Psychological Medicine (2010), **40**, 2001–2011. © Cambridge University Press 2010
doi:10.1017/S0033291710000310

ORIGINAL ARTICLE

Memory and strategic processing in first-degree relatives of obsessive compulsive patients

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Background. The same executive dysfunctions and alterations in neuroimaging tests (both functional and structural) have been found in obsessive-compulsive patients and their first-degree relatives. These neurobiological findings are considered to be intermediate markers of the disease. The aim of our study was to assess verbal and non-verbal memory in unaffected first-degree relatives, in order to determine whether these neuropsychological functions constitute a new cognitive marker for obsessive-compulsive disorder (OCD).

Method. Recall and use of organizational strategies in verbal and non-verbal memory tasks were measured in 25 obsessive-compulsive patients, 25 unaffected first-degree relatives and 25 healthy volunteers.

Results. First-degree relatives and healthy volunteers did not show differences on most measures of verbal memory. However, during the recall and processing of non-verbal information, deficits were found in first-degree relatives and patients compared with healthy volunteers.

Conclusions. The presence of the same deficits in the execution of non-verbal memory tasks in OCD patients and unaffected first-degree relatives suggests the influence of certain genetic and/or familial factors on this cognitive function in OCD and supports the hypothesis that deficits in non-verbal memory tasks could be considered as cognitive markers of the disorder.

Received 21 March 2009; Revised 19 January 2010; Accepted 26 January 2010; First published online 10 March 2010

Key words: Endophenotype, executive dysfunction, neuropsychology, non-verbal memory, obsessive-compulsive disorder, organizational strategies, verbal memory.

Introduction

Endophenotypes are neurophysiological, biochemical, endocrinological, neuroanatomical, cognitive or neuropsychological phenomena that constitute intermediate markers of brain dysfunction. They are located between clinical manifestations of the disease (phenotype) and the distal genotype (Gottesman & Gould, 2003; Bearden & Freimer, 2006).

Several recent studies of unaffected first-degree relatives (UFD), carried out by the same group, have analysed the existence of endophenotypes in obsessive-compulsive disorder (OCD). One of these studies (Chamberlain *et al*. 2007) showed that unaffected relatives of OCD probands presented deficits in cognitive flexibility and motor inhibition that were similar to those recorded in obsessive patients. Menzies *et al*. (2007) also found a significant association between impaired execution of the stop-signal test (a measure of motor inhibition) and certain structural alterations in the brain of OCD patients and relatives compared with healthy controls, such as grey matter reductions in orbitofrontal and right inferior frontal regions and grey matter increases in cingulate, parietal and striatal regions. Results using functional neuroimaging techniques have identified reduced activation of the lateral orbitofrontal cortex (OFC), lateral prefrontal cortex (LPFC) and parietal cortex during reversal learning in patients with OCD and their unaffected relatives (Chamberlain *et al*. 2008). Similarly, white matter abnormalities in frontal and parietal regions have been

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found in obsessive patients and in their relatives (Menzies *et al*. 2008). These findings support the hypothesis that these neurobiological markers can be considered as endophenotypes of OCD.

Neuropsychological deficits may constitute interesting endophenotypic markers of psychiatric disorders because they are quantitative, have moderate heritability within the normal population (Dougherty *et al*. 2003) and can be extended to animal models of the disorder (Glahn *et al*. 2004). Previous studies have proposed several measures of executive functions, such as motor inhibition, cognitive flexibility and reversal learning as cognitive endophenotypes for OCD (Chamberlain *et al*. 2007, 2008; Menzies *et al*. 2007). Memory impairments are among the most consistent findings in OCD. Studies of non-verbal memory in OCD report poorer free recall of information, mediated by poor organization during its processing (Savage *et al*. 1999; Deckersbach *et al*. 2000; Savage *et al*. 2000), while storage capacity remains intact (Savage *et al*. 1996). As regards studies of verbal memory, some report no differences between obsessive patients and the general population (Christensen *et al*. 1992; Dirson *et al*. 1995), while others (Deckersbach *et al*. 2000; Savage *et al*. 2000) point to differences in the recall of verbal episodic information. The latter studies suggest that poor recall in obsessive patients is mediated by alterations in the way in which information is organized (i.e. the use of semantic strategies), as in the case of non-verbal memory. Some authors argue that deficits in the organization of information, both verbal and non-verbal, are the consequence of executive dysfunction, which, ultimately, may reflect alterations in the frontostriatal circuits involved in the neurobiology of OCD (Abbruzzese *et al*. 1997; Savage *et al*. 1999, 2000; Deckersbach *et al*. 2000).

The aim of our study was to analyse whether deficits in organization and recall of verbal and non-verbal information constitute an endophenotype in OCD. Accordingly, among other variables we measured the recall and use of organizational strategies during the processing of verbal and non-verbal tasks in OCD patients, UFD and healthy volunteers (HV). Our hypothesis was that UFD, like OCD patients, would show impaired neuropsychological performance compared with healthy controls.

Methods and materials

Participants

In total, 75 subjects were included in the study: 25 outpatients with a diagnosis of OCD; 25 UFD; 25 unrelated HV. Patients were recruited from a series of consecutive admissions to the Obsessive-Compulsive Disorders Unit of Bellvitge University Hospital in Barcelona, between 2006 and 2008. All those included met the criteria for OCD described in DSM-IV (American Psychiatric Association, 1994) and, in each case, the diagnosis was confirmed by two experienced psychiatrists (P.A. and C.S.) through two separate interviews conducted 1 month apart using the Structured Clinical Interview for DSM-IV Axis I Disorder (First *et al*. 1997*b*). Exclusion criteria were: a history of substance abuse and/or dependence; neurological disease (except tics); having suffered a head injury with loss of consciousness; a history of bipolar disorder; a history of psychotic episodes; having undergone electroconvulsive therapy and/or neurosurgery.

OCD patients with other co-morbid psychiatric disorders were not excluded from the study, since OCD was both the dominant pathology and the reason for seeking treatment. The SCID-I-CV was used to assess the presence of Axis I disorders and the Structured Clinical Interview for DSM-IV Axis II Personality Disorders (SCID-II) was used to assess the presence of personality disorders (First *et al*. 1997*a*). Six OCD patients (24%) presented co-morbidity with other Axis I psychiatric disorders: major depressive disorder in two cases and dysthymic disorder in four. Four more patients (16%) presented co-morbidity with an Axis II disorder: obsessive-compulsive personality disorder was the most frequent (three patients), followed by schizotypal personality disorder (one patient). A clinical version of the Yale–Brown Obsessive Compulsive Scale (YBOCS) Symptom Checklist (Goodman *et al*. 1989), which includes >50 examples of obsessions and compulsions, was used to obtain scores on five previously identified symptom dimensions (Mataix-Cols *et al*. 1999) designated as symmetry/ordering, hoarding, contamination/cleaning, aggressive/checking and sexual/religious obsessions. If a patient identified at least one of the specific symptoms under one of these dimensions, the dimension was considered present; otherwise, the dimension was considered absent. A total of 50 patients (60%) presented aggressive/checking obsessions, 14 (56%) contamination/cleaning obsessions, seven (28%) symmetry/ordering obsessions, two (8%) sexual/religious obsessions and eight (30%) hoarding obsessions.

A total of 24 obsessive patients (96.6%) were receiving psychopharmacological treatment at the time of the neuropsychological assessment. Treatment with psychoactive drugs had remained stable and unchanged for a period of at least 12 weeks prior to the assessment. Among patients receiving this treatment, 16 (64%) were receiving monotherapy: nine were taking selective serotonin reuptake inhibitors (SSRIs) and seven clomipramine. Eight patients (32%) had a

prior history of resistance to at least three treatments with SRIs alone and were receiving a combination of clomipramine and SSRIs. One patient was unmedicated. In total, 17 patients had completed a cognitive-behavioural therapy (CBT) programme comprising a minimum of 20 weekly 1-h sessions, which basically involved exposure with response prevention techniques and cognitive restructuring. CBT was not considered necessary in four patients who presented significant levels of symptom resolution with pharmacological treatment. Four patients commenced CBT but dropped out before completing the first five sessions. No patients were receiving psychotherapy at the time of the neuropsychological assessment.

We enrolled 32 patients at the beginning of the study, but eligible first-degree relatives were only available in 25 cases. All patients authorized us to contact their relatives for interview. HV were recruited from local communities. UFD and HV were excluded if they had a past or current history of a psychiatric or neurological disorder, treatment with psychotropic medication, substance dependence and/or abuse or head injury. These data were collected retrospectively through direct interview. We used the Structural Clinical Interview for DSM-III-R: Non-Patient Version to exclude psychiatric disorders (Spitzer *et al*. 1989) in both groups. We initially evaluated 35 UFD, but 10 were excluded: five with a past history of psychotropic medication and two who met criteria for OCD, two for alcohol abuse and one for panic disorder. Of the 25 remaining UFD, 14 (56%) were parents, seven (28%) were siblings and four (16%) offspring.

Written informed consent was obtained from each subject after a complete description of the study, which was approved by the hospital's ethics committee.

Socio-demographic and clinical variables

The clinical data analysed in the sample included sociodemographic variables such as sex, age and educational level (years of education).

General non-verbal intelligence was assessed using Raven's Advanced Progressive Matrices (Raven & Court, 1996). Hand dominance was determined by means of the Spanish version of the Edinburgh Handedness Inventory (Oldfield, 1971) and a current mental health questionnaire, the General Health Questionnaire (GHQ; Goldberg & Hillier, 1979), was administered to the whole sample.

Presence of subclinical obsessive-compulsive symptoms was assessed in HV and UFD using the Padua Inventory-Washington State Revision (PI-WSUR, Burns *et al*. 1996). This inventory was designed to provide a purer measure of obsessive-compulsive symptoms than the original questionnaire by Sanavio (1988), in which several items evaluated worry-like themes more than obsessive contents. The PI-WSUR includes five subscales: obsessive thoughts about harm to self/others; obsessive impulses to harm self/others; contamination obsessions and washing rituals; checking compulsions; dressing/grooming rituals. The Spanish version of the instrument was applied (Ibàñez *et al*. 2002; Morillo *et al*. 2007). In the patient group, OCD severity was measured using the clinical version of the YBOCS (Goodman *et al*. 1989).

Depression was measured in all subjects with the 21-item version of the Beck Depression Inventory (BDI; Beck *et al*. 1961) and state-related anxiety was measured with the State subscale of the State-Trait Anxiety Inventory (STAI; Spielberger *et al*. 1982).

Neuropsychological assessment

Attention

Attention was assessed using the Spanish version of the Digit Span Test from the Wechsler Adult Intelligence Scale (Wechsler, 1981).

Verbal memory

Verbal memory was assessed using the Spanish-Complutense Verbal Learning Test (TAVEC). The reliability, validity and psychometric properties of this test were established in a previous study (Benedet & Alejandre, 1998). The test comprises three lists. The first (list A) contains 16 items from four different categories (fruit, spices, items of clothing and tools) and is presented five times. After each presentation, subjects are assessed according to the number of words remembered correctly. We measured the number of words after the first trial, after the fifth trial, the total number of words in the five trials (learning rate), the number of intrusions (words recited by the subject but that do not feature in list A), the number of perseverations (repetition of words, both correct ones and intrusions) and the use during recall of semantic strategies/clusters (grouping words according to categories) and/or series-based strategies/clusters (grouping words by the order in which they are presented). The second list (list B) comprises 16 different items to those in list A, which are also taken from different categories; its aim is to cause interference after the fifth attempt to learn list A. After administration of list B, subjects are assessed on their short-term free recall of list A. Following a 20-min rest period, during which time other tests are administered for the purpose of distraction, subjects' long-term free recall is assessed. Finally, a third list comprising 44 words (including the 16 from list A) is presented in order to

https://doi.org/10.1017/S0033291710000310 Published online by Cambridge University Press

measure subjects' recognition. The characteristics and research aims of the TAVEC are similar to those of the California Verbal Learning Test (Delis *et al*. 1987) and so it is possible to compare the results obtained with the two instruments at both clinical and research levels.

Non-verbal memory

Non-verbal memory was assessed using the Rey–Osterrieth Complex Figure Test (RCFT; Osterrieth, 1944). Subjects are initially presented with a RCFT to copy. A period of 3 min after completing the task, during which time other distraction tests are administered, subjects are asked to draw what they remember of the original figure in order to assess immediate recall. To measure delayed recall, after a further 30-min period, during which subjects are distracted with other tasks, they are once again asked to draw what they remember of the original figure. During the test the experimenter copies the subject's drawings in order to analyse the organization. At the end of the assessment, to measure recognition, subjects are presented with a fixed number of figures, of which only some (12) form part of the original figure. The organization and accuracy of the drawing are scored during the three phases: copying; immediate recall; delayed recall.

The accuracy of the copy and the immediate and delayed recall figures and recognition were scored using the system developed by Meyers & Meyers (1995). The organization of the drawing was assessed using the system developed by Savage *et al*. (1999), which divides the RCFT into five segments (base rectangle, two diagonals, horizontal midline, vertical midline and the vertex of a triangle). The scoring, which ranges from 0 to 6, takes into account the construction of each of the five segments as non-fragmented units.

All the subjects (OFC, HV and UFD) were clinically evaluated by a psychiatrist of the Obsessive-Compulsive Research Unit (C.S.) before inclusion in the study. All the neuropsychological tests were administered and scored by a trained examiner, a psychiatrist who does not work in our hospital and who was blind to group membership.

Statistical analysis

Analyses were carried out using PASW17 for Windows. First, the clinical, sociodemographic and neuropsychological variables of the three groups were compared, using χ^2 tests for categorical variables and one-way analyses of variance (ANOVA) for quantitative variables. Scheffé's multiple comparison procedure was used to assess differences between groups. Differences in the presence of subclinical obsessive-compulsive symptoms (assessed with the PI-WSUR) between HV and UFD were evaluated with the non-parametric Mann–Whitney *U* test.

Second, analysis of covariance (ANCOVA) was also performed to assess differences in the neuropsychological performance between the three groups, adjusting for the covariates age, level of anxiety and depression.

Third, Spearman's Rho correlations stratified by group were estimated to evaluate the association between clinical variables (age, STAI, BDI, PI-WSUR and YBOCS) and neuropsychological measures. In this analysis, only the variables that achieved significant differences ($p<0.05$) between HV and UFD in the earlier ANCOVA analysis were considered.

Finally, multiple linear regressions (STEPWISE procedure) were adjusted in order to explore the association of group (codified as HV = 0 and UFD = 1) with the neuropsychological measures. Age, level of anxiety, depression and subclinical obsessive-compulsive symptoms were entered as covariates. Probabilities for stepwise entry and removal were 0.05 and 0.10 respectively.

Results

Clinical and demographic characteristics

Table 1 shows the distribution of the demographic and clinical characteristics in the sample. Groups did not differ in terms of age, years of education, sex, handedness or general intelligence. However, statistical differences were found for state anxiety levels (STAI; $p<0.001$), depressive symptoms (BDI; $p<0.001$) and general mental health (GHQ; $p<0.001$). Specifically, OCD patients had higher mean scores on the STAI and BDI scales than HV ($p<0.001$) or UFD ($p=0.002$ and $p<0.001$ respectively). As expected, OCD scored higher on the GHQ than HV ($p=0.001$) and UFD ($p=0.009$). No differences were found between HV and UFD on the STAI ($p=0.109$), BDI ($p=0.106$) and GHQ ($p=0.523$) mean scores, whereas UFD had higher mean scores on the subclinical obsessive-compulsive symptoms scale (PI-WSUR) than HV ($p=0.033$).

Neuropsychological performance

Table 2 shows the distribution of the neuropsychological variables (means and standard deviation) for the three groups, and the results of the ANOVA procedures. As regards attention, HV had higher mean scores for the digit symbol task than UFD ($p=0.046$) (Table 2).

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Table 1. *Comparison of demographic and clinical characteristics*

				Comparison across groups	
	HV ($n=25$)	UFD ($n=25$)	OCD ($n=25$)	Statistic[a]	p
Categorical variables					
Sex (males), n (%)	12 (48.0)	12 (48)	12 (48)	$\chi^2(df=2)=0.00$	1
Handedness (right), n (%)	25 (100)	23 (92.0)	24 (96.0)	$\chi^2(df=2)=2.08$	0.353
Quantitative variables					
Age, mean (S.D.)	43.6 (13.9)	44.9 (11.9)	43.6 (10.8)	$F(df=2)=0.08$	0.916
Years education, mean (S.D.)	12.6 (3.7)	12.1 (5.7)	12.5 (7.4)	$F(df=2)=0.05$	0.949
Raven, mean (S.D.)	9.4 (2.4)	7.8 (3.3)	8.1 (1.9)	$F(df=2)=2.92$	0.060
STAI, mean (S.D.)	10.4 (5.4)	15.6 (8.2)	24.6 (10.9)*	$F(df=2)=17.84$	<0.001
BDI, mean (S.D.)	1.8 (1.7)	5.7 (5.9)	19.8 (9.2)*	$F(df=2)=55.17$	<0.001
GHQ, mean (S.D.)	0.9 (2.3)	2.6 (4.4)	8.5(9.6)*	$F(df=2)=8.81$	<0.001
PI-WSUR, mean (S.D.)	7.2 (5.7)*	11.7 (8.4)*	–	$U(df=1)=203.0$[b]	0.033
YBOCS, mean (S.D.)	–	–	25.5 (5.8)	–	–

HV, Healthy volunteers; UFD, unaffected first-degree relatives; OCD, obsessive-compulsive disorder; df, degrees of freedom; STAI, State-Trait Anxiety Index; BDI, Beck Depression Inventory; GHQ, General Health Questionnaire; PI-WSUR, Padua Inventory-Washington State Revision; YBOCS, Yale-Brown Obsessive Compulsive Scale.

[a] χ^2 for categorical variables and analysis of variance procedures for quantitative variables.

[b] Mann–Whitney's U test comparing only HV to UFD.

* Group that differs from the rest in *post-hoc* comparisons.

Table 2. *Comparison of neuropsychological performance mean scores*

	HV ($n=25$)		UFD ($n=25$)		OCD ($n=25$)		ANOVA		
	Mean	S.D.	Mean	S.D.	Mean	S.D.	F (df = 2)	p	Significant contrasts[a]
Attention									
Digit symbol	16.52	4.71	13.60	4.03	13.96	3.37	3.82	0.027	HV > UFD
TAVEC									
Trial 1 recall	7.24	2.01	6.80	2.04	5.16	1.40	8.87	<0.001	(HV = UFD) > OCD
Trial 5 recall	11.88	2.89	12.32	2.46	10.20	2.33	4.73	0.012	UFD > OCD
Total correct trials (learning rate)	51.76	11.47	49.60	14.81	41.36	9.15	5.20	0.008	HV > OCD
Semantic clustering	16.08	12.99	14.52	9.13	7.44	4.09	5.91	0.004	(HV = UFD) > OCD
Serial clustering	5.96	5.98	6.08	4.14	4.40	2.22	1.14	0.325	
Short-delayed recall 1st list	11.04	3.72	11.28	3.30	9.04	3.16	3.27	0.044	
Long-delayed recall 5th list	11.56	3.61	11.92	3.12	8.92	2.74	6.65	0.002	(HV = UFD) > OCD
Perseverations	4.84	3.66	6.76	4.98	5.80	5.63	0.99	0.377	
Intrusions	1.12	1.59	3.80	3.75	2.96	2.81	5.76	0.005	HV < UFD
Recognition	14.80	1.38	15.00	1.12	13.80	2.02	4.28	0.018	UFD > OCD
RCFT									
Copy	33.92	2.31	31.56	5.43	31.34	3.58	3.22	0.046	
Immediate recall	20.86	5.12	15.48	7.40	10.82	5.08	17.73	<0.001	HV > UFD > OCD
Delayed recall	21.32	5.20	15.58	6.85	10.20	5.13	23.13	<0.001	HV > UFD > OCD)
Recognition	20.80	2.33	19.28	2.37	19.88	2.13	2.82	0.066	
Copy organization	4.92	0.95	3.08	1.61	3.20	1.19	16.21	<0.001	HV > (UFD = OCD)

HV, Healthy volunteers; UFD, unaffected first-degree relatives; OCD, obsessive-compulsive disorder; ANOVA, analysis of variance; df, degrees of freedom; TAVEC, Spanish-Complutense Verbal Learning Test; RCFT, Rey-Osterrieth Complex Figure Test.

[a] Scheffé's *post-hoc* comparison (only significant results are tabulated).

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With regard to verbal memory, the groups presented different mean scores on some measures on the TAVEC: recall after the first and fifth trials, number of items recalled over five successive learning trials (learning rate), semantic strategies, short and long delayed recall, number of intrusions and recognition. HV had higher scores than OCD on recall after the first trial ($p=0.001$), learning rate ($p=0.012$), semantic strategies ($p=0.008$) and long delayed recall ($p=0.017$) and lower scores than UFD on intrusions ($p=0.006$). UFD scored higher than OCD on recall after the first ($p=0.010$) and fifth ($p=0.018$) trials, semantic strategies ($p=0.036$), long delayed recall ($p=0.006$) and recognition ($p=0.029$). Although the global effect of group was statistically significant for short delayed recall ($p=0.044$), non-significant *post hoc* comparisons (using Scheffé's contrasts) were found between groups.

With regard to non-verbal memory, statistical differences between groups also appeared on several measures of the RCFT: copy, immediate and delayed recall and use of organizational strategies. The three groups differed on immediate and delayed recall, with HV scoring higher than UFD ($p=0.009$ and $p=0.003$ respectively) and OCD ($p<0.001$) and UFD scoring higher than OCD ($p=0.027$ and $p=0.006$ respectively). HV also had higher scores on organizational strategies than UFD and OCD ($p<0.001$), whereas there were no differences between UFD and OCD. Although the global effect of group was statistically significant for copy ($p=0.046$), non-significant *post hoc* comparisons were found using Scheffé's contrasts (Fig. 1).

Table 3 presents the adjusted means and standard errors of neuropsychological variables for the three groups and results of the ANCOVA for each measure, adjusted for age, anxiety and depression. Most of the results remained unchanged with regard to the results of the ANOVA (Table 2). However, differences between the three groups disappeared for digit symbol ($p=0.084$), short ($p=0.297$) and delayed ($p=0.169$) recall and recognition ($p=0.344$) on the TAVEC and the copy task on the RCFT ($p=0.231$). Moreover, UFD scored significantly higher than OCD on learning rate on the TAVEC ($p=0.016$), but the groups did not differ on delayed recall on the RCFT ($p=0.345$). In summary, when age, anxiety and depression were added as covariates, differences between HV and UFD were only observed for the following variables: intrusions on the TAVEC ($p=0.004$); immediate ($p=0.014$) and delayed ($p=0.005$) recall; use of organizational strategies ($p<0.001$) on the RCFT.

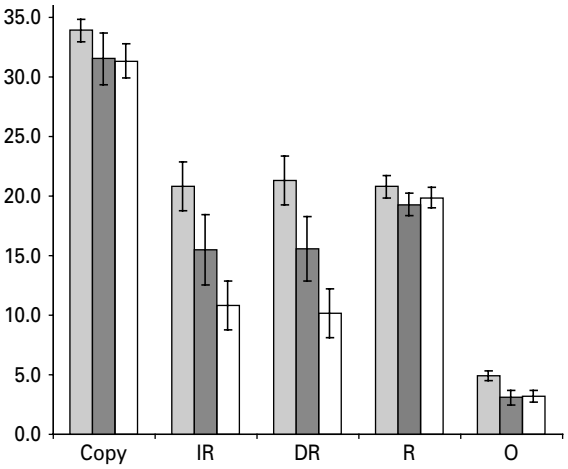

Fig. 1. Error bars (±2 S.E.) for means of the primary Rey-Osterrieth Complex Figure test (RCFT) scores. HV (□), healthy volunteers; UFD (■), unaffected first-degree relatives; OCD (□), obsessive-compulsive disorder; Copy, copy of RCFT; IR, immediate recall; DR, delayed recall; R, recognition; O, organization.

Correlation analysis

Table 4 shows the correlation coefficients between clinical measures and neuropsychological variables of non-verbal memory in each group. Age was inversely correlated with measures of recall and recognition in HV and UFD (r coefficients between -0.39 and -0.53). Levels of anxiety and depression were also inversely correlated with recall and recognition in UFD (r values ranging from -0.44 to -0.54), whereas in HV only depression correlated significantly with recall (r coefficients between -0.43 to -0.50). Subclinical obsessive-compulsive symptoms (scored with PI-WSUR) did not show significant correlations with any of the RCFT measures in HV and UFD (absolute r values between 0.01 and 0.36). In OCD none of the correlations was statistically significant (absolute r values between 0.10 and 0.32), except severity of obsessive-compulsive symptomatology (scored with YBOCS), which was inversely correlated with immediate recall of RCFT ($r=-0.46$, $p=0.020$).

As regards the correlations between clinical measures and neuropsychological variables of verbal memory, age was only negatively related to the different domains of recall, recognition and semantic clustering in HV (r values between -0.53 and -0.68, $p<0.01$) and to learning rate in OCD ($r=-0.41$, $p=0.042$). In OCD, long-delayed recall was also negatively associated with anxiety ($r=-0.44$, $p=0.029$). Finally, in UFD only recognition correlated negatively with depression ($r=-0.54$, $p=0.006$).

As for attention, the scores for digit span test correlated negatively with age in HV ($r=-0.44$, $p=0.029$) and UFD ($r=-0.56$, $p=0.004$) and with depression in OCD ($r=-0.43$, $p=0.033$).

https://doi.org/10.1017/S0033291710000310 Published online by Cambridge University Press

Table 3. *Comparison of neuropsychological performance adjusted for age, anxiety and depression*

	HV ($n=25$)		UFD ($n=25$)		OCD ($n=25$)		ANCOVA adjusted for age, anxiety and depression			
	Mean	S.E.	Mean	S.E.	Mean	S.E.	F (df = 2)	p	Contrasts[a]	HV *v.* UFD (p)
Attention										
Digit symbol	15.66	0.90	13.34	0.79	15.09	1.06	2.56	0.084	–	
TAVEC										
Trial 1 recall	7.39	0.42	6.97	0.37	4.84	0.49	6.00	0.004	(HV = UFD) > OCD	
Trial 5 recall	11.79	0.57	12.46	0.50	10.15	0.67	3.19	0.047	UFD > OCD	
Total correct trials (learning rate)	52.60	2.74	50.58	2.40	39.55	3.23	3.68	0.030	(HV = UFD) > OCD	
Semantic clustering	16.64	2.23	14.96	1.95	6.45	2.63	3.38	0.040	(HV = UFD) > OCD	
Serial clustering	5.88	1.07	6.14	0.94	4.42	1.26	.49	0.616	–	
Short-delayed recall 1st list	10.67	0.76	11.28	0.66	9.41	0.89	1.23	0.297	–	
Long-delayed recall 5th list	10.94	0.71	11.78	0.63	9.68	0.84	1.83	0.169	–	
Perseverations	5.77	1.14	7.37	1.00	4.25	1.34	1.78	0.176	–	
Intrusions	1.36	0.69	3.89	0.61	2.63	0.82	4.67	0.013	HV < UFD	0.004
Recognition	14.38	0.35	14.90	0.30	14.32	0.41	1.08	0.344	–	
RCFT										
Copy	32.93	0.87	31.25	0.76	32.64	1.03	1.50	0.231	–	
Immediate recall	19.15	1.28	15.24	1.12	12.77	1.51	4.65	0.013	HV > (UFD = OCD)	0.014
Delayed recall	19.64	1.22	15.33	1.07	12.14	1.44	6.70	0.002	HV > (UFD = OCD)	0.005
Recognition	20.54	0.51	19.31	0.45	20.10	0.60	2.13	0.127	–	
Copy organization	4.72	0.31	2.96	0.27	3.53	0.37	10.79	< .001	HV > (UFD = OCD)	< 0.001

HV, Healthy volunteers; UFD, unaffected first-degree relatives; OCD, obsessive-compulsive disorder; TAVEC, Spanish-Complutense Verbal Learning Test; RCFT, Rey–Osterrieth Complex Figure Test.

[a] Scheffé's *post-hoc* comparison (only significant results are tabulated).

Table 4. *Spearman's Rho correlations between neuropsychological variables of non-verbal memory* (*Rey-Osterrieth Complex Figure Test*) *and clinical measures*

Group	Variables	Age	STAI	BDI	PI-WSUR	YBOCS
HV	Immediate recall	−0.39	−0.16	−0.50*	−0.36	–
	Delayed recall	−0.44*	−0.27	−0.43*	−0.32	–
	Recognition	−0.47*	0.21	−0.07	−0.01	–
	Copy organization	−0.06	0.29	−0.20	−0.04	–
UFD	Immediate recall	−0.40*	−0.50*	−0.46*	0.15	–
	Delayed recall	−0.43*	−0.46*	−0.46*	0.13	–
	Recognition	−0.53**	−0.44*	−0.54**	0.21	–
	Copy organization	−0.01	−0.19	−0.26	−0.08	–
OCD	Immediate recall	−0.18	−0.29	−0.20	–	−0.46*
	Delayed recall	−0.22	−0.24	−0.23	–	−0.30
	Recognition	0.10	−0.16	0.15	–	−0.03
	Copy organization	0.32	−0.10	−0.23	–	0.12

HV, Healthy volunteers; UFD, unaffected first-degree relatives; OCD, obsessive-compulsive disorder; STAI, State-Trait Anxiety Index; BDI, Beck Depression Inventory; PI-WSUR, Padua Inventory-Washington State Revision; YBOCS, Yale-Brown Obsessive Compulsive Scale.

* $p < 0.05$, ** $p < 0.01$.

https://doi.org/10.1017/S0033291710000310 Published online by Cambridge University Press

Table 5. *Predictors of verbal and non-verbal memory*

Criteria	Predictors	*B* (95% CI)	*β*	*t*	*p*	*F* (*p*)	R^2
Intrusions	Group	2.68 (1.04 to 4.32)	0.43	3.29	0.002	10.81 (0.002)	0.167
Immediate recall	Group	−3.62 (–7.12 to −0.13)	−0.27	−2.02	0.043	9.50 (<0.001)	0.342
	Depression	−0.40 (–0.79 to 0.00)	−0.32	−2.62	0.049		
	Age	−0.17 (–0.31 to −0.04)	−0.27	−2.09	0.012		
Delayed recall	Group	−4.10 (–7.42 to −0.77)	−0.26	−1.97	0.017	10.70 (<0.001)	0.373
	Depression	−0.37 (–0.74 to 0.01)	−0.33	−2.74	0.055		
	Age	−0.17 (–0.30 to −0.05)	−0.31	−2.48	0.009		
Copy organization	Group	−1.84 (–2.59 to −1.09)	−0.58	−4.93	<0.001	24.28 (<0.001)	0.322

R^2, Adjusted R^2 coefficient.
Results obtained with multiple lineal regression (stepwise procedure).
Group codified: 0 = health volunteers; 1 = unaffected first-degree relatives.

Predictors of neuropsychological performance

Table 5 presents the results of the four final models obtained with multiple-regression: one for each measure that previously presented differences between HV and UFD (after adjusting for age, anxiety and depression, see Table 3). UFD were associated with more intrusions [95% confidence intervals (CI) for B: 1.04–4.32, $p = 0.002$] and HV with better immediate recall (95% CI for B: 0.13–7.12, $p = 0.043$), delayed recall (95% CI for B: 0.77–7.42, $p = 0.017$) and copy organization (95% CI for B: 1.09–2.59, $p < 0.001$). As regards recall on the RCFT, older participants and those with higher levels of depression also showed worse immediate and delayed recall (β coefficients ranging from −0.26 to −0.33).

Discussion

To our knowledge, this is the first study to explore verbal and non-verbal memory and information-processing strategies in UFD of OCD patients. In the execution of the RCFT, our UFD sample presented a cognitive pattern similar to the characteristic profile of obsessive patients, with impairments both in recall and in the use of organizational strategies in information processing; however, in verbal memory tasks, their neuropsychological performance did not present the dysfunctions seen in OCD patients.

Non-verbal memory

The profile of dysfunction on the execution of RCFT in UFD was indistinguishable from that of OCD patients. This pattern of cognitive dysfunction in UFD and OCD but not in HV remained unchanged after covarying for age, anxiety and depression. The results of the multiple-regression model confirmed our hypothesis; only UFD were associated with worse copy organization on the RCFT, although other independent variables such as age and intensity of depression were associated with poor performance in recall measures on the RCFT. The findings regarding the use of organizational strategies suggest that UFD present the same cognitive deficits in the information-encoding process as those reported in obsessive patients (Savage *et al*. 1999, 2000; Deckersbach *et al*. 2000; Penades *et al*. 2005) and in patients with Parkinson's (Grossman *et al*. 1993). Similarly, the impairments in information recall replicate the results obtained in several studies in obsessive patients (Savage *et al*. 1999, 2000; Deckersbach *et al*. 2000; Segalas *et al*. 2008). Our results corroborate those of other studies, which found the same cognitive deficits in different measures of executive functions in both obsessive patients and first-degree family members, supporting the notion that these neuropsychological deficits may be endophenotypes of OCD (Chamberlain *et al*. 2007, 2008; Menzies *et al*. 2007). These findings, which are free of the possible bias deriving from medication or from the existence of a

https://doi.org/10.1017/S0033291710000310 Published online by Cambridge University Press

psychiatric disorder in UFD, indicate that the use of organizational strategies and the recall of non-verbal information during the execution of the RCFT should be considered as a deficit with a familial component. There are several possible explanations for these results. One explanation is genetically based: non-verbal memory dysfunctions could be considered as possible endophenotypes in OCD, although further work is needed to determine the hereditability of these cognitive domains. A second explanation would point to the effect of family factors such as parenting styles, care, control and discipline that are associated with cognition and the development of anxiety disorders (Gallagher & Cartwright-Hatton, 2008), which we did not control in this study.

Verbal memory

OCD patients performed worse on the TAVEC in tasks that assess learning and information processing. These results are in agreement with those of many studies performed in obsessive patients (Deckersbach *et al*. 2000; Savage *et al*. 2000; Savage & Rauch, 2000; Cabrera *et al*. 2001), though not all (Christensen *et al*. 1992; Dirson *et al*. 1995). These impairments were not found in our two groups of control subjects (UFD and HV); in these groups, cognitive performance was preserved and did not display the dysfunctions found in the patients' group. Classically, semantic clustering has been used as a marker of verbal information processing, both in neurological diseases such as Parkinson's and Huntington's chorea (Massman *et al*. 1990), which share a neurobiological substrate similar to that of OCD (Starkstein *et al*. 1988; Huber & Glatt, 1992) and in studies of obsessive patients (Deckersbach *et al*. 2000; Savage *et al*. 2000). Nevertheless, recent reports have described semantic intrusions as being a new cognitive marker of frontal lobe epilepsy and reflect impairments on encoding verbal information in Parkinson's disease as well (Hernandez *et al*. 2003; Weintraub *et al*. 2004). The high number of intrusions in UFD (higher even than in patients) may reflect alterations in information processing in these subjects. The superior performance of UFD compared with HV on certain measures of learning (e.g. recall after the fifth trial) is striking, although HV learnt a greater quantity of words after the five attempts and there were no significant differences between the two control groups, HV and UFD. The results for verbal memory did not identify it as a useful cognitive marker of OCD. Verbal and non-verbal memory present differences in neurobiological bases and functional independence in organizational strategies (Lezak, 1995; Deckersbach *et al*. 2000). Given the existence of these biological differences between the two kinds of memory, our results could be explained by the fact that verbal memory is less likely to be affected by a familial component (genetic or parenting factors) than non-verbal tasks in OCD and UFD, although this conclusion is only tentative at present.

Clinical variables and neuropsychological performance

UFD and HV did not show statistical differences in levels of anxiety and depression. Only presence of subclinical obsessive-compulsive symptoms was significantly higher in UFD than in HV, although Axis I and II pathology was ruled out by the administration of specific scales (First *et al*. 1997*a*, *b*). UFD showed an inverse correlation between age, BDI and STAI and measures of recall on the RCFT; higher scores on the BDI were negatively associated with recognition on the TAVEC. In HV, age and BDI were inversely correlated with measures of recall and recognition on the RCFT; recall, recognition and semantic clustering on the TAVEC were negatively associated with age. These results suggest that HV and UFD present different degrees of cognitive vulnerability to the clinical variables studied, which, in the final analysis, may reflect underlying neurobiological differences.

In the case of OCD patients, severity of obsessive symptoms (measured with the YBOCS) was associated negatively with immediate recall on the RCFT, the intensity of depressive symptoms (scored with the BDI) was inversely correlated with attention and higher levels of anxiety were associated with worse recall of verbal information. These results partially corroborate those of previous studies in OCD patients, which reported associations between the intensity of the responses on the YBOCS obsession subscale and performance on non-verbal memory tasks (Penades *et al*. 2005). Nonetheless, in our sample of OCD we did not replicate the correlations between the severity of the depressive symptoms and performance on the RCFT reported in previous studies (Moritz *et al*. 2003; Segalas *et al*. 2008). Those studies found that higher scores of depressive symptoms measured in their samples modulated cognitive performance on non-verbal memory tasks. However, unlike the samples used in the Moritz *et al*. (2003) and Segalas *et al*. (2008) studies, our patients presented only mild depressive symptoms, which could explain the lack of association between depressive symptoms and the execution of non-verbal memory tasks in our patients.

Limitations

The relatively small sample size could be considered a limitation of the study. Another possible limitation is the use of first-degree family members in the search

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for endophenotypes, as not all family members will necessarily present the marker studied. Our UFD sample included parents, siblings and children of obsessive patients. In future studies, we suggest that the UFD should comprise only obligate-carriers (unaffected relatives with both an affected child and parent) or the parametric influence of familial loading (the number of affected relatives) (Faraone *et al*. 2000).

On the basis of our findings and taking into account the limitations of the study, we can conclude that UFD and OCD patients show the same pattern of cognitive dysfunction during the execution of a non-verbal memory task. This supports the hypothesis that deficits in non-verbal memory could be considered an endophenotype of OCD. These results need to be confirmed through broader studies to determine the heritability of these cognitive domains.

Acknowledgements

This study was supported in part by grants 010210 from the Fundació la Marató TV3, Barcelona, 2005 FI 00738 from the Agència de Gestió d'Ajuts Universitaris i de Recerca, Generalitat de Catalunya, by the European Commission under the Seventh Framework Programme (FP7-ICT-215839–2007; Playmancer Project), by the Instituto de Salud Carlos (III) Centro de Investigación en Red de Salud Mental (CIBERSAM) and by Fondo de Investigaciones Sanitarias de la Seguridad Social, FIS PI071029 and FIS PI071044.

Declaration of Interest

None.

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