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# Neuropsychological functioning across different states of bipolar disorder: mania, hypomania and depression

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**Summary**

**Aim:** The aim of the study was to compare neuropsychological functioning across different states of bipolar disorder: mania/hypomania and depression.

**Method:** Cognitive functions were examined in 30 patients with bipolar disorder aged 18–68 who fulfilled DSM-IV criteria for a depressive episode (Hamilton Depression Rating Scale score ≥11) and 30 patients aged 23–68 who fulfilled DSM-IV criteria for a manic or hypomanic episode (Young Mania Rating Scale ≥11). The comparison group consisted of 30 healthy individuals aged 23–71 with no history of psychiatric or neurological disorders. A neuropsychological battery assessed executive functions and fluency, working memory and attention, psychomotor speed and reaction time.

**Results:** Patients with bipolar disorder showed cognitive dysfunctions in working memory, fluency, attention, psychomotor speed and reaction time in relation to the comparison group. The manic/hypomanic group showed impairment on the Wisconsin Card Sorting Test (WCST), a measure of executive functions, which was not observed in depressive patients. Manic/hypomanic patients had a significantly greater impairment of executive functions than the depressed patients.

**Discussion:** The results of this study are partly consistent with the results of previous studies in this area.

**Conclusions:** A poorer neuropsychological performance was observed in different states of bipolar disorder but in the manic/hypomanic state the cognitive deficits associated with executive functions were more serious.

**bipolar disorder/cognitive dysfunctions/executive functions/working memory/neuropsychological tests.**

## INTRODUCTION

Previous research has shown that cognitive dysfunctions are present both during the acute phases of bipolar illness and during remission. The cognitive function is impaired in bipolar disorder in several areas, such as attention, executive function, verbal memory and psychomotor speed [1-3]. However, the relationship between the clinical state and cognitive deficits is still unclear. Cognitive impairment during the euthymic phase is well documented [4–10], but research comparing cognitive functions in different states of bipolar disorder is scarce and its results are ambiguous. Some studies point to sim-

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ilar cognitive dysfunctions in different clinical states [2,11], but others show that cognitive function is more impaired during hypomania/mania than during the depressive period [12-15].

The aim of the present study was to compare neuropsychological functioning across different states of bipolar disorder: mania/hypomania and depression.

## METHOD

The study was performed at the Central Clinical Hospital in Łódź, Poland. The patients' diagnosis was determined by a psychiatrist using the DSM-IV criteria, the 18-item Hamilton Depression Rating Scale (HDRS), and the Polish version of the Young Mania Rating Scale (YMRS). Patients with other disorders that could be related to neuropsychological impairment (a significant physical or neurological illness, a history of head injury, neurodegenerative disorder, substance abuse or dependence in the past year, intellectual disability, electroconvulsive therapy (ECT) in the past year) were excluded. The study group consisted of 60 patients with DSM-IV diagnosis of bipolar I or II disorder. Thirty depressed bipolar patients (HDRS score ≥11) and 30 patients in the manic or hypomanic episode (YMRS ≥11) participated in the study. The control group consisted of 30 healthy volunteers without a history of psychiatric or neurological disorders and substance abuse. We checked that the control group had no first-degree relatives with a diagnosis of bipolar disorder. There were no significant differences between patients and controls with regard to age, gender or education level. Patients with psychotic symptoms and severe mania were excluded because of their inability to complete neuropsychological tests. The study was approved by the local ethics committee and a written informed consent was obtained from all participants.

### Cognitive assessment

A battery of neuropsychological tests were administered to assess working memory and executive functions, attention, psychomotor speed and reaction time. All cognitive assessments were conducted in a single session by one qualified psychologist. The following tests were used.

- Trial Making Test (TMT): part A of the test measures psychomotor speed and part B measures the ability to shift strategy and assess executive functions and visuospatial working memory. The outcome considered was the time it took participants to complete each part.
- The Controlled Oral Word Association Test FAS: this test measures verbal fluency and is also a sensitive assessment of executive functions because it requires the participant to come up with their own strategy. Participants are asked to generate as many words as possible beginning with the letters F, A and S, in three 1-minute trials. The variable considered was a number of correct responses.
- Stroop Color-Word Interference Test (SCWT): this test was used to evaluate selective attention and executive functions. Part 1 requires the participant to read 50 colour names written in black ink, as quickly as possible, which is a measure of verbal ability and attention. In part 2, the colour words are printed in incongruent ink colours, and the participant is asked to name the colour instead of reading the words. These conflicting instructions measure the ability to change demands and suppress a habitual response in favour of an unusual one. We measured the time it took the participants to complete each part.
- Wisconsin Card Sorting Test (WCST): it assesses working memory and executive functions. The following outcome variables were considered: the number of perseverative errors, the number of categories completed, the conceptual level achieved and the number of trials to complete the first category.
- The N-back test, 1-back version; the test measures visuospatial working memory and reaction time. The considered variables included a number of correct responses and reaction time.

### Statistical analysis

The three groups' (depressed, manic or hypomanic, and healthy participants) demographic characteristics were compared with the use of analysis of variance (ANOVA); clinical variables were compared using the *t*-test and the chi-square test, as appropriate. Group differences in neuropsychological functioning were tested by one-way ANOVA or Welch test, depending on the homogeneity of variance, followed by the Bonferroni or T3 Dunnett tests *post hoc*.

## RESULTS

### Clinical and demographic characteristics

The clinical and demographic characteristics of the bipolar patients and healthy controls are shown in Table 1.

**Table 1.** Demographic and clinical characteristics of depressed, manic/hypomanic and healthy comparison subjects

| Characteristics | Depressed group (N=30) | | Hypomanic or manic group (N=30) | | Healthy comparison group (N=30) | | ANOVA | |
|---|---|---|---|---|---|---|---|---|
| | M | SD | M | SD | M | SD | F | df |
| Age (years) | 45,6 | 12,6 | 48,1 | 11,5 | 46,2 | 12,2 | 0,35 | (2,87) |
| Educational level (years) | 13,5 | 3,2 | 13,3 | 2,4 | 13,8 | 2,7 | 0,31 | (2,87) |
| | | | | | | | t | df |
| Age at onset (years) | 33,7 | 10,8 | 35,6 | 10,5 | - | - | -0,68 | 58 |
| Duration of illness (years) | 12,4 | 8,4 | 12,4 | 9,3 | - | - | 0,02 | 58 |
| Numer of episodes | | | | | | | | |
| Total | 9,4 | 6,5 | 9,7 | 6,9 | - | - | -0,10 | 58 |
| Manic/hypomanic | 2,9 | 2,8 | 5,0 | 4,1 | - | - | -2,26* | 52 |
| Depressed | 6,5 | 4,6 | 4,7 | 3,9 | - | - | 1,68 | 58 |
| Numer of hospitalizations | 3,2 | 1,7 | 4,2 | 2,8 | - | - | -1,63 | 47 |
| Hamilton Depression Scale score | 20,4 | 8,1 | - | - | - | - | - | - |
| Young Mania Rating Scale score | - | - | 19,4 | 8,7 | - | - | - | - |
| | N | % | N | % | N | % | χ2 | df |
| Sex | | | | | | | | |
| Female | 18 | 60 | 18 | 60 | 20 | 67 | | |
| Male | 12 | 40 | 12 | 40 | 10 | 33 | 0,480 | 2 |
| Previous psychotic symtoms | 10 | 33 | 17 | 57 | - | - | 3,30 | 1 |
| Mental disorders in family | 6 | 20 | 7 | 23 | - | - | 0,98 | 1 |
| Bipolar Type I | 12 | 43 | 27 | 90 | - | - | 15,56*** | 1 |
| Medication | N=28 | | N=29 | | | | | |
| Mood stabilizers | 28 | 100 | 29 | 100 | - | - | - | |
| Antidepressants | 22 | 79 | 2 | 7 | - | - | 30,02*** | 1 |
| Neuroleptics | 10 | 36 | 25 | 86 | - | - | 14,42*** | 1 |
| Antycholinergics | 10 | 36 | 7 | 24 | - | - | 1,10 | 1 |

*p<0,05. ***p<0,001

As shown in Table 1, statistical analysis revealed no significant differences in the participants' demographic variables regarding gender, age and educational level. The patient groups

showed no significant differences regarding age at onset, duration of illness, total number of episodes, number of depressive episodes, number of hospitalizations, previous psychotic symptoms, and family history of mental disorders. However, the manic or hypomanic group had significantly more manic episodes than the depressive group and in the manic group there were more patients with bipolar I diagnosis than in the depressive group. All patients were receiving drug treatment, but in three cases information on medicines that were being taken was not available. All patients were taking a mood stabilizer. Regarding antidepressant treatment, it was significantly more common among patients in the depressive state, and antipsychotic treatment was significantly more common in patients with hypomania/mania.

### Cognitive assessment

Neuropsychological performance in manic/hypomanic and depressive bipolar patients and a comparison with the healthy control group are presented in Table 2.

**Table 2.** Neuropsychological performance of depressed, manic or hypomanic and healthy comparison subjects

| Variables | Depressed group (N=30) | | Hypomanic or manic group (N=30) | | Healthy comparison group (N=30) | | ANOVA | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | M | SD | M | SD | M | SD | F | df | P | Boferroni/ T3 Dunnet Post Hoc Test* |
| Wisconsin Card Sorting Test | | | | | | | | | | |
| Categories completed | 4,7 | 2,1 | 3,5 | 2,4 | 5,7 | 0,6 | 10,96 | (2,87) | <0,001 | M<D,C |
| Perseveratives errors | 14,0 | 11,9 | 24,4 | 17,5 | 10,6 | 7,5 | 9.09 | (2,87) | <0,001 | M<D,C |
| Conceptual level achieved | 64,6 | 11,8 | 50,0 | 23,1 | 67,3 | 8,1 | 10,56 | (2,87) | <0,001 | M<D,C |
| Trials to complete first category | 24,5 | 20,1 | 31,7 | 23,4 | 17,2 | 12,9 | 4,24 | (2,87) | 0,017 | M<C |
| Stroop A (sec.) | 28,1 | 8,6 | 29,8 | 13,4 | 21,8 | 2,8 | 6,01 | (2,86) | 0,004 | D,M<C |
| Stroop B (sec.) | 84,3 | 30,1 | 78,7 | 22,5 | 60,1 | 18,5 | 8,24 | (2,86) | 0,001 | D,M<C |
| TMT A (sec.) | 54,8 | 35,0 | 45,1 | 17,6 | 34,7 | 20,1 | 4,67 | (2,86) | 0,01 | D<C |
| TMT B (sec.) | 152,1 | 122,8 | 137,7 | 93,9 | 84,7 | 51,8 | 4,26 | (2,86) | 0.02 | D,M<C |
| FAS | 11,4 | 3,5 | 13,3 | 5,6 | 16,6 | 4,2 | 9.15 | (2,87) | <0,001 | D,M<C |
| N – back | | | | | | | | | | |
| Correct | 13,3 | 6,3 | 10,7 | 5,7 | 17,9 | 5,9 | 9,96 | (2,76) | <0,001 | D,M<C |
| Reaction Time | 1289 | 406 | 1155,8 | 360,5 | 946,3 | 432,8 | 3,16 | (2,73) | 0,48 | - |

D – depressed, M – manic or hypomanic, C – healthy comparision. Groups on the left-hand side of the equation had worse neuropsychological performance.
*p<0,05.

Both bipolar groups displayed poorer neuropsychological performance on measures of verbal working memory and verbal fluency, which is related to frontal executive function. Manic/hypomanic and depressive patients obtained lower scores on the Stroop Test A and B and on the Controlled Oral Word Association Test FAS than healthy controls.

The manic/hypomanic patients also showed neuropsychological impairment on the measure of frontal executive functions (WCST). They made more perseverative errors, which revealed difficulties in adaptation to changing conditions, completed fewer test categories, needed more trials to complete the first category and achieved a lower conceptual level. On the WCST the man-

ic/hypomanic patients had lower scores than both controls and the depressed patients, whereas depressed patients performed as well as controls. Both bipolar groups were also impaired on visuospatial working memory measured by the N-back test. The depressed patients scored lower on some attentional tasks (TMT part A) and both patient groups scored lower on the same strategy shifting tasks (TMT part B).

## DISCUSSION

In the TMT part A and B depressed patients and hypomanic/manic patients obtained similar results, which were significantly different from those of controls. This indicates the presence of disorders in visuospatial working memory. A prolonged time of completing TMT part A may be caused by disorders in attention continuity, whereas a significantly longer time of completing part B may be the result of disorders in attention shifting and difficulties in visual searching. It may also be caused by deficits in complex mechanisms of cognitive control that is performed by executive functions, which suppress learned reactions and supervise a way of acting consistent with instructions. These deficits indicate disorders in functioning of the dorsolateral part of the prefrontal cerebral cortex. The results obtained are consistent with the previous study of Basso et al. [11], and indicate a significantly worse performance in the TMT part A and B by patients in the periods of mania and depression compared with healthy persons. The study by McGrath et al. [16] also confirms a significantly worse performance in the TMT by patients with mania as compared with healthy persons, whereas in the study by Martinez-Aran et al. [7] patients in the period of depression scored worse on both parts of the TMT than healthy persons. However, we observed no significant differences on this test between patients in the hypomania state and healthy persons. In a study by Mahli et al. [17] there were no significant differences in performance in the TMT part A and B between patients in the period of depression and healthy persons, while patients in hypomania performed significantly worse than healthy persons only in part A. Similar results were obtained by Mahlberg et al. [18]. Regarding the Stroop test, patients with depression and those with hypomania/mania achieved similar scores on both parts, but scored significantly worse than healthy controls. The results highlight the patients' disorders in attention selectiveness and control associated with executive functions that are responsible for suppressing well-learned reactions (reading) and following instructions which demand an untypical reaction (naming the colour of the print). These disorders indicate a dysfunction in the supraorbital part of the prefrontal area of the brain. Neuroimaging studies of the brain performed on patients who were doing the Stroop test indicate a lowered activity in the left part of the supraorbital cerebral cortex in patients with bipolar disorder in various phases of the illness [19,20]. Previous research has indicated a significantly worse performance on the Stroop test by patients in the period of mania or hypomania [7,17,21,22] as compared with a control group.

Scores on the WCST were significantly worse only in the mania/hypomania group as compared with healthy persons, but patients in the depression state had similar results to those in the control group. This suggests that disorders in executive functioning affect patients in the period of hypomania or mania. Patients in this group needed many more attempts to complete the first category of WCST (on average, they completed it only with the 32$^{nd}$ card). Some patients did not successfully complete any category, while healthy controls completed properly at least 4 categories. Moreover, patients had a significantly lower percentage of answers that were consistent with the logical concept and they made more than twice as many perseverative errors. These results indicate that the patients' groups had serious difficulties in analyzing the informative context and disorders in forming a logical concept. Deficits were observed in planning and controlling one's activity and also in adapting it to the changing conditions (rigidity and schematicity of acting were revealed). The results of the WCST are related to the activity in the dorsolateral and ventrolateral parts of the prefrontal cerebral cortex: the dorsolateral part is responsible for discovering the rule that governs cards distribution, and the ventrolateral part is in charge of adjusting a working strategy [23].

The results I have obtained in the group of patients in the period of hypomania or mania are consistent with reports from other researches. Many of the existing studies indicate disorders in executive functions measured with the WCST in this group of patients [7,12,16,24]. As far as patients in the depressive phase are concerned, the study by Martinez-Aran et al. [7] shows that they made significantly more perseverative errors in the WCST than healthy persons, yet there were no differences in the number of properly completed categories between those groups. On the other hand, in the study by Mahli et al. [17] there were no statistically significant differences in performance on the WCST between patients in depression and healthy controls. Patients in depression and those in hypomania/mania obtained similar results on the N-back test, but scored significantly worse than healthy controls (they gave fewer correct answers). Moreover, patients in depression had longer reaction times than controls, which indicates disorders in visuospatial working memory. To perform the test correctly, the person needs to keep a number in their working memory and to press it on the keyboard when another number appears (1-back version). The correct performance is also dependent on good visual-motor coordination and on suppressing the dominant reaction to press the number that is currently seen on the screen. In the hypomania/mania patients no prolongation of time reaction was observed in the N-back test, which suggests that longer times of completing the TMT and the Stroop test result from disordered processes of working memory and supervisory control over executive functions.

The functional magnetic resonance imaging of bipolar patients and healthy persons doing the N-back test in a study by Frangou et al. [23] uncovered some differences in brain activity only with a greater burdening of working memory (versions 1-, 2-, 3-back). In healthy persons, this resulted in increased activity in the dorsal part of the prefrontal cerebral cortex and in the frontal part of the cingulate gyrus. In the group of patients increased activity was observed in the upper part of the frontal area (B10), which is responsible for keeping the superior goal in memory while processing information of secondary meaning. Some studies comparing the functioning of the working memory measured with the N-back test in patients with bipolar disorder and healthy persons show [26] working memory impairments in patients in the depressive state. But in another study [27] patients in the period of remission had lower scores on the N-back test versions 2 – and 3-back than healthy persons. Similar results were obtained by Adler et al. [28], who showed worse performance in the 2-back version among the examined patients as compared with healthy persons, but in the study by Monks et al. [29] there were no statistically significant differences in the 2-back test between the groups of bipolar patients and healthy persons.

Results obtained in the FAS test among patients in the period of depression and those in the period of hypomania/mania are similar and also significantly worse than in the control group, which indicates impairment in verbal fluency. Completing the task in the FAS test is dependent on the supervisory control of executive functions, as fluency demands effective word recall according to a given criterion, suppressing words that are not related to the criterion, and also self-monitoring the process (remembering words which have been already listed) [30]. An effective working of verbal fluency is related to the functioning of the prefrontal areas of the brain. The results of this study are consistent with previous research which indicates significantly worse functioning of phonetic verbal fluency measured with FAS in depressed patients as compared with healthy persons [7,11]. Numerous studies show reduced verbal fluency in patients in a severe episode of depression [30] but also in patients in remission [31]. In the study by Basso et al. [11] manic patients generated a significantly lower number of words according to a given letter criterion than healthy persons, and in a study by Mahli et al. [17] hypomanic patients scored significantly worse than healthy persons for semantic fluency. However, in a study by Martinez-Aran et al. [7] there were no significant differences in FAS performance between those two groups of patients and healthy persons.

Comparing cognitive functioning of bipolar patients in depression and mania or hypomania has revealed some differences only with regard to executive functions measured with the WCST. Performance in this test was significantly worse in the hypomania/mania group than in the depression group, which indicates that disorders

in executive functions are more intense in the period of mania or hypomania than in the period of depression. These results are in contrast to those of Martinez-Aran et al. [7] and Gruber et al. [12], where patients in varied periods of the illness had similar scores on the WCST [7] and on the Modified Card Sorting Test (MCST) [12]. However, Dixon et al.'s [22] study confirms the current results and points to greater disorders in executive functions in manic as compared with depressive patients. Furthermore, these studies reveal a significant relation between the cognitive disorders and intensity of positive disorders in thinking among manic patients. Murphy et al. [13,14] indicate the presence of disorders in executive functions among both manic and depressive patients, yet they are determined by different difficulties. Patients in the period of mania had problems with focusing attention and suppressing an incorrect reaction, while patients in the period of depression displayed difficulties with shifting attention [13]. In comparison with depressive patients, those in the period of mania also made more incorrect decisions in the task that consisted in making bets and gaining points, which was significantly correlated with the intensity of symptoms [14]. There were no significant differences between patients in varied periods of the illness as regards their performance in the TMT, Stroop, N-back and FAS. This indicates similar functioning of visuospatial (TMT, N-back) and verbal (Stroop) working memory and executive functions (FAS, Stroop, TMT, N-back). These results are consistent with reports by other authors [7,11,22].

### Limitations and future directions

A serious limitation of this study is the influence of medicines taken by the patients on their cognitive functioning. Undoubtedly, it is an interfering variable, both in terms of comparing cognitive functioning in patients who take medicines and in healthy persons with no pharmacological treatment, and also when comparing patients at various stages of the illness who are receiving different treatment. Research indicates both a worsening and an improvement in cognitive functioning after pharmacological treatment [7]. A serious disadvantage of the presented studies is the lack of patients' IQ data before the illness. It would also be interesting to see a long-term study examining whether cognitive functioning changes in the same patients depending on the episodes of the illness (depression, hypomania or mania, and remission). This would allow to eliminate the influence of interindividual differences in cognitive functioning. Another limitation of the present study is the small sample size, which was caused by the difficulties in finding patients who fulfill all the inclusion criteria. Yet, despite the small size of the groups, the differences in cognitive functioning between patients and controls were displayed very clearly. Because of some difficulties in examining patients in active periods of the illness (especially those in the episode of hypomania or mania), the examination time, and consequently the battery of tests, were limited. As a result, some significant aspects of cognitive functioning, i.e. verbal memory and learning, were not examined in the study. Including the measurement of verbal learning would allow for checking whether executive functions are a mediator in learning disorders in bipolar patients.

### Clinical implications

The results obtained in this study indicate the presence of marked disorders in working memory and executive functions in varied periods of bipolar disease, but more intense in the period of hypomania/mania than in depression. Thus, we should acknowledge these deficits as a significant element of the clinical picture of the illness and include them in the process of diagnosis and treatment. Executive functions present a superior system that is responsible for integration and organization of a course of varied, mostly complex, cognitive processes that make human behaviour planned, deliberate, conscious and selective, and human reactions – flexible and controlled [32]. Executive functions and working memory play a very important role in human life because they render it possible to realize tasks and needs, to adapt to the changing environment and to cope effectively with its demands. Moreover, reports from other studies [1] indicate that cognitive deficits in executive

functions and working memory are maintained in the periods of remission, which undoubtedly lowers the patients' life quality and makes their psychosocial functioning more difficult. As difficulties in psychosocial functioning are a source of stress, this may contribute to another illness episode. It is important to introduce pharmacological treatment that would improve cognitive functions and to elaborate some specific methods of neuropsychological rehabilitation for patients in varied periods of bipolar disorder. In comparison with healthy persons, bipolar patients in the period of depression have marked cognitive deficits regarding various types of working memory and also some aspects of executive functions. Yet, no disorders in the executive functions measured with the WCST (concept formation and flexibility of thinking) have been observed. In comparison with healthy persons, in bipolar patients in the period of mania or hypomania there is a clear presence of disorders in varied aspects of working memory and executive functions.

Comparing the cognitive functioning of bipolar patients in different episodes of the disease has revealed differences that regard only the executive functions measured with the WCST, which are markedly disordered in the period of mania/hypomania, in contrast to depression. Results of the remaining tests indicate a similar level of disorders regarding varied aspects of working memory and verbal fluency. This points to more serious difficulties in cognitive functioning in the period of hypomania or mania than in the period of depression.

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