Executive dysfunction in late-life depression

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Summary

Aim. Nowadays there are numerous reports stressing the occurrence of cognitive functions disorders in late-life depression (LLD). More and more frequently the studies stress the role of executive dysfunctions in LLD. The purpose of the study was an evaluation of the components of executive functions in non-demented LLD patients, as well as an evaluation of the relation between the individual components of executive functions and the level of depressiveness.

Methods. The study included 87 persons with depression and 100 persons in the control group. For the purpose of a screening evaluation of cognitive functions the Mini–Mental State Examination (MMSE) was applied. For the evaluation of the level of executive functions efficiency the following were chosen: a) Trail Making Test (TMT), b) Verbal Fluency Tests (VFT) and c) go/no-go task (GNG).

Results. A significant difference was found in the levels of efficiency of all the components of executive functions in patients with late-life depression. The patients with depression demonstrated the slowest psychomotor speed and worse results in the tests evaluating cognitive flexibility, semantic fluency and inhibition. Statistically significant relation was observed between the higher result in GDS-SF (Geriatric Depression Scale – Short Form) and the worse performance in the GNG test.

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Conclusions. The patients with depression demonstrated a significant impairment of executive functions. A relation was found between the cognitive control disorder and the level of depressiveness. Executive dysfunctions can play an important role in the persistence of depressive symptoms. Identification of patients with depression and executive dysfunctions has significant therapeutic implications.

Key words: depression, executive functions, elderly people

Introduction

Depression that occurs for the first time in late life (hence called late-life depression – LLD) is a major issue in ageing populations. Both depression and dementia are the most frequent mental illnesses in the age group above 65 years of age [1]. Moreover, in elderly patients depressive disorders are often concurrent with cognitive dysfunctions [2, 3]. It should also be stressed that the level of cognitive dysfunctions is related to the severity of depression [4]. In addition to cognitive impairment in LLD, the following symptoms are distinguished: depressed mood, anhedonia, sleep disturbances, changes in appetite, decreased energy, feelings of guilt, psychomotor slowing and suicidal thoughts [5]. It is also believed that cognitive dysfunctions that persist after the depression remission in patients with LLD can be related to neurobiological changes [6]. It has been proven that the presence of depression involves an increased risk of the occurrence of dementia [7, 8] and is a major risk factor for suicide [9]. Some researchers believe that depression can also be a prodromal symptom of dementia [10]. The clinical picture of LLD partly differs from depression as observed in younger patients. It is surmised that LLD is a heterogeneous affective disorder including cognitive impairment [11]. What is interesting, the prevalence of LLD does not differ between the two sexes [12]. The feeling of sadness is less characteristic of LLD, in case of which excitation, somatic symptoms, insomnia or fatigue are observed more frequently [13]. It is thought that LLD is usually related to executive dysfunctions [2, 3, 14]. Recently, the number of studies investigating the role of executive functions (EF) in everyday activity is growing. This results in numerous theoretical models that vary in terms of defining and describing EF. In the broad sense of this term, EF are responsible for the commencement and maintenance of performing a task, switching between competitive activities, strategy planning, suppressing habitual behaviors and integrating various cognitive modalities [15, 16]. One of the multifactorial models of EF implies a homogeneity of common skills as well as a diversity of each of the three components in EF: a) updating, that is a continuous process of monitoring, fast adding or changing of the working memory content; b) shifting, that is cognitive flexibility understood as the ability to switch from one task or mental state to another; and c) inhibition, that is the ability to replace the reply dominant in a given situation with a different one [15, 16]. Disorders within the EF most frequently lead to disorganization of behavior in result of the loss of cognitive

self-regulation. In the existing literature, there is no consistent opinion as to which cognitive dysfunctions are specifically characteristic of LLD. Studies to date indicate in particular: the impairment of cognitive flexibility [17], verbal fluency [18], behavior planning [17, 19], attention, cognitive inhibition, working memory or linguistic expression [20]. It is worth pointing out that disorders of other cognitive functions, such as memory [10, 21], visual and spatial functions [4, 20, 22] and psychomotor speed [21, 23, 24], are also observed in LLD. Some authors of studies on the comorbidity of executive dysfunctions and LLD even suggest the introduction of the term "the depression dysexecutive syndrome of late life" (DED) [18]. Patients with DED are characterized by psychomotor slowing down and loss of interests along with less distinct vegetative symptoms which in turn are characteristic of elderly patients with depression without cognitive dysfunctions [18]. It is a major problem that late life depression is often undiagnosed and therefore improperly treated [25]. Untreated LLD has serious consequences, such as the increase in the disability level and mortality of elderly persons [26, 27]. The presence of cognitive dysfunctions in patients with latelife depression is related to impaired or delayed response to antidepressant therapy [28, 29]. Including neuropsychological examination in the process of diagnosis of patients with LLD has unquestionable practical implications. The main purpose of this study was to compare the levels of the efficiency of executive functions (cognitive flexibility, control and initiating) in a group of patients over the age of 60 with and without depression. It also explored the relation between the components of executive functions (cognitive flexibility, control and initiating) and the level of depressiveness in a group of depressive patients over 60 years of age. A hypothesis was proposed that depressive patients are characterized by a greater severity of dysfunctions of all the EF components as compared to persons without depression, and that certain EF components are particularly related to the level of depressiveness.

Material and methods

The total of 187 persons (118 women and 69 men) aged from 60 to 83 participated in the study, and they were qualified from among the patients participating in the Project entitled "The Implementation of the Project of Diagnostics, Geriatric Prevention, with the application of elements of Telecare as a method of better adjustment of the healthcare system to the needs of the rapidly growing population of persons over 60", co-funded by the Norwegian Financial Mechanism for the years 2009–2014 and the Financial Mechanism of the European Economic Area for the years 2009–2014, implemented by Nowa Rehabilitacja Sp. z o.o. at the Medical and Rehabilitation Centre in Krakow. The criterion for the inclusion to the study was the age over 60. The exclusion criteria in relation to the study were: the presence of neurological diseases and other mental illnesses, use of antipsychotics and antiepileptics, as well as alcohol and/or medication addiction. All the participants consented to take part in the study. The study was a cross-sectional observation carried out for the period of about six months from September 2015 to February 2016. The study group consisted of 87 persons with depression, and the control group included 100 persons without depressive disorders. The evaluation of cognitive efficiency and mood was carried out by an experienced clinician. The study group included patients who met the criteria for depression according to the DSM-5, obtained more than 6 points in the GDS test and did not report any depressive episodes before the age of 60. Almost 35% of people with depression were currently under treatment with antidepressants. The control group included persons matched for age, sex and education to the study group, who did not report the occurrence of depressive disorders at present or in the past.

All the examined persons were subject to the screening evaluation of the cognitive functioning with the application of the Mini–Mental State Examination (MMSE). On the basis of the corrected MMSE the study included the persons who obtained the result within the norm of 27–30 points. It is commonly assumed that the result below 27 points can prove the occurrence of cognitive disorders. Obtaining 24 to 26 points by the examined person can prove the presence of mild cognitive impairment without dementia, and the result lower than 24 points (the so-called cut-off point) can suggest the presence of dementia process [30]. In this article the corrected results of MMSE, were chosen for the statistical analysis.

For the evaluation of the EF components selected on the basis of the EF concept discussed in the Introduction, the methods commonly used in the neuropsychological examination were selected [15, 16]. For the evaluation of cognitive flexibility the Trail Making Test (TMT) was selected, and for the evaluation of the skill of updating the Verbal Fluency Tests (VFT) was selected, while for the evaluation of inhibition ability the clinical and experimental methods were selected (go/no-go task – GNG). In order to reduce the so-called floor effect, the authors decided to choose the tests that would allow for the evaluation of the selected components of executive functions and at the same time would not be too difficult for elderly and depressive persons.

The Trail Making Test consists of two parts evaluated separately (A and B). Part A is used for the evaluation of psychomotor speed, while part B first of all involves the visual and spatial working memory and cognitive flexibility. It is believed that part B is a sensitive indicator of executive dysfunctions [31].

The Verbal Fluency Tests is aimed at generating by the person under study as many words as possible in the given time according to the criterion set by the person carrying out the test. The test consists of two parts. The first part aims at the enumeration by the person under study of as many names of animals as possible (semantic fluency). In the second part the person under study is asked to enumerate as many words beginning with the letter "K" (phonetic fluency) within the same period of time. The final result of the trial is the total number of words enumerated without any repetitions and correctly named in each of the two trials.

For the evaluation of motor control, the standardized task of controlling conflicting motor responses was used, appropriate for this age group (go/no-go task) [32]. In the first part the person under study has to react in the manner opposite to the movement of the person carrying out the study. They have to knock on the table once, while the examiner knocks twice. Then, the opposite has to be done; the person has to knock on the table twice, while the examiner knocks on it only once. Then, in the second part, the instruction changes. The person under study has to react only when the examiner knocks twice. Each part consisted of 25 trials, and the maximum possible score for each trial was 25 correct reactions. For the entire task the result oscillates between 0 and 50. A similar method of scoring was successfully used in other studies applying the go/no-go type tasks [33, 34]. In the first part the person under study is expected to learn a certain motor model of reaction. On the other hand, in the second part there is a necessity to inhibit the motor reaction learnt before.

For the evaluation of the level of the intensity of depressive symptoms the 15 item Short Form Geriatric Depression Scale (GDS-SF) was used. This scale is used as a screening tool enabling the evaluation of the severity of depressive symptoms in elderly persons. The scoring is as follows: the score from 0 to 5 points means no depression, and the score from 6 to 15 points indicates the presence of depression.

The body mass index (BMI) was calculated according to the pattern: $BMI = body mass [kg]/(height [m])^2$.

Results

The elements of descriptive statistics were applied in the analysis. The results were presented as mean values for groups with standard deviation (SD) or as percentage. In order to evaluate the normality of the distribution of the analyzed variables the Shapiro-Wilk test was applied. In comparisons between the groups the Student's t-test was used, and in the case when the normality assumption was not fulfilled – the Mann-Whitney U test was used. In order to assess the significance of individual factors potentially affecting the level of efficiency of executive functions multiple regression analysis was used. For the comparison of the two categorical variables the Chi-square test was selected. The statistical analysis was performed with the application of the Statistica 8.0 PL software by StatSoft Company.

Table 1 shows the characteristics of the group under study, taking into account the demographic and clinical variables in the division into two groups depending on the level of depression. The comparison between the groups did not indicate any differences in respect of age, BMI and education. No differences were revealed either in the distribution according to sex in the two groups compared. Both groups did not differ either with respect to marital status, attitude towards taking stimulants and reported subjective cognitive complaints (SCC). In the group of persons with

depression more chronic comorbidities were found. In addition, in patients with depression there were significantly more persons defining their present personal situation as stressful, complaining about sleep disorders and treated with antidepressants. In the comparisons between the groups a significant difference was found in the levels of executive functions efficiency in persons with and without depression. It took the patients with depression significantly longer to complete the parts A and B of the TMT and they also had fewer correct reactions in the GNG test. Also they have generated fewer words during VFT in the semantic fluency category. Three models of multiple regression were constructed in order to compare the effect of potential variables on the level of executive functions efficiency (fluency, cognitive flexibility and self-control). It was found that for the whole studied group 13% of variability in the level of semantic fluency and 21% of variability in the level of cognitive flexibility were explained by the model. The study demonstrated that both age and the number of years of education are independent predictors of the level of semantic fluency efficiency and cognitive flexibility. After adjustment due to sex, age, the number of years of education, the number of diseases, the presence of diabetes, stress and sleep disorders in the whole studied group, it was established that the level of depressiveness is an independent predictor of the level of cognitive control efficiency ($\beta = -0.343$, p = 0.000). It has been shown that 25% of the variability in the level of cognitive control is explained by the model. Furthermore, both sleep disorders ($\beta = -0.315$, p = 0.009) and depression ($\beta = -0.326$, p = 0.016) are independent predictors of the level of cognitive control. 26% of variability in the level of cognitive control was explained by the model (Table 2).

		LLD (-)		LLD (+)			
		٩)	l = 100)		n		
Variable	Category	N (%)	M±SD	N (%)	M ± SD	р	
Age		-	66.81 ± 4.84	-	68.07 ± 5.98	0.208	
Years of education		-	14.61 ± 2.98	-	13.56 ± 3.29	0.053	
BMI		-	27.71 ± 3.75	-	28.11 ± 3.74	0.394	
Carr	Women	61 (61)	-	57 (66)	-	0.523	
Sex	Men	39 (39)	-	30 (34)	-		
Marital status	Relationship	71 (71)	-	58 (67)	-	0.522	
	Single	29 (29)	-	29 (33)	-		
Smoking status	Smoking	10 (10)	-	13 (15)	-	0.304	
	No smoking	90 (90)	-	74 (85)	-		
Alcohol use	Drinker (1–2x/week)	22 (22)	-	18 (21)	-	0.007	
	Abstinent	78 (78)	-	69 (79)	-	0.827	

Table 1. Demographic and cl	linical variables in relation to th	e level of depression ($N = 187$)
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73 (73)	-	62 (71)	-	0.791				
18 (18)	-	38 (44)	-	0.000				
35 (35	-	74 (85)	-	0.000				
-	2.64 ± 1.29	-	3.17 ± 1.38	0.004				
5 (5)	-	33 (35)	-	0.000				
Clinical data (medical history)								
65 (65)		65 (75)		0.151				
11 (11)		15 (17)		0.218				
5 (5)		6 (7)		0.582				
14 (14)		21 (24)		0.076				
77 (77)		73 (84)		0.234				
Neuropsychological test								
-	20.53 ± 5.49	-	18.76 ± 6.18	0.034				
-	15.47 ± 5.71	-	14.39 ± 5.57	0.141				
-	46.07 ± 17.55	-	54.51 ± 23.39	0.004				
-	97.68 ± 49.24	-	120.71 ± 59.42	0.003				
-	48.47 ± 2.71	-	46.29 ± 5.12	0.003				
	18 (18) 35 (35 - 5 (5) 65 (65) 11 (11) 5 (5) 14 (14)	$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	18 (18) - 38 (44) - 35 (35) - 74 (85) - - 2.64 \pm 1.29 - 3.17 \pm 1.38 5 (5) - 33 (35) - 65 (65) 65 (75) - 11 (11) 15 (17) - 5 (5) 6 (7) - 14 (14) 21 (24) - 77 (77) 73 (84) - - 20.53 \pm 5.49 - 18.76 \pm 6.18 - 15.47 \pm 5.71 - 14.39 \pm 5.57 - 46.07 \pm 17.55 - 54.51 \pm 23.39 - 97.68 \pm 49.24 - 120.71 \pm 59.42				

TMT A – Trail Making Test Part A; TMT B – Trail Making Test Part B; GNG – go/no-go task; SCC – subjective cognitive impairment; M – mean; SD – standard deviation

Table 2. The relationship between the level of executive functions and demographic
and clinical variables in the whole study group $(N = 187)$ and in the group
of patients with depression $(N = 87)$

Evelopaton (veriables	N	Model 1		Model 2		Model 3	
Explanatory variables	IN	FS		TMT B		GNG	
The whole study group	187	Beta	р	Beta	р	Beta	р
Sex		0.082	0.281	0.035	0.657	0.019	0.113
Age		-0.156	0.044	0.274	0.000	-0.111	0.137
Years of education		0.214	0.005	-0.292	0.000	0.129	0.077
Comorbidity		-0.014	0.961	-0.124	0.129	0.069	0.454
Diabetes		0.055	0.518	-0.049	0.552	0.052	0.525
Stress		-0.037	0.621	-0.059	0.493	0.018	0.915
Sleep disorders		-0.081	0.282	0.046	0.772	-0.064	0.688
Antidepressant treatment		-0.174	0.451	0.179	0.459	0.146	0.544
GDS		-0.018	0.811	0.089	0.238	-0.343	0.000
R		0.361		0.459		0.471	

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R ²		0.131		0.211		0.253	
р		0.013		0.000		0.000	
LLD group (+)	87						
Sex		0.183	0.163	0.018	0.869	0.064	0.598
Age		-0.033	0.818	0.271	0.025	-0.151	0.238
Years of education		0.244	0.093	-0.444	0.000	0.212	0.125
Comorbidity		-0.067	0.634	-0.122	0.311	0.011	0.936
Diabetes		0.086	0.545	-0.146	0.251	0.062	0.971
Stress		0.097	0.444	0.601	0.585	0.004	0.599
Sleep disorders		-0.219	0.098	0.197	0.091	-0.315	0.009
Antidepressant treatment		-0.109	0.406	-0.091	0.436	0.059	0.636
GDS		-0.051	0.709	0.131	0.281	-0.326	0.016
R		0.427		0.599		0.505	
R ²		0.182		0.359		0.257	
p		0.183		0.001		0.003	

FS – Semantic fluency; TMT B – Trail Making Test Part B; GNG – go/no-go task; GDS – Geriatric Depression Scale

Discussion

In view of the conducted studies, as well as the findings formulated by other authors, one can say that depression is related to the reduced executive functions efficiency. The patients with the symptoms of depression, in comparison to healthy people, demonstrated more severe psychomotor slowing down, poorer semantic fluency, poorer cognitive flexibility, and poorer inhibition of automatic motor reactions. In the present study one of the evaluated cognitive components was verbal fluency understood as the ability to initiate words both phonetically and semantically. Only the latter one proved to be significantly poorer in the group of depressive patients. The authors of other reports also found the impairment of verbal fluency in the group of elderly patients with depression [18, 35].

The study carried out by Ravdin et al. [36] provides slightly different results. In this study of elderly persons with mild symptoms of depression only the impairment of phonetic fluency was found in comparison to healthy persons. In turn, other researchers found that LLD was related to dysfunctions in the scope of cognitive flexibility but not in the scope of verbal fluency [37]. It has been found that both semantic fluency and phonetic fluency are equally significant tools with respect to susceptibility to depression. On the other hand, it is believed that the presence of verbal fluency deficits can reflect not only executive dysfunctions but also psychomotor slowing down [38]. Perhaps in the following studies it would be worth taking into account the influence of modifying cognitive factors in the evaluation of the EF deficits profiles. In other studies the impairment of cognitive flexibility [14, 17, 24] as well as the presence of psychomotor slowing down [21, 23, 24] were also observed among the patients with LLD.

Researchers have shown that patients with depression performed significantly poorer on the TMT as compared to healthy subjects. What is more, patients with organic depressive disorders obtained significantly lower results in tests assessing executive functions and visuospatial functions than patients with depressive disorders [39, 40]. Persons with LLD find it difficult to change their mental attitude, to perform cognitive tasks simultaneously and they demonstrate psychomotor slowing down. The loss of the skill to coordinate a number of tasks fast and effectively in order to attain the aim, can, apart from emotion regulation deficits, be the key cognitive mechanism of helplessness or loss of interests. In the course of the analysis of the dependence between the components of cognitive functions and demographic and clinical factors in the group of depressive patients, a relation was found between the level of depressiveness and sleep disorders and the impairment of cognitive control in the group of patients with depression. The depressive patients find it more difficult to start the inhibition processes, which may result in a biased information processing. The results obtained by other authors also suggest that the presence of executive dysfunctions can contribute to the occurrence of depressive symptoms by the impairment of the ability to control ruminative thinking [41]. In this work the authors have also observed the relation between the higher level of education and lower age, and better semantic fluency and cognitive flexibility. What seems interesting, patients with depression did not differ from the control group in respect of reported subjective cognitive complaints. In both compared groups, about 70% of the examined persons reported cognitive disorders, most frequently those concerning memory and attention. In turn, patients with depression more frequently reported sleep disorders (difficulties to fall asleep, interrupted sleep, waking up early). It is believed that permanent insomnia is a risk factor of LLD occurrence and it can also result in the persistence of illness in the group of patients receiving standard antidepressant treatment [42]. Sleep disturbances are also common among patients in the period of pre-clinical dementia [43]. It is worth stressing here that in the conducted study significantly more patients with LLD evaluated their present personal situation as stressful. Thus, a question arises whether the loss of the resources to cope with stress and, consequently, the evaluation of the situation as the one beyond the person's individual capabilities, can be related to executive dysfunctions. In the group of patients with LLD the EF system responsible for the inhibition of inappropriate actions functions improperly. The inappropriate emotional regulation in the group of patients with LLD can result from

executive dysfunctions occurring in consequence of neurobiological dysfunctions. It is believed that irregularities within the frontal–subcortical and limbic networks can play an important role in the LLD pathophysiology [44]. Numerous studies applying neuroimaging methods have also indicated the reduction and asymmetry within the frontal lobe in patients with LLD [45].

It is more and more frequently reported that LLD is related to the network dysfunction model rather than to the lesion pathology model in the context of biological mechanisms occurring in the course of the illness [46]. Physiologically, the aging of cognitive functions occurs according to an incongruous pattern. Complaints about the cognitive functioning can be a manifestation of the natural impairment of cognitive processes. However, it does not change the fact that an early diagnosing of persons within the group of an increased risk of developing LLD is of crucial significance in everyday clinical practice. What is more, the identification of the cognitive correlates of LLD can significantly contribute to the diagnostic and therapeutic process. Cognitive impairment in depression is frequent phenomenon, albeit underrated and rarely undergo therapeutic interventions [47]. It is also worth emphasizing here that executive dysfunctions increase the risk of the failure of antidepressant therapy [48-50]. Clinically significant responses to the use of cognitive-behavioral therapy were demonstrated in almost half the cases of LLD [51]. In the evaluation of late-life depression it is also advisable to take into account the somatic comorbidities. In the conducted study, patients with LLD demonstrated more somatic comorbidities. Therefore, it cannot be ruled out that the presence of somatic illnesses can also modify depressive symptoms. Undoubtedly, there is a disadvantageous relation between depressive disorders and somatic diseases both in terms of psychology and pathophysiology [52]. Numerous studies have shown that cognitive dysfunctions and metabolic changes in elderly persons are interrelated, but there is insufficient data to explain the mechanisms of these relations [53].

This study has some methodological limitations and should be interpreted with caution. The population of geriatric patients is encumbered with coexistence of diseases and the phenomenon of polypharmacy. Therefore, further studies should be conducted with larger group of patients in order to determine the effect of a broader range of clinical variables and the type of treatment applied to the level of executive functions.

Conclusions

Analysis of data collected during the study described above, made it possible to show the relations between executive functions and the LLD. The early identification of deficits in executive functions is an important element in planning stages of treatment. Modification of the patient's environment by the introduction of compensatory strategies and interventions will allow for optimization of their everyday functioning. Late-life depression that is not subject to treatment can in consequence lead to the increase of disability, and thus the impairment of everyday functioning and loss of independence. The constantly growing number of elderly persons in the community makes one reflect upon searching for neuropsychological aspects of late-life depression.

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