·Original Article·

Neuropsychological study of patients with obsessive-compulsive disorder and their parents in China: searching for potential endophenotypes

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Abstract: **Objective** The existence of neuropsychological deficits has been implicated in obsessive-compulsive disorder (OCD), particularly memory, attention, and executive functions. However, few studies have focused on neuropsychological deficits in the relatives of OCD patients. The aim of this study was to investigate cognitive deficits in OCD patients and their parents. **Methods** Forty patients with OCD, 48 parents of these patients, and 87 healthy controls completed a neuropsychological testing battery. **Results** Both OCD patients and their parents showed impairments in delayed verbal memory and delayed visual memory. Furthermore, they performed worse than healthy controls in problem-solving ability. **Conclusion** Our study demonstrated familial aggregation of delayed memory deficits and impaired problem-solving ability, which may be the potential neuropsychological endophenotypes of hereditary susceptibility to OCD.

Keywords: obsessive-compulsive disorder; neuropsychological tests; memory deficits; problem-solving ability; endophenotype

1 Introduction

Obsessive-compulsive disorder (OCD) is character-ized by recurrent, persistent and intrusive thoughts or images that cause anxiety or distress (obsessions), and repetitive behaviors or mental acts aimed at reducing this distress or anxiety (compulsions). Recent studies reported that OCD has a lifetime prevalence of 2%–3% in the gen-eral population[1]. Many neuroimaging and genetic studies of OCD suggest that neurobiological abnormalities play an important role in its etiology and course. Unfortunately, the results of many studies are contradictory, because of the heterogeneous nature of obsessive-compulsive symp-

toms. However, there are indeed some common cognitive characteristics in individuals with OCD[2].

Neuropsychological testing is increasingly recognized as a valid approach to understanding the underlying neuro-biology of OCD. Neuropsychological functions have been proposed as a potential intermediary or, as suggested by Chamberlain *et al.* (2005)[3], an "endophenotype" that lies somewhere between the clinical manifestations of the dis-order and its neurobiological etiology. Several recent studies of unaffected first-degree relatives have reported the exis-tence of endophenotypes in OCD[4-8]. Unfortunately, their findings are inconsistent. Chamberlain *et al.*[4] reported that deficits in cognitive flexibility and motor inhibition may represent cognitive endophenotypes for OCD. Similarly, Menzies *et al.*[5] suggested that motor inhibitory control may mediate the genetic risk for OCD, providing the first evidence for a neurocognitive endophenotype of OCD.

Viswanath et al.[6] showed that deficits in decision-making and behavioral reversal were potential endophenotypes in OCD. Cavedini et al.[7] also found that executive dysfunction may qualify as a suitable endophenotype candidate for OCD. Segalàs et al.[8] reported that OCD patients and their unaffected first-degree relatives showed the same deficits in the execution of non-verbal memory tasks. More recently, Rajender et al.[9] suggested that set-shifting and inhibitory control were shared deficits in patients with OCD and their relatives, and proposed visuoconstructive abilities and delayed verbal recall as potential endophenotypes for OCD.

Memory functions comprise verbal and non-verbal memory. The Rey Complex Figure Test (RCFT) is frequently used in OCD studies of memory. Savage et al.[10] reported that OCD patients were impaired on verbal and non-verbal measures of organizational strategy with the RCFT and the California Verbal Learning Test. These findings are consistent with neurobiological models proposing frontal-striatal system dysfunction in OCD. Moreover, OCD patients are impaired in both verbal and non-verbal memory performance[11]. Recent studies suggest that memory dysfunction in OCD patients is, in part, secondary to an inability to apply efficiently elaborated strategies[12]. Deficits in spatial memory have also been reported in OCD[13]. However, the results of some studies are inconsistent with these findings. Overall, investigations into memory functions in OCD suggest that the impairment of memory may be secondary to organizational deficits, implicating executive dysfunction as the primary contributor to the OCD profile.

Executive functions, also known as higher-order cognitive functions, include set-shifting ability, verbal fluency, and planning and problem-solving ability. The Wisconsin Card Sorting Test (WCST) is one of the most commonly used to assess set-shifting ability. Although Okasha et al.[14] reported that OCD patients had impairment in set-shifting ability on the WCST, most studies found no difference between OCD patients and normal controls. For verbal fluency, findings are inconsistent due to differences in measures. The most common task to assess planning and problem-solving ability is the Tower of Hanoi. Cavedini et

al.[15] found that OCD patients performed this worse than controls. As noted above, many studies suggest executive deficits in OCD, characterized by increased response latencies, perseveration of previous (inappropriate) responses, and difficulties in effectively using feedback to adapt to changing conditions and environments[16].

Family and twin studies support the hypothesis that genetic factors play an important role in the pathogenesis of OCD. Meanwhile, the first-degree relatives of probands with OCD are often examined for subclinical symptoms. The present study aimed to test the hypothesis that cognitive deficits occur not only in OCD patients, but also in their unaffected relatives.

2 Subjects and methods

2.1 Participants This prospective, controlled study was conducted at West China Hospital of Sichuan University, China, and was approved by the Ethics Committee of West China Hospital. We recruited 40 untreated or first-episode patients meeting the DSM-IV[17] criteria for OCD (OCD group) and 48 of their parents (parent group). Untreated patients were defined as those without medication for at least 2 months. Those with a comorbid diagnosis of schizophrenia, mood disorder or other anxiety disorders, substance abuse, Tourette syndrome, or a history of head trauma or neurological disease were excluded. The severity of OCD symptoms was assessed using the 10-item modified Yale-Brown Obsessive Compulsive Scale (Y-BOCS)[18]. Symptoms of depression and anxiety were assessed using the 24-item Hamilton Depression Rating Scale[19].

Meanwhile, 87 healthy individuals were recruited for the control group, matching the patients and their parents in age, gender, education, and hand dominance. The control subjects were interviewed using the Y-BOCS and their scores were <7. Those who had a history of any psychiatric disorder, neurological illness or substance abuse and a known family history of psychiatric disorders were excluded by Mini International Neuropsychiatric Interview[20]. The inter-rater reliability (Kappa) among the psychiatrists was >0.80 for all neuropsychological tests. All participants provided written informed consent.

2.2 Neuropsychological testing battery

2.2.1 Wechsler Memory Scale (WMS) Logical Memory subtest This task measures verbal memory, including immediate and delayed logical memory. Participants heard a short story and were then asked to recall it immediately and after a 30-min delay.

2.2.2 WMS Visual Memory subtest This includes immediate and delayed visual memory and measures non-verbal memory. Participants were shown two geometrical figures, each for 10 s, and then were asked to draw them immediately and after a 30-min delay.

2.2.3 Stroop Color-Word Test, Chinese version This test measures cognitive flexibility and mental set-shifting ability. It consists of a Word subtask (reading common words unrelated to the concept of color) and a Color-Word subtask (reading words that are themselves color names). The four colors used in our study were blue, green, red, and brown. Participants were required to name the colors in which the stimuli were printed, and to disregard their verbal content [i.e., 红 ("red" in Chinese) printed in blue, 绿 ("green" in Chinese) printed in red, 蓝 ("blue" in Chinese) printed in brown, 褐 ("brown" in Chinese) printed in green…In Stroop Word test, participant should read: red, green, blue, brown…; In Stroop Color-Word test, participant should read: blue, red, brown, green…]. The test-retest reliability of the Chinese version of the Word subtask is 0.91 and the Color-Word subtask 0.90[21].

2.2.4 Trail-Making Test (TMT, parts A and B) This test measures the speed of information processing, sequencing, mental flexibility, visual search and motor function. It consists of two parts; in part A, participants were required to make pencil line connections in numerical order between 25 encircled numbers, which were randomly arranged on the test sheet (i.e., 1→2→3→4…); in part B, participants were required to make pencil line connections on another test sheet with 13 encircled numbers and 12 Chinese characters in alternating order, i.e., 1→ 一 ("one" in Chinese) →2→ 二 ("two" in Chinese)→3→ 三 ("three" in Chinese)…. The time required to complete each part of the task was recorded.

2.2.5 Verbal fluency This test measures the spontaneous production of words of a given category within a limited amount of time. Subjects were asked to produce the names of as many kinds of animal as possible in one minute.

2.2.6 Tower of Hanoi This is generally recognized to be sensitive to frontal lobe dysfunction. It consists of a platform with three thin pegs and four disks of different sizes. The disks are placed on the pegs and the subject can move them from one peg to another. The planning time (time between onset of the problem and moving the first ring), the performance time, and the movement time were recorded.

2.2.7 Wisconsin Card Sorting Test-Simplified (WCST-S) This test assesses the "set-shifting" ability of participants. Forty-eight cards were used and performance was assessed by the number of categories completed, number of errors, percentage of perseverative errors, and number of failures to maintain the category set.

2.3 Statistical analyses All statistical analyses used the Statistical Package for the Social Sciences (SPSS) for Windows software, version 17.0, and a two-tailed significance level was set at $P <0.05$. In order to control for the confounding effects of age, linear regression models were used to generate the standardized residuals (ZREs) of scores of age factor. The ZREs were then used in the statistical analyses. The ZREs of performances in neuropsychological tests were compared between groups by one-way analysis of variance (ANOVA), followed by the Bonferroni *post hoc* test.

3 Results

3.1 Description of study population

3.1.1 OCD group *vs* OCD control group (control group I) Forty OCD patients in the OCD group and 40 healthy individuals in control group I were finally included in this study. There were no significant differences between these groups in terms of age, gender, and years of education ($P > 0.05$) (Table 1).

3.1.2 Parent group *vs* parent control group (control group II) A total of 48 OCD parents were included in the parent group and 47 healthy people in control group II. There were no significant differences between these groups in terms of age, gender, and years of education ($P >0.05$).

Table 1. Demographic and clinical data of obsessive-compulsive disorder (OCD) group and control group I

	OCD (*n* = 40)	OCD control (*n* = 40)	t / χ^2	P
Age (years)	21.70 ± 5.73	22.55 ± 5.82	−0.659	0.512
Male:female	13:7	11:9	χ^2 = 0.205	0.651
Education (years)	12.63 ± 2.46	12.50 ± 2.52	0.220	0.826
Mean age at onset (years)	18.35 ± 4.67			
Y-BOCS	25.83 ± 5.14			

Y-BOCS, Yale-Brown Obsessive Compulsive Scale.

Table 2. Neuropsychological performance of obsessive-compulsive disorder (OCD) group, control group I, parent group and control group II

	OCD (*n* = 40)		Control group I (*n* = 40)		Parent group (*n* = 48)		Control group II (*n* = 47)	
	mean	SD	mean	SD	mean	SD	mean	SD
Logical Memory								
Immediate	10.25	4.27	8.44	3.73	10.06	4.01	14.03	3.53
Delayed	7.25	3.81	5.17	3.70	8.06	4.48	12.13	4.13
Visual Memory								
Immediate	19.55	3.19	18.13	3.99	20.11	3.59	22.40	2.34
Delayed	18.75	3.82	17.25	4.63	19.37	4.03	21.45	2.75
Stroop-W time (s)	54.16	9.17	70.80	23.62	74.92	59.37	57.98	11.38
Stroop-CW time (s)	154.94	49.98	181.32	45.24	188.70	62.23	137.81	28.25
TMT-A (s)	42.43	19.10	48.18	14.29	48.47	14.01	38.53	11.38
TMT-B (s)	61.43	22.63	71.43	26.73	69.47	20.32	50.81	14.29
Verbal Fluency	23.28	6.12	19.69	5.10	21.15	5.20	23.48	5.87
Tower of Hanoi								
Planning time (s)	4.69	2.60	4.46	2.26	4.76	4.30	3.55	1.83
Performance time (s)	24.77	7.06	24.25	7.29	20.42	6.81	16.83	4.06
Total score	53.30	12.12	52.24	9.89	52.79	8.77	56.70	8.96
WCST								
Correct	36.58	6.48	32.44	8.69	33.53	4.83	34.42	5.96
Error	10.93	6.66	14.42	9.42	12.51	6.49	10.10	7.82
Perseverative error	2.98	2.84	4.94	4.83	3.38	2.97	2.70	4.18
Non-perseverative error	7.95	4.49	9.44	5.61	9.15	4.36	7.33	4.52
Category	5.33	1.12	4.74	1.48	5.04	1.20	5.35	1.23

Control group I, OCD control group; control group II, parent control group; Stroop-CW, Stroop Color-Word subtask; Stroop-W, Stroop Word subtask; TMT, Trail-Making Test; WCST, Wisconsin Card-Sorting Test.

3.2 Comparison of neuropsychological performance between OCD group, OCD control group, parent group and parent control group Table 2 shows the raw data of the neuropsychological performance of the OCD group, control group I, parent group and control group II.

3.2.1 Neuropsychological performance in OCD group

and control group I OCD patients showed worse performance on logical memory (immediate and delayed) and visual memory (immediate and delayed) than the control group. Worse performance in terms of performance time in the Tower of Hanoi was also found in the OCD group. However, there were no differences in planning time and total score between the two groups, nor were there differences in verbal fluency and the WCST (Table 3).

3.2.2 Neuropsychological performance in OCD and parent groups There were no differences between the OCD and parent groups in gender ($F = 1.408$, $P = 0.144$) and years of education ($F = 1.453$, $P = 0.052$). Nor were there any differences between these groups in any of the tests (Table 3).

3.2.3 Neuropsychological performance in parent and parent control groups The parent group performed worse on delayed logical memory and delayed visual memory than the parent control group. These groups differed in the performance time of the Tower of Hanoi, but not in any of the other tests (Table 3).

3.2.4 Neuropsychological performance in OCD and parent control groups The OCD group performed worse on immediate logical memory, delayed logical memory, immediate visual memory, delayed visual memory, and performance time in the Tower of Hanoi than the parent control group (Table 3).

Table 3. Mean differences in standardized residuals of neuropsychological performance by multiple comparisons among obsessive-compulsive disorder (OCD), control I, parent and control II groups

	OCD *vs* control I	OCD *vs* parents	OCD *vs* control II	Parent *vs* Control I	Parent *vs* control II	Control I *vs* control II
Logical Memory						
Immediate	−0.94**	−0.22	−0.58*	0.72**	−0.36	0.36
Delayed	−1.12**	−0.21	−0.82**	0.91**	−0.61**	0.29
Visual Memory						
Immediate	−0.81**	−0.08	−0.61*	0.73**	−0.50	0.20
Delayed	−0.68**	−0.11	−0.60*	0.58*	−0.53*	0.08
Stroop-W time (s)	−0.10	0.05	−0.11	0.15	−0.15	−0.01
Stroop-CW time (s)	0.38	0.28	0.08	−0.11	−0.20	−0.30
TMT-A (s)	0.28	0.13	0.09	−0.14	−0.05	−0.19
TMT-B (s)	0.51	0.20	0.26	−0.31	0.05	−0.25
Verbal Fluency	−0.05	0.20	−0.04	0.24	−0.24	0.01
Tower of Hanoi						
Planning time (s)	0.40	0.38	0.26	−0.02	−0.12	−0.14
Performance time (s)	1.13**	0.39	0.91**	−0.74**	0.52*	−0.22
Total score	−0.35	−0.23	−0.26	0.12	−0.04	0.09
WCST						
Correct	0.31	0.26	0.11	−0.05	−0.14	−0.19
Error	0.12	−0.08	0.14	−0.20	0.23	0.02
Perseverative error	0.08	−0.14	0.25	−0.22	0.39	0.16
Non-perseverative error	0.14	−0.01	0.03	−0.15	0.04	−0.11
Category	−0.03	0.10	−0.09	0.13	−0.20	−0.06

Control group I, OCD control group; control group II, parent control group; Stroop-CW, Stroop Color-Word subtask; Stroop-W, Stroop Word subtask; TMT, Trail-Making Test; WCST, Wisconsin Card-Sorting Test. *P <0.05; **P <0.01.

4   Discussion

So far, many studies have reported that patients with OCD exhibited memory impairments[8,10,11,22-25]. Memory deficits are among the most consistent neurocognitive deficits in patients with OCD, and may reflect changes in the frontostriatal circuits involved in the neurobiology of OCD[10,11,26]. fMRI studies show reduced activation of the lateral orbitofrontal cortex, lateral prefrontal cortex and parietal cortex in OCD patients and their unaffected relatives[27]. However, only a few studies on cognitive impairments in OCD relatives have been reported[5-9,28].

In our prospective and controlled study, we investigated the neurocognitive performance of OCD patients, their parents and healthy controls. We found that the OCD patients performed worse in the logical memory (immediate and delayed) and visual memory (immediate and delayed) tests than the control groups. These findings are consistent with previous studies[10-12]. We also found that the parents of OCD patients performed significantly worse than healthy controls (control group II) in the delayed logical and delayed visual memory tests, which is in line with the findings of Rajender[9].

However, in our study, although parents of OCD patients showed no impairment in immediate logical and immediate visual memory, there were no significant differences between OCD patients and their parents in all the tests. This result did not support the findings of Rajender (2011)[9], which showed significant impairments in immediate and delayed visual memory in OCD patients compared with their relatives and controls, and significant differences on domains of attention, planning time and visual memory between OCD patients and their relatives. This discrepancy may be due to the difference in sample size between the two studies.

In our study, OCD patients and their parents were similar in impaired delayed memory functioning, both verbal and non-verbal. They were both slower to analyze the features of stimuli than healthy controls. In delayed memory tasks, they used a poorer organizational strategy than healthy controls. Such an impairment in delayed memory in patients with OCD has also been reported in

previous studies[11,29] and is suggested to be due to the failure to use appropriate organizational abilities. Sawamura *et al.* (2005)[30] used a variation of the time-limited verbal learning task and reported that OCD patients exhibit impairments in recall and recognition, with a decrease in the spontaneous use of semantic strategies. Clinically, many OCD patients remain doubtful even when faced with the core critical object, thus rendering a primary problem with memory unlikely[31]. For example, many patients engage in repetitive checking behavior, which might be a failure to appropriately encode memories for self-actions[3]. Our findings suggest that impaired working memory, including delayed verbal and non-verbal memory, may be a neuropsychological candidate endophenotype of vulnerability to OCD. Endophenotypes represent intermediate measures (or markers) between top-level symptoms and bottom-level genetic contributions[32]. Twin and family studies have demonstrated that genetic factors play an important role in OCD. Memory impairment might be regarded as a cognitive endophenotypic marker for vulnerability to OCD, and an intermediate between clinical symptoms and genetic load.

The memory dysfunction in OCD seems to be largely mediated by organizational deficits during the encoding phase that in turn makes recall more difficult. Therefore, we hypothesized that the memory impairment in OCD might be responsible for the failure of organizational strategies. This is consistent with the organizational model of Savage *et al.*[26] which posits that disrupted frontostriatal circuits induce executive dysfunctions, which result in secondary memory impairment.

Memory deficits in the parents of OCD patients are probably attributable to genetic influence, a key factor in the development of brain functions. Although our primary findings suggest that the memory impairment in OCD may exhibit familial aggregation, further investigation into the neuropsychological deficits of OCD relatives in larger samples is needed.

Moreover, we found that both OCD patients and their parents had worse performance times in the Tower of Hanoi test, indicating the impairment of executive functioning in

OCD, such as problem-solving. Our results contradict previous reports, which found deficits in planning time in the unaffected relatives of OCD probands[33]. This discrepancy may be due to the heterogeneous symptoms. Recent studies suggested that the problem-solving impairment was due to deficits in spatial working memory, thus resulting in an increased difficulty in keeping an action plan in memory[34]. Our findings suggest that impairment of executive functioning, especially problem-solving, may also be a candidate neuropsychological endophenotype of vulnerability to OCD.

However, certain limitations of this study are worth noting. First, the sample size was modest. Studies with larger independent samples of unaffected relatives of OCD probands are required. Second, the symptoms in this study population were heterogeneous.

In summary, the primary issue affecting OCD research is the heterogeneity of symptoms. Dividing patients into mutually exclusive subtypes is difficult as they are rarely mono-symptomatic[35]. Results of such neuropsychological assessments can thus provide clinical researchers with important cues in their quest for a better understanding of OCD.

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