neuroscience* **250**, 11–15.

Sheehan D, Lecrubier Y, Janavs J, Knapp E, Weiller E, Bonora LI, Amorim P, Lepine JP, Sheehan MF, Baker RR, Sheehan KH (1994). *Mini-International Neuropsychiatric Interview* (*MINI*). University of South Florida Institute for Research in Psychiatry: Tampa, FL.

Squire LR (1992). Memory and the hippocampus: a synthesis from findings with rats, monkeys, and humans. *Psychological Review* **99**, 195–231.

Steinglass JE, Walsh BT, Stern Y (2006). Set shifting deficit in anorexia nervosa. *Journal of the International Neuropsychological Society* **12**, 431–435.

Strupp BJ, Weingartner H, Kaye W, Gwirtsman H (1986). Cognitive processing in anorexia nervosa. A disturbance in automatic information processing. *Neuropsychobiology* **15**, 89–94.

Tchanturia K, Anderluh MB, Morris RG, Rabe-Hesketh S, Collier DA, Sanchez P, Treasure JL (2004). Cognitive flexibility in anorexia nervosa and bulimia nervosa. *Journal of the International Neuropsychological Society* **10**, 513–520.

Tchanturia K, Davies H, Campbell IC (2007). Cognitive remediation therapy for patients with anorexia nervosa: preliminary findings. *Annals of General Psychiatry* **6**, 14–19.

Tchanturia K, Morris RG, Surguladze S, Treasure J (2002). An examination of perceptual and cognitive set shifting tasks in acute anorexia nervosa and following recovery. *Eating and Weight Disorders* **7**, 312–315.

van Niekerk JK, Huppert FA, Herbert J (2001). Salivary cortisol and DHEA: association with measures of cognition and well-being in normal older men, and effects of three months of DHEA supplementation. *Psychoneuroendocrinology* **26**, 591–612.

Winterer J, Gwirtsman HE, George DT, Kaye WH, Loriaux DL, Cutler Jr. GB (1985). Adrenocorticotropin-stimulated adrenal androgen secretion in anorexia nervosa: impaired secretion at low weight with normalization after long-term weight recovery. *Journal of Clinical Endocrinology and Metabolism* **61**, 693–697.

Zakzanis KK, Campbell Z, Polsinelli A (2010). Quantitative evidence for distinct cognitive impairment in anorexia nervosa and bulimia nervosa. *Journal of Neuropsychology* **4**, 89–106.

Zumoff B, Walsh BT, Katz JL, Levin J, Rosenfeld RS, Kream J, Weiner H (1983). Subnormal plasma dehydroisoandrosterone to cortisol ratio in anorexia nervosa: a second hormonal parameter of ontogenic regression. *Journal of Clinical Endocrinology and Metabolism* **56**, 668–672.