COGNITIVE FUNCTIONS IN FIRST-EPISODE DEPRESSION AND RECURRENT DEPRESSIVE DISORDER

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SUMMARY

Background: Cognitive deficits in the course of depressive disorders affect mainly memory, attention and the frontal functions. They are associated with both an earlier onset of symptoms and prolonged episodes. The main aim of the study was to verify the hypothesis of differences in the effectiveness of cognitive processes between patients with a first episode of depression (ED-I) and recurrent depressive disorders (rDD).

Subjects and methods: The study comprised 210 subjects: patients with ED-I (n=60) and patients with rDD (n=150). The assessment of cognitive functions was based on performance of the Trail Making Test, the Stroop Test, the Verbal Fluency Test, the California Verbal Learning Test (CVLT) and the digit span from WAIS-R.

Results: There were no statistically significant differences between the analysed groups in the severity of depressive symptoms. The negative impact of depressive symptoms on the effectiveness of cognitive functions was observed. The ED-I group recorded better results compared to the rDD group in terms of the speed of information processing, visual-spatial and auditory-verbal memory and executive functions, auditory-verbal immediate and delayed memory, ability to learn and verbal fluency. The same differences were observed with respect to the patients from the ED-I group and the patients with the second episode of depression (ED-II) in the course of rDD.

Conclusions: There are significant differences in cognitive functioning of patients with a depressive episode and recurrent depressive disorders. These differences are already visible from the second episode of a major depressive disorder. Memory, verbal fluency and frontal functions are reduced.

Key words: depressive disorders - recurrent depression - cognitive functions

INTRODUCTION

Cognitive deficits in the course of depressive disorders, predominantly related to memory processes and the so-called frontal functions, have been deeply explored in recent years (Lee et al. 2012). The cognitive impairment, which is correlated to both the earlier onset of depressive symptoms and the prolongation of episodes, may in return contribute to the ineffectiveness of an antidepressant therapy and impede full recovery, thus leading to incomplete functional remission (Papakostas 2014). Moreover, according to Lee et al. (2013), the effectiveness of cognitive processes is a key predictor of improvement determining patients’ professional and social capability. The special role in this case is attributed to the auditory-verbal and visual-spatial working memory as well as the speed of information processing.

The course of depression can be episodic – characterised by complete remission or long asymptomatric periods, and recurrent with short periods between relapses. The first episode takes place by and large as a result of stressful life events, referred to as triggers. The age at which the first episode occurs, the duration, frequency and severity of relapses are highly variable between individuals (Rodgers et al. 2012).

Around 50-60% of the people who have gone through the first episode of depression encounter recurrences. In nearly half of the hospitalised patients another episode of depression develops within the first 2 years after discharge from the hospital. It is estimated that 20% of patients diagnosed with recurrent depressive disorders experience two episodes in their lifetime, while 60% – three or more (average number of phases: 3 to 4) (Mead et al. 2008). Each new episode is associated with a worse prognosis and, therefore, suboptimal response to pharmacological treatment (Richardson et al. 2008).

The main objective of the study was to verify the hypothesis of differences in the effectiveness of selected cognitive processes between patients with the first episode of depression (ED-I) and recurrent depressive disorders (rDD).

SUBJECTS AND METHODS

Subjects

The study was carried out in a group of 210 subjects: ED-I group – 60 patients, rDD group – 150 patients.

The patients were selected for the study based on the inclusion criteria for ED and rDD outlined in ICD-10 (1992) (F32.0-F32.2, F33.0-F33.8).

All the subjects were examined during the course of their hospitalisation. The presence of somatic diseases or axis I and II disorders, other than a depressive episode, was considered an exclusion criterion. Other
exclusion criteria included inflammatory or autoimmune disorders, unwillingness to give informed consent, and injuries to the CNS that could have affected cognitive function. For all subjects, a case history was obtained prior to participation using the standardised Composite International Diagnostic Interview (CIDI) (Patten 1997).

All the examined subjects were medication-free at the onset of the study.

All the patients were native Poles, inhabitants of central Poland and unrelated to one another. The process of selecting the individuals to the test group was random, without replacement sampling. Before deciding to participate in the study, the subjects were informed of its purpose, assured that participation was voluntary, and guaranteed that personal data and the results of the tests would be kept confidential. Written informed consent for the participation was obtained from each subject according to the study protocol that was approved by the Bioethical Committee of the Medical University of Lodz (No. NN/603/08/KB).

Methods

The assessment of cognitive functions was based on the Trail Making Test (TMT), the Stroop Test, the Verbal Fluency Test (VFT), the California Verbal Learning Test (CVLT) and the Digit Span from Wechsler Adult Intelligence Scale-Revised (WAIS-R). Depression severity was assessed using the 17-item Hamilton Depression Rating Scale (HDRS). Descriptions of the tests and scales were presented elsewhere (Talarowska et al. 2012). A statistical analysis of the results was based on the raw scores for each of the tests.

The following cognitive functions were evaluated: information processing speed (Digit Symbol from WAIS-R), executive functions and working memory (TMT, Stroop test), verbal memory (immediate and delayed memory) and learning ability (CVLT), and verbal fluency (VFT).

The HDRS, Stroop Test, TMT, CVLT and VFT were carried out at the onset of therapy. All the patients were examined on admission during the symptomatic phase. Examinations of the patients were conducted by the same person in each case: the same psychologist examined the patients using neuropsychological tests, including an evaluation of the obtained results, while the HDRS test was performed by the same psychiatrist.

Statistical analyses

The statistical analysis of the collected material included calculation of both descriptive and inferential statistics. A two-tailed critical region was employed in the statistical hypothesis testing.

Qualitative characteristics of the experimental and control groups were expressed as frequencies shown as percentages. To characterise the average values for quantitative features, the arithmetical mean (M) was calculated. The measures of statistical dispersion included the range of values between the minimum and the maximum, and the standard deviation (SD).

Distributions were analysed using the Shapiro-Wilk test. To compare nonparametric variables in the test groups the Pearson χ² (qualitative variables) test, the Mann-Whitney U test for two independent groups, and the Wilcoxon matched pairs test for two dependent groups (quantitative variables) were used. To evaluate the relations between the analysed variables, Spearman’s R rank order correlation coefficients were estimated. For all the analyses, statistical significance was defined as p<0.05 (Kirkwood & Sterne 2003). All data analyses were performed using STATISTICA PL, version 10.

RESULTS

Average age of all the participants (N=210) was: M=48.41 years (SD=10.97), minimum age – 18 years, maximum age – 67 years. In the ED-I group mean age was: M=44.72 (SD=13.03), and in the rDD group mean age was: M=49.89 (SD=9.68).

Women predominated in both groups (over 60% of the study participants). In both treatment groups, people with secondary and higher education constituted the greatest proportion of respondents. The characteristics of the study group in terms of gender and education are presented in Table 1.

Table 1. The comparison the study groups in terms of gender and education

<table>
<thead>
<tr>
<th></th>
<th>ED-I (N=50)</th>
<th>rDD (N=160)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>32 (53.33)</td>
<td>95 (63.33)</td>
<td>127 (60.48)</td>
</tr>
<tr>
<td>Male</td>
<td>28 (46.67)</td>
<td>55 (36.67)</td>
<td>83 (39.52)</td>
</tr>
<tr>
<td>Education</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary</td>
<td>3 (5.00)</td>
<td>12 (8.00)</td>
<td>15 (7.14)</td>
</tr>
<tr>
<td>Vocational</td>
<td>11 (18.33)</td>
<td>29 (19.33)</td>
<td>40 (19.04)</td>
</tr>
<tr>
<td>Secondary</td>
<td>29 (48.33)</td>
<td>85 (56.67)</td>
<td>114 (54.28)</td>
</tr>
<tr>
<td>High</td>
<td>17 (28.33)</td>
<td>24 (16.00)</td>
<td>41 (19.52)</td>
</tr>
</tbody>
</table>

ED-I - first episode of depression; rDD - recurrent depressive disorders; n - number of samples

Statistically significant differences between the groups in terms of age (Z=2.44, p=0.014) were observed. No statistically significant differences were observed between the examined groups in terms of gender (χ²=1.79, p=0.181) and education (χ²=4.45, p=0.211).

No statistically significant differences between the analysed groups in terms of intensification of depressive disorders (Table 2) were observed. Such differences were not observed either on the day when the patients joined the experiment or after obtaining a response to the pharmacological treatment. In both groups, average intensification of the symptoms of depressive disorders on the first day of the experiment corresponded to the severe intensification of depressive disorders based on
Table 2. The severity of depressive disorders among ED-I group and rDD group

<table>
<thead>
<tr>
<th>Variable</th>
<th>ED-I (N=50) M (SD)</th>
<th>rDD (N=160) M (SD)</th>
<th>Mann Whitney U test</th>
<th>Z</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>HDRS-I</td>
<td>22.29 (6.73)</td>
<td>23.44 (6.89)</td>
<td></td>
<td>-0.756</td>
<td>0.449</td>
</tr>
<tr>
<td>HDRS-II</td>
<td>12.28 (5.24)</td>
<td>12.55 (4.89)</td>
<td></td>
<td>-0.896</td>
<td>0.369</td>
</tr>
<tr>
<td>Number of depression episodes</td>
<td>-</td>
<td>4.36 (1.98)</td>
<td></td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

ED-I – first episode of depression; rDD-recurrent depressive disorders; HDRS-I – Hamilton Depression Rating Scale at the onset of therapy; HDRS-II – Hamilton Depression Rating Scale after pharmacological treatment; M – mean; SD – standard deviation

 Among the patients with rDD, the average number of episodes of depression totalled 4.36 (Table 2). There was no significant correlation between the number of previous episodes and the deterioration of cognitive functioning: TMT part A (p=0.171), TMT part B (p=0.374), part RCNb of the Stroop test (p=0.459), part NCWd of the Stroop test (p=0.558), verbal fluency – ‘animals’ (p=0.853), verbal fluency – ‘sharp objects’ (p=0.627), verbal fluency – ‘letter k’ – (p=0.441), CVLT – first attempt (p=0.171), CVLT – number of words in 30 min (p<0.001), digit span test (p=0.532). The next conducted analysis (Spearman’s rank correlation coefficients) confirmed the negative influence of depressive

Table 3. A comparison of the tests results obtained in ED-I group and rDD group

<table>
<thead>
<tr>
<th>Variable</th>
<th>ED-I M (SD) Min. Max.</th>
<th>rDD M (SD) Min. Max.</th>
<th>Mann Whitney U test</th>
<th>Z</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>TMT A-time</td>
<td>36.08 (16.37) 13 99</td>
<td>52.78 (41.71) 8</td>
<td></td>
<td>-284</td>
<td>-3.38</td>
</tr>
<tr>
<td>TMT B-time</td>
<td>82.78 (37.41) 27 201</td>
<td>110.98 (68.07) 23</td>
<td></td>
<td>485</td>
<td>-2.92</td>
</tr>
<tr>
<td>RCNb-time</td>
<td>25.85 (7.07) 13 46</td>
<td>33.46 (19.31) 15</td>
<td></td>
<td>158</td>
<td>-2.22</td>
</tr>
<tr>
<td>NCWd-time</td>
<td>61.71 (18.15) 22 115</td>
<td>80.26 (50.72) 36</td>
<td></td>
<td>360</td>
<td>-2.41</td>
</tr>
<tr>
<td>VFT -animals</td>
<td>22.16 (6.99) 10 36</td>
<td>19.41 (6.38) 4</td>
<td></td>
<td>38</td>
<td>2.55</td>
</tr>
<tr>
<td>VFT-sharp objects</td>
<td>10.23 (3.75) 2 19</td>
<td>8.82 (3.3) 2</td>
<td></td>
<td>18</td>
<td>2.28</td>
</tr>
<tr>
<td>VFT-the letter k</td>
<td>16.31 (4.91) 7 26</td>
<td>14.69 (6.02) 2</td>
<td></td>
<td>1</td>
<td>4.02</td>
</tr>
<tr>
<td>CVLT-first attempt</td>
<td>6.21 (1.97) 3 12</td>
<td>5.67 (1.93) 2</td>
<td></td>
<td>12</td>
<td>1.91</td>
</tr>
<tr>
<td>CVLT-number of words in 30 min</td>
<td>9.67 (3.53) 1 16</td>
<td>7.85 (3.39) 1</td>
<td></td>
<td>16</td>
<td>3.44</td>
</tr>
<tr>
<td>Digit span</td>
<td>44.04 (12.59) 24 78</td>
<td>37.97 (13.03) 10</td>
<td></td>
<td>70</td>
<td>2.37</td>
</tr>
</tbody>
</table>


Table 4. A comparison of the tests results obtained in ED-I group and ED-II group

<table>
<thead>
<tr>
<th>Variable</th>
<th>ED-I M (SD) Min. Max.</th>
<th>ED-II M (SD) Min. Max.</th>
<th>Mann Whitney U test</th>
<th>Z</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>TMT A-time</td>
<td>36.08 (16.37) 13 99</td>
<td>46.48 (29.24) 16</td>
<td></td>
<td>-133</td>
<td>-1.35</td>
</tr>
<tr>
<td>TMT B-time</td>
<td>82.78 (37.41) 27 201</td>
<td>102.51 (60.75) 43</td>
<td></td>
<td>257</td>
<td>-0.99</td>
</tr>
<tr>
<td>RCNb-time</td>
<td>25.85 (7.07) 13 46</td>
<td>35.2 (23.29) 16</td>
<td></td>
<td>106</td>
<td>-0.91</td>
</tr>
<tr>
<td>NCWd-time</td>
<td>61.71 (18.15) 22 115</td>
<td>83.33 (49.13) 38</td>
<td></td>
<td>230</td>
<td>-1.54</td>
</tr>
<tr>
<td>VFT -animals</td>
<td>22.16 (6.99) 10 36</td>
<td>19.46 (6.06) 8</td>
<td></td>
<td>36</td>
<td>1.74</td>
</tr>
<tr>
<td>VFT-sharp objects</td>
<td>10.23 (3.75) 2 19</td>
<td>8.66 (3.01) 2</td>
<td></td>
<td>17</td>
<td>1.88</td>
</tr>
<tr>
<td>VFT-the letter k</td>
<td>16.31 (4.91) 7 26</td>
<td>14.53 (5.99) 6</td>
<td></td>
<td>27</td>
<td>1.67</td>
</tr>
<tr>
<td>CVLT-first attempt</td>
<td>6.21 (1.97) 3 12</td>
<td>5.7 (2.45) 2</td>
<td></td>
<td>12</td>
<td>1.56</td>
</tr>
<tr>
<td>CVLT-number of words in 30 min</td>
<td>9.67 (3.53) 1 16</td>
<td>7.66 (3.95) 2</td>
<td></td>
<td>16</td>
<td>2.55</td>
</tr>
<tr>
<td>Digit span</td>
<td>44.04 (12.59) 24 78</td>
<td>39.84 (14.95) 17</td>
<td></td>
<td>70</td>
<td>1.04</td>
</tr>
</tbody>
</table>


Table 3 presents the results of the cognitive function evaluation tests in both groups.

Statistically significant differences in the completion of all the tests were observed. The patients in the ED-I group recorded better results as compared to the rDD group in terms of the speed of information processing, visual-spatial and auditory-verbal working memory and executive functions, auditory-verbal immediate and delayed memory, ability to learn new material, and verbal fluency.
symptoms on the cognitive efficiency of all the studied patients (N=210): TMT part A (p<0.001), TMT part B (p<0.001), part RCNwb of the Stroop test (p<0.001), part NCWd of the Stroop test (p<0.001), verbal fluency – ‘animals’ (p<0.001), verbal fluency – ‘sharp objects’ (p<0.02), verbal fluency – ‘letter k’ – (p<0.001), CVLT – first attempt (p<0.001), CVLT – number of words in 30 min (p<0.001). The digit span test did not provide any statistical significance (p=0.450).

At the next stage of the analysis, results of the cognitive function tests conducted in the patients with the first (ED-I) and second episode of depression (ED-II) (Table 4) were compared.

No significant differences between the patients with ED-I and ED-II in terms of gender (χ²=0.81, p=0.366), education (χ²=2.97, p=0.394), age (Z=-1.04, p=0.296) and depression symptoms measured at the onset of therapy (Z=-1.49, p=0.135) were observed.

As shown in Table 4, the group of patients with the second episode of depression recorded worse results than the group with the first episode of depression in all the tests. Statistical significance was found for delayed auditory memory.

**DISCUSSION**

The obtained results prove the presence of cognitive impairment in the patients with the first depressive episode as well as recurrences. As emphasised above, the decline is observed in the speed of information processing, visual-spatial and auditory-verbal working memory, executive functions, auditory-verbal immediate and delayed memory, the ability to learn new material, and verbal fluency. Although we did not observe statistically significant differences in the severity of the symptoms of the disease between the ts with ED-I and rDd (Table 2, using the HDRS scale), the patients from the latter group recorded significantly worse results in all the tests aimed at cognitive functions assessment. Besides, the results presented by Karabekiroğlu et al. (2010) tally with ours. They observed an increased number of perseverative errors and decreased verbal fluency among patients with rDd as compared to those with the first episode of depression. Moreover, a longitudinal Whitehall II study (Singh-Manoux et al. 2010), which lasted 18 years, revealed a relationship between an early onset of the symptoms of depression and the deterioration of the effectiveness of cognitive processes in middle age. Due to Byers and Yaffe (2011), an early onset and frequent episodes of depression increase the risk of dementia by 2 to 4 times. Green et al. (2003) showed a correlation between the presence of episodes of depression and the development of Alzheimer’s disease (AD), even when the first symptoms of mood disorders had preceded the onset of AD by more than 25 years.

A significant difference between the groups in terms of age can be a limitation of this study. However, an additional analysis carried out between the patients with the first and second episode of depression (Table 4) also demonstrated significant differences in cognitive functioning of the patients, with no significant differences in the age of the respondents. The results are in line with the results obtained by Schmid and Hammar (2013). They assessed cognitive functioning of patients one year after the onset of the first depressive episode. In the study group, despite the remission of affective symptoms, other functions – like executive function and verbal fluency – were clearly reduced.

Sarapas et al. (2012) considered two interpretations of the coexistence of cognitive deficits and depressive symptoms: as state effects and as a trait-like relationship. According to the first hypothesis, depressive symptoms are the only reason for cognitive impairment, the level of which corresponds with the severity of depression (e.g. reduction in the speed of processing is a result of fatigue that accompanies patients). According to the second hypothesis, cognitive dysfunctions are a constant feature of the functioning of patients with depression. In the cited work the authors presented the results of a 26-year longitudinal study, which demonstrated that the number and severity of subsequent episodes of depression influenced efficiency reduction of information processing.

The analysis of the results brings us to a conclusion that the several-decade-old and well-known view which assumes complete remission of depressive symptoms between episodes can be found insufficient. According to Zajecka (2013), even in the group of patients achieving complete symptomatic remission some residual symptoms remain, which lower the efficiency of patients and increase the risk of relapse. This group includes: fatigue, sleep disorders and cognitive dysfunctions. What is more, Zimmerman et al. (2012) reported that nearly half of the patients with depressive disorders, diagnosed with symptomatic remission based on the scales assessing the severity of depressive symptoms, subjectively did not define their status as remission. It should be emphasised that mood improvement in a depressive patient is not always accompanied by a steady increase in all cognitive functions (Reppermund et al. 2009). Neu et al. (2005) and Biringer et al. (2005) observed that after 6-month remission, patients underperformed in comparison to healthy people in the field of verbal memory and verbal fluency. Neither was any improvement observed in episodic memory (Airaksinen et al. 2006), attention span (Weiland-Fiedler et al. 2004) and visual-spatial functions (Jaracz et al. 2002).

Our hypothesis is also based on the presence of structural and functional changes in the hippocampus and frontal lobes in the patients with depressive symptoms, which increase with each episode of the disease (de Diego-Adelillo et al. 2013, Trivedi & Greer 2014). The most prevalent structural changes in the brain of the patients with depressive disorders include...
CONCLUSIONS

There are significant differences in cognitive functioning between patients with a depressive episode and recurrent depressive disorders. These differences become noticeable as early as the second episode of major depressive disorder occurs. The deficits involve memory, verbal fluency and the so-called frontal lobe functions.

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Conflict of interest: None to declare.

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