

## Cognitive functions in remitted unipolar female depressive patients during maintenance treatment with antidepressants

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**Aim:** Several studies have shown that depression is associated with cognitive deficits, however, it is not clear if cognitive impairment persists upon recovery. The authors' goal was to examine a neuropsychological performance in unipolar depressive female patients during remission.

**Methods:** The Wisconsin Card Sorting Test (WCST), the Verbal Fluency Test (VFT) and the Giessen Maze Test were administered to 21 remitted female patients and matched 17 control subjects. All patients had been for at least 6 months on maintenance treatment with antidepressants before the study.

**Results:** Patients achieved worse results than the control group on the Giessen Maze Test. No differences between both groups in WCST and VFT were noticed.

**Conclusions:** These results point to deficits of visuospatial cognitive functions mostly related to the right hemisphere in unipolar patients which persisted despite of long-term remission.

*Key words:* depression, remission, cognitive function

### Introduction

Cognitive deficits constitute an important part of the symptomatology of depression. Most of the studies using neuropsychological tests in depressive patients reported impairments of working memory, executive functions related to frontal lobes and abnormalities of performance on visuo-spatial tasks. Depressed patients show significantly worse performance on “frontal lobe tests” as the Wisconsin Card Sorting Test, Trail Making Test, Stroop test and word fluency test compared to healthy controls [1, 2, 3, 4, 5, 6, 7, 8].

Functional neuroimaging studies have revealed a decrease of regional cerebral blood flow (rCBF) and glucose metabolism in the frontal cortex [9, 10, 11, 12]. Decreased rCBF in medial prefrontal cortex correlated with cognitive and attention impairment [13, 14]. Moreover, relationships between cognitive impairment in mood disorders and structural brain abnormalities such as deep white matter hyperintensities [15, 16] or a reduction of midsagittal areas of brain structures measured on MRI [17], were described.

Cognitive disturbances in affective disorders were also related to age [18, 19], number of hospitalisations [20] and number of affective episodes [21]. Conflicting results concerning the impact of depression severity on impairment on cognitive tasks were reported. Some authors found correlation between task performance and severity of depression measured with Hamilton Rating Scale for Depression [22, 23, 24, 25], while others failed to confirm these findings [4,18].

Several studies reported a positive effect of successful antidepressant treatment on cognitive functions in depressed patients. Normalisation of verbal fluency in severely depressed in-patients [4] and improvement of memory task [21, 22] after successful treatment with antidepressants were reported.

However, deficits on memory tasks and executive function may persist upon recovery [4, 26, 27] especially in elderly patients with severe depression [18] and elderly depressed patients with higher degree of cognitive impairment during acute episodes [27].

Since a substantial proportion of unipolar depressed patients need maintenance treatment, the influence of antidepressants on cognitive function should be noted. Both in healthy volunteers and in depressed patients tricyclic antidepressants were shown to induce impairment of cognitive function [29, 30, 31] while fluoxetine [30], citalopram [31] and moclobemide [32] do not adversely affect cognitive functions.

The objective of the present study was to assess the cognitive abilities in remitted women with major depressive disorder, during maintenance treatment with antidepressants using selected neuropsychological tests.

## **Methods**

### **Patients**

Twenty-one euthymic female outpatients (mean age  $46,3 \pm 8,7$ ) who met the DSM-IV criteria for major depressive disorder, recurrent, were included in the study. The remission was defined as a score 7 or less on the Hamilton Rating Scale for Depression (HRDS). A minimum of 6 month's remission and 2 previous depressive episodes were necessary to fulfil the inclusion criteria. Patients with a history of cerebrovascular disease, risk factors for arteriosclerosis (hypertension, hypercholesterolemia), dementive disorder and head injury were excluded. A sample was recruited from the outpatient clinic at the Department of Adult Psychiatry in Poznań. From all patients with affective disorders 21 women and 2 men who fulfilled inclusion and exclusion criteria were chosen. Since only 2 male patients were found, they were not included into further analysis. The selection of only female patients is justified since sex related differences in intrahemispheric organisation were described.

All patients were on stable doses of antidepressants: fluoxetine (20 mg/day, n=8), moclobemide (300-600 mg/day, n=4), mianserin (60 mg/day, n=2), dibenzepine (240-480 mg/day, n=3), and clomipramine (125mg/day, n=4)

The control group consisted of 17 healthy females (mean age  $45,5 \pm 7,4$ ) matched for age and level of education with experimental group, recruited from the medical staff

of our Department. Control subjects fulfilled the same exclusion criteria as patients, as well as had a negative history of psychiatric disorders.

### Neuropsychological assessment

1. The Wisconsin Card Sorting Test (WCST) was administered in the computerised version prepared by Heaton (33) for assessment of working memory and executive functions. Number of trials, percent of perseverative and non-perseverative responses, numbers of correct responses and trials to complete first category were calculated.
2. Two tasks of verbal fluency (VFT) were used:
  - a. The category task: generating words for animals, fruits and vegetables as many as possible during a one-minute period.
  - b. The letter test: generating words beginning with letters F, A, S as many as possible within one minute.
3. The Giessen Maze Tests (GMT) were used for the assessment of visual and motor co-ordination (simple mazes) and executive functions ("frontal" complex mazes). The Giessen Maze Test has been introduced as a new tool for evaluation a frontal deficit and cortical-subcortical circuitry dysfunction in patients with schizophrenia [34, 35]. In this study this test was used for the assessment of cognitive disturbances in depression. The subject has to move the cursor through the concomitant 12 mazes displayed on the computer screen. The following parameters are analysed: the time of performance of the particular maze, the length of the path of the cursor (route) numbers of error 1 (cursor touches the wall) and error 2 (total duration of acoustical feedback when the cursor touches the walls of the maze).

### Statistical analysis

The statistical significance was assessed by Student's t test for independent groups. Relationships between clinical characteristics and neuropsychological scores were evaluated by Pearson's linear correlation coefficient.

### Results

The characteristics of two groups with respect to age, education, duration of illness, age of onset, number of previous episodes and duration of remission are given in Table 1. Age and level of education did not differ between the remitted patients and healthy controls.

The performance on WCST did not differ between the euthymic patients and controls. No significant differences in the percentage of perseverative responses and number of cards to complete first category, non-perseverative and perseverative errors were found. There was no significant difference in results of verbal fluency between the patients and the normal controls as well. (Table 2)

Table 1

Group characteristics (mean  $\pm$  SD)

	Euthymic patients N=21	Control group N=17
Age	40,3 $\pm$ 8,7	45,5 $\pm$ 7,4
Education (y)	13,3 $\pm$ 1,7	15 $\pm$ 2
Length of illness (y)	10 $\pm$ 8	
Age of onset to illness	30 $\pm$ 10	
Number of episodes	3 $\pm$ 2	
Duration of remission (months)	15 $\pm$ 8	

Table 2

Results of Wisconsin Card Sorting Test (WCST) and Verbal Fluency (VF) in euthymic unipolar patients and in control group (mean  $\pm$  SD)

	Euthymic patients N=21	Control group N=17
WCST		
Number of trials	93 $\pm$ 20	91 $\pm$ 18
% of perseverative errors	13,9 $\pm$ 9	12 $\pm$ 5,6
% of non-perseverative errors	11 $\pm$ 5	9 $\pm$ 4
% of conceptual level responses	68 $\pm$ 20	74 $\pm$ 10
number of correct categories	5 $\pm$ 2	6 $\pm$ 0,5
Trials to complete first category	15 $\pm$ 14	12 $\pm$ 3
Verbal fluency		
Category test	45 $\pm$ 10	50 $\pm$ 9
Letter test	40 $\pm$ 13	36 $\pm$ 8

On the Giessen Maze Test patients made slightly more errors of type 1 and 2 and the time of performance was longer. It reached a statistical significance on maze 4 ( $161,5 \pm 47$  vs.  $116,8 \pm 43,8$ ,  $p < 0.0005$ )

We also investigated the effect of age, number of previous episodes and age of onset of disease on results of the neuropsychological tests. The age was correlated with the time of performance of mazes 4, 5, 9 (table 3) and the route of maze 1 ( $r=0,58$ ,  $p=0,02$ ), 4 ( $r=0,64$ ,  $p=0,009$ ), 6 ( $r=0,52$ ,  $p=0,04$ ) and 9 ( $r=0,55$ ,  $p=0,03$ ). It means that the older patients had a worse performance in the Giessen Maze Test. In further analysis the partial correlation coefficient controlled for age of patients, between age of onset of depression and results of GMT was calculated. The age of onset correlated with time of performance of maze 1 ( $r=0,62$ ,  $P=0,03$ ) and maze 2 ( $r=0,65$ ,  $p=0,02$ ). There was no significant correlation between the number of previous episodes and performance on WCST, VFT and GMT.

Table 3  
Correlation between patients' age, age of onset of disease controlled for age (partial correlation coefficient) and time of performance on Giessen Maze Test

Time of performance - labyrinth	age		age of onset to disease controlled for age	
	R	p	R	p
1	0,51	0,052	0,02	0,08
2	0,43	0,10	0,05	0,02
3	0,32	0,24	0,42	0,12
4	0,04	0,01	0,51	0,00
5	0,51	0,046	0,47	0,12
6	0,40	0,00	0,40	0,11
7	0,37	0,17	0,31	0,32
8	0,20	0,20	0,57	0,053
9	0,51	0,042	0,40	0,10
10	0,00	0,73	0,20	0,35
11	0,24	0,32	0,23	0,46
12	0,30	0,12	0,52	0,07

### Discussion

Our results point on mild neuropsychological impairment on selected tasks in euthymic female patients with recurrent major depressive disorder. Results of the WCST and the VFT in the patient group were similar to those found in normal controls. It suggests that working memory, executive and verbal functions be not disturbed in a group of euthymic female patients during maintenance treatment with different classes of antidepressants. Our results are consistent with data obtained by Trichard et al. [4] who found a normalisation of verbal fluency with successful treatment in a group of 23 severely depressed in-patients before discharge from the hospital. Six of their patients were also assessed at 5-6 months after inclusion and at this point the patient performance was similar to control group. Our findings indicate that functional abnormalities of frontal lobes probably contribute a state-dependent deficit in depression. This is in line with some neuroimaging studies pointing on the increase of prefrontal metabolism and rCBF after successful antidepressant treatment [9, 10, 11, 12]. It should be also mentioned that some authors found normal verbal functions even during a depressive episode [22, 25].

On the Giessen Maze Test, the time of performance was longer in depressive patients. It was particularly evident during more difficult tasks, especially those, which required efficient executive functions such as labyrinth 4. This finding correspond with the hypothesis of Weingartner et al. [36] who suggested that patients with depression

had difficulty with “effortful tasks” as compared to “automatic tasks”. Longer time of performance, impairment of psychomotor co-ordination and visuospatial working memory may suggest a disturbance of spatial functions in a group of euthymic female patients with major depressive disorder. Our results suggest that psychomotor speed and visuo-spatial functions (mostly connected with right hemisphere and cortical-subcortical circuitry) do not normalise after successful treatment and may persist beyond a clinical improvement. The growing number of evidences point to a relationship between depression and right hemisphere function. Several investigators using neuropsychological tests have suggested that depressed patients perform worse on spatial task than healthy subjects [37, 38, 39, 41]. A number of studies using event-related potentials [42, 43, 44, 45], EEG [46, 47] simple reaction time task [48], confirmed abnormal function of the right hemisphere in patients with depression and in subjects experienced induced depressed mood. Liotti and Mayberg [49] analysing results of functional neuroimaging studies and neuropsychological deficits in depression argued that negative mood affects right hemisphere function by interacting with a right-hemisphere dominant mechanism of attentional control. Since resolution of symptoms of depression was accompanied by normalisation of brain metabolism as it was reported by means of functional neuroimaging studies it may point that disturbances of right hemisphere functions are reversible in remitted state. Our results, indicating poor performance on Giessen Maze Test during remission may imply that some dysfunctions are traits of patients with a unipolar affective disorder.

We also found worse results of the Giessen Maze Test especially the time of performance, which is related to a decrease of psychomotor speed, were related to the age of patients and the later onset of affective disorder. These relationships were not observed in control subjects. The nature of neuropsychological dysfunction persisting upon recovery from depression is not clear. Some brain imaging studies point that discrete brain lesion may play a role. The worse neuropsychological performance was related to larger amount of white matter hyperintensities (WMH) and later age of onset of depression. [50]. Both late and early onset in elderly depressed patients showed mild abnormalities in some “right hemisphere” cognitive skills. It was also postulated that presence of mild to moderate depression may result in premature “ageing” of specific cognitive abilities [51]. Repeated exposure to an elevated level of glucocorticoids during depressive episodes was suggested as a potential neurotoxic factor [52]. Contrary to other studies describing the correlation between the worse neuropsychological performance and number of depressive episodes [53], number of hospitalisations [20] we did not find such relationship. This is probably due to a small sample of patients and the fact that 43% of patients had only 2 previous episodes of depression.

The main finding of our study which implicates a longer time of performance in spatial tasks and a positive correlation between the time of performance and age and age of onset of disease during remission may point to a subtle psychomotor slowing as a trait of patients with unipolar depression.

All of our patients were on stable doses of different classes of antidepressants for at least 6 months. Most of them received novel antidepressants but the group was too small to analyse the influence of novel and older antidepressants on the results of neuropsychological tasks.

### Conclusions

1. No disturbances of working memory, executive and verbal functions in a group of female patients during symptomatic remission of major depressive disorder were found.
2. Despite of long-term remission, patients showed a decrease of psychomotor speed and visuo-spatial functions related to age and later onset of the illness.

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