ORIGINAL ARTICLE

Working memory impairment as a common component in recurrent depressive disorder and certain somatic diseases

Piotr Gałecki [1*], Monika Talarowska [1*], Dariusz Moczulski [2], Kinga Bobińska [1], Katarzyna Opuchlik [3], Elżbieta Gałecka [4], Antoni Florkowski [1], Andrzej Lewiński [4]

1 Department of Adult Psychiatry, Medical University of Lodz, Lodz, Poland
2 Department of Internal Medicine and Nephrodiabetology, Medical University of Lodz, Lodz, Poland
3 Department of Internal Medicine and Cardiac Rehabilitation, Medical University of Lodz, Lodz, Poland
4 Department of Endocrinology and Metabolic Diseases, Medical University of Lodz, Lodz, Poland

**both authors equally contributed to this work*

Correspondence to: Prof. Andrzej Lewiński
Department of Endocrinology and Metabolic Diseases,
Medical University of Lodz,
Rzgowska 281/289, 93-338 Lodz, Poland.
TEL: +48 42 271 17 05; FAX: +48 42 271 13 43; E-MAIL: alewin@csk.umed.lodz.pl

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Abstract

OBJECTIVES: Deterioration of the working memory is regarded as one of the most important deficits in a number of somatic diseases. The purpose of the present study was to compare the effectiveness of working memory in 4 groups of patients: 1) diagnosed with recurrent depressive disorder (rDD), 2) with diabetes type 1 (DM1), 3) with diabetes type 2 (DM2), 4) with arterial hypertension (HA) and in healthy controls (HC). **METHODS:** The study comprised 300 subjects: rDD (n=99), DM1 (n=31), DM2 (n=31), HA (n=30) and HC (n=109).Cognitive function assessment was based on Trail Making Test (TMT) and the Stroop test. **RESULTS:** Analysis of variance (ANOVA) indicated statistically significant differences of the mean values among particular groups for each of the analysed results of the Stroop Test and TMT (p<0.0001). Patients with DM1 performed better in both TMT and Stroop tests, when compared to those diagnosed with HA. Patients with HA obtained better results than patients with DM2. Patients with rDD performed significantly worse than those with DM1 in both parts of TMT (A/time: p=0.022, B/time: p<0.001) and in the Stroop test (RCNb/time: p<0.001; NCWd/time: p=0.001; NCWd/errors: p=0.443). They also obtained worse results than patients with DM2 and HA, however, the differences were not statistically significant. **CONCLUSIONS:** 1) Our study has confirmed previous results showing association between depressive disorder and cognitive impairment. 2) Patients with rDD had worse performance on working memory tasks than the patients with DM type 1, DM type 2 and HA. 3) Further investigation is needed to clarify the role of inflammatory and oxidative and nitrosative stress (O&NS) processes in neurocognitive dysfunctions occurring in recurrent depression and somatic disease.

Abbreviations:
rDD - recurrent depressive disorder
DM - diabetes mellitus
DM1 - diabetes type 1
DM2 - diabetes type 2
HA - arterial hypertension
HDRS - Hamilton Depression Rating Scale
HC - healthy controls
TMT - Trail Making Test
RCNb - reading colour names in black
NCWd - naming colour of word – different
HbA1C - glycated hemoglobin
HDL - high density lipoproteins
LDL - low density lipoproteins
BMI - body mass index

INTRODUCTION

Working memory can be seen as a mental buffer for temporal information retrieval from long-term memory, temporal storage of new information, and manipulation of this information in service of ongoing mental tasks (Wild-Wall *et al.* 2011). It refers to an ability to maintain, manipulate, and access mental representations as needed to support complex cognition. It predicts higher-order cognitive abilities such as executive functions (i.e. goal setting and planning), abstract reasoning, problem solving, making decisions and general fluid intelligence. It subserves other domains of mental life, including long-term memory and language comprehension (Rouder *et al.* 2011). Working memory also reflects a more general ability to control attention and exert top-down control over cognition (Broadway & Engle 2011). Deterioration of the working memory is regarded as one of the most important deficits in a number of somatic diseases (Talarowska *et al.* 2010). Dysfunctions of the working memory and other cognitive functions are related to an abnormal functioning of the anterior, associative cortical region of the brain the, so-called, prefrontal cortex (Peltz *et al.* 2011).

Several cross-sectional and longitudinal studies in the last decade confirmed an association between type 1 diabetes (DM1), type 2 diabetes (DM2) (Talarowska *et al.* 2009; Macander *et al.* 2011), arterial hypertension (HA) (Richard Jennings *et al.* 2010; Grande *et al.* 2011), depressive disorders (Kaneda 2009; Talarowska *et al.* 2010) and cognitive decline. Cognitive functions in depressive disorder and somatic diseases are regulated and influenced by many factors and their mechanisms are still poorly understood. There are several hypotheses which aim to explain the mechanisms of pathogenesis that is potentially involved in cognitive impairment in the above mentioned diseases and disorders. Growing evidence suggests the crucial role of oxidative stress, inflammation and vascular dysfunction in developing neuropsychiatric (Gałecki *et al.* 2009) and neurocognitive disorders (i.e., Mild Cognitive Impairment – MCI, Alzheimer's disease – AD and vascular dementia – VD) (Mangiafico *et al.* 2006; Rojas-Fernandez & Moorhouse 2009; Umur *et al.* 2011).

Rafnsson *et al.* (2007) have demonstrated that plasma fibrinogen, interleukin-6 (IL-6), and intercellular adhesion molecule 1 (ICAM-1) are negatively associated with performance on all cognitive measures (verbal declarative memory, nonverbal reasoning, verbal fluency and information processing speed). The authors conclude that systemic markers of inflammation and hemostasis are associated with a progressive decline in general and specific cognitive abilities in older adults, independent of major vascular comorbidity. C-reactive protein (CRP) is also associated with an increased risk of cognitive decline and dementia (Alley *et al.* 2008). According to Mangiafico *et al.* (2006), CRP predicts poorer performance on cognitive tests of verbal working memory, attention, perceptuomotor speed, visuoconstructive performance and mental flexibility. Marioni *et al.* (2009) showed that increased levels of plasma fibrinogen CRP were associated with poorer general cognitive ability, non-verbal reasoning, executive functions, processing speed, and mental flexibility after 5 years of follow-up and after adjustment for age and sex.

The purpose of the present study has been to compare the effectiveness of working memory in 4 groups of patients: diagnosed with depression disorder, diagnosed with DM1, diagnosed with DM2, and those with HA, as well as in the group of HC.

According to our initial hypothesis, patients with depressive disorder show greater deterioration of cognitive functions when compared to patients with DM or HA, which may be associated with systemic inflammatory processes.

PATIENTS AND METHODS

Patients

The study was carried out in a group of 300 subjects (women n=162, 54%) aged 20–65 yrs (M=40.92 yrs, SD=13.84). The participants were divided into 5 groups: patients with recurrent depressive disorder (rDD, n=99), patients with DM1 (n=31), patients DM2 (n=31), patients with HA (n=30) and HC (n=109). All patients were native Poles, inhabitants of the central voivodships of Poland and were unrelated.

Education was measured by the number of school years completed. The education period ≤11 years was considered as primary, 12–13 years – as secondary and >13 years – as higher education (according to the Polish educational system). Demographic characteristics and clinical course data are presented in Table 1 and in Table 2, respectively. No evaluations of the intellectual functions of the enrolled patients were carried out prior to the psychological examination. However, on the basis of medical records and anamnesis, it was established that none of the participants had been diagnosed with mental disability or any of the analyzed intellectual deficits. In all the included subjects, case history was obtained prior to main study procedure, using the standardized Composite International Diagnostic Interview (CIDI) (Patten 1997).

Tab. 1. Demographic characteristics of the study groups.

Characteristics		Gender		Age in years	Education level			Disease duration in years
		Female	Male		Primary	Secondary	High	
rDD *n* = 99	n	55	44	–	31	56	12	–
	%	55.56	44.44	–	31.31	56.57	12.12	–
	M (±SD)	–	–	48.35 (11.46)	–	–	–	6.96 (8.11)
DM1 *n* = 31	n	23	8	–	6	19	6	–
	%	74.19	25.81	–	19.35	61.29	19.35	–
	M (±SD)	–	–	38.09 (11.64)	–	–	–	14.67 (±9.05)
DM2 *n* = 31	n	8	23	–	13	14	4	–
	%	25.81	74.19	–	41.94	45.16	12.91	–
	M (±SD)	–	–	46.00 (7.88)	–	–	–	15.83 (7.81)
HA *n* = 30	n	5	25	–	8	12	10	–
	%	16.67	83.33	–	26.67	40.00	33.33	–
	M (±SD)	–	–	56.5 (6.27)	–	–	–	9.31 (8.01)
HC *n* = 109	n	71	38	–	0	49	60	–
	%	65.14	34.86	–	0	44.95	55.05	–
	M (±SD)	–	–	56.51 (7.27)	–	–	–	–
Total	n	162	138	–	58	150	92	–
	%	54.00	46.00	–	19.33	50.00	30.67	–
	M (±SD)	–	–	40.92 (13.84)	–	–	–	6.04 (7.11)

rDD – recurrent depressive disorders; DM1 – patients with type 1 diabetes; DM2 – patients with type 2 diabetes; HA – patients with arterial hypertension; HC – healthy controls; n – number of patients; % – percentage; M – mean; ± SD – standard deviation

Tab. 2. Characteristics of selected parameters and laboratory results in particular groups of patients.

Characteristics		BMI				Total cholesterol level mg/dl				LDL mg/dl				HDL mg/dl		
		27–40	25–27	20–25	18–20	<175	175–200	200–239	>240	<100	100–150	150–190	>190	>55	35–55	<35
rDD *n* = 99	n	34	12	42	11	–	–	–	–	–	–	–	–	–	–	–
	%	34.3	12.1	42.4	11.1	–	–	–	–	–	–	–	–	–	–	–
DM1 *n* = 31	n	3	12	11	5	12	5	5	6	11	13	3	1	5	16	7
	%	9.6	38.7	35.4	16.1	42.8	17.8	17.8	21.4	39.2	46.4	10.7	3.5	17.8	57.1	25.1
DM2 *n* = 31	n	21	3	6	1	12	6	4	6	11	8	6	3	3	15	10
	%	67.7	9.6	19.3	3.2	42.8	21.4	14.2	21.4	39.2	28.5	21.4	10.7	10.7	53.5	35.7
HA *n* = 30	n	22	2	6	0	11	10	4	2	10	13	1	2	7	15	4
	%	73.3	6.7	20.1	–	40.7	37.1	14.8	7.4	38.4	50.1	3.8	7.6	26.9	57.6	15.3
Total	n	80	29	65	17	35	21	13	14	32	34	10	6	15	46	21
	%	41.8	15.1	34.1	8.9	42.1	25.3	15.6	16.8	39.1	41.4	12.2	7.3	18.2	56.1	25.6

rDD – recurrent depressive disorders; DM1 – patients with type 1 diabetes; DM2 – patients with type 2 diabetes; HA – patients with arterial hypertension; HS – healthy subjects; n – number of patients; BMI – Body Mass Index (27–40 – obesity, 25–27 – overweight , 20–25 – normal body weight, 18–20 – body weight deficiency); HDL – high density lipoproteins; LD L – low density lipoproteins.

Ethics

An informed, written consent for participation in the study was obtained from each subject, according to the protocol, approved by the Bioethical Committee of the Medical University of Lodz (No RNN/603/08/KB).

Recurrent depressive disorders (rDD)

Patients with rDD were selected for the study according to the inclusion criteria of ICD-10 (F 32.0–7.32.2, F 33.0–F 33.8) (1993). All the subjects were examined during hospitalisation. The study group included subjects, hospitalised for the first time for depressive episode and depression treatment-naive, as well as those treated for many years before and with multiple hospitalisation episodes in history, the latter admitted for various degrees of health deterioration. The presence of axis I and II disorders, other than depressive episode, and the diagnosis of somatic diseases and injuries of the central nervous system (CNS), which could have affected the cognitive performance, were regarded as exclusion criteria.

The severity of depression was assessed by the 21-item Hamilton Depression Rating Scale (HDRS) (Hamilton 1960; Moonseong *et al.* 2007). Depressive symptom intensity levels were classified by the grades, specified in the study by Demyttenaere and De Fruyt (2003). The mean value of HDRS for rDD patients was *M*=24.34, *SD*=6.53. Number of subjects with mild, moderate, severe, and very severe depression symptoms are presented in Figure 1.

Diabetes (DM)

The subjects diagnosed with type 1 and type 2 DM were patients hospitalised at the Department of Diabetology and Metabolic Diseases of Medical University of Lodz. The qualification of subjects into the study group, DM type 1 or type 2, was based on the criteria of the Polish Diabetological Society (Diabet Prakt. 12 suppl. A: 1–46, 2011). The presence of axis I and/or axis II disorders were regarded as exclusion criteria.

The mean value of glycated hemoglobin (HbA_{1C}) in both groups of the diabetic patients together was *M*=9.47, *SD*=2.69 (DM1: *M*=9.17, S*D*=1.46, DM2: *M*=9.78, *SD*=3.55). Whole venous blood was collected for HbA_{1C} measurements. Measurements were established using High-Performance Liquid Chromatography (HPLC).

Hypertension (HA)

All the patients diagnosed with HA were treated in Clinic of Internal Medicine and Cardiac Rehabilitation, Medical University of Lodz. The qualification of subjects into the study group was based on the criteria of the ESC and ESH Guidelines (2007) as follows: normal: 120–129 mm/Hg (systolic blood pressure, SBP) and 80–84 mm/Hg (diastolic blood pressure, DBP); high normal: 130–139 mm/Hg (SBP) or 85–89 mm/Hg (DBP); grade 1 HA (mild): 140–159 mm/Hg (SBP) or 90–99 mm/Hg (DBP); grade 2 HA (moderate): 160–179 mm/Hg (SBP) or 100–109 mm/Hg (DBP); grade 3 HA (severe): ≥180 mm/Hg (SBP) or ≥110 mm/Hg (DBP). Individuals with axis I or II comorbidity were excluded from the study.

Blood pressure was measured on the day of cognitive functions assessment and prior to neuropsychological testing. Patients were treated with antihypertensive drugs. Figure 2 and 3 show the blood pressure measures in patients from HA group.

Healthy controls (HC)

The HS group consisted of 109 healthy individuals with family history negative for psychiatric disorders. The healthy controls included community volunteers, enrolled into the study on the criteria of the psychiatric CIDI interview (Patten 1997). Controls with somatic or psychiatric diagnoses, concerning axis I and II disorders, were excluded from the study. Individuals with the history of neurological or psychiatric disorder or with family history of mood disorders, substance abuse or dependence were also excluded.

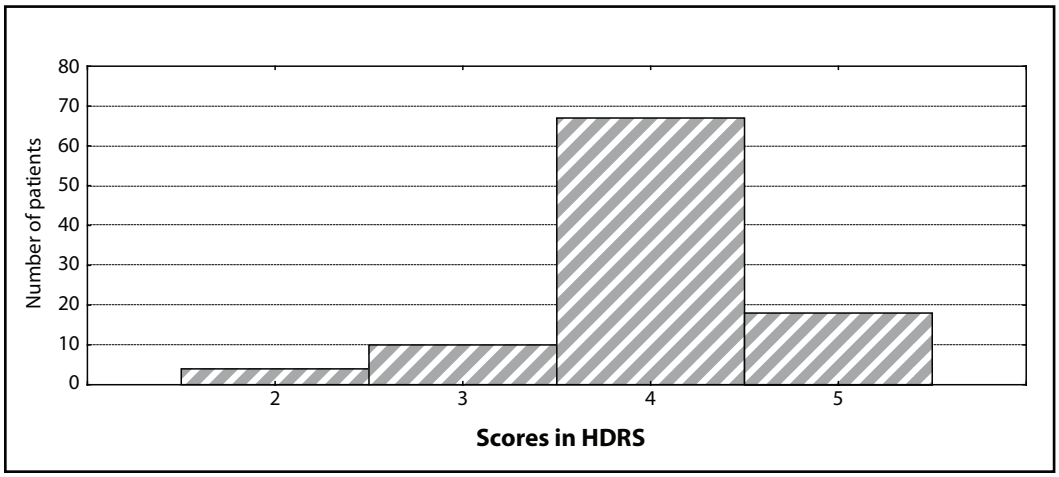

Fig. 1. The severity of depression symptoms measured with HDRS. 2-8-12 – mild depression; 3-13-17 – moderate depression; 4-18-24 – severe depression; 5-30-52 – very severe depression.

Tools for cognitive function assessment

Cognitive function assessment was based on the Trail Making Test (TMT) and Stroop Test.

Part A of TMT was applied for evaluation of psychomotor speed, while part B was used for assessment of spatio-visual performance, working memory and executive functions. The time periods, required to complete each part, were estimated. The authors based their analysis on raw results (Reitan 1958; Sánchez-Cubillo *et al.* 2009).

The Stroop Test (Colour-Word Interference Test) was performed with the use of paper cards. We used a Polish version based on the original Stroop Test cards. The test is used for working memory and attention processes evaluations. The Stroop Test consists of two parts: RCNb (reading colour names in black – where the tested subject has to read as quickly as possible 10 rows of written text with 5 words in each row, the words being the names of colours, printed in black ink on a white paper sheet) and NCWd (naming colour of word – different) – where the tested subject has to name as quickly as he/she can the ink colours of particular words, while the ink colour of a given word does not correspond to the colour which the word designates. In the reported study, the dependent variables were: the number of errors made in the second part, and the duration of each test part performance (Stroop 1935; Audenaert *et al.* 2001).

Regarding the patients with rDD, HDRS, The Stroop Test and TMT were applied at the symptomatic phase, before or shortly after previous antidepressant drug regime modification. In the DM and HA group the cognitive assessment was conducted during hospitalisation. In the HC group, neuropsychological testing was carried out in a single session. The assessment was performed by the same person in each particular case, the same psychologist examined the patients with neuropsychological tests, including an evaluation of obtained results, while the HDRS test was performed by the same physician-psychiatrist. Patients were qualified to the DM and HA group by the same person, diabetologist or cardiologist, respectively.

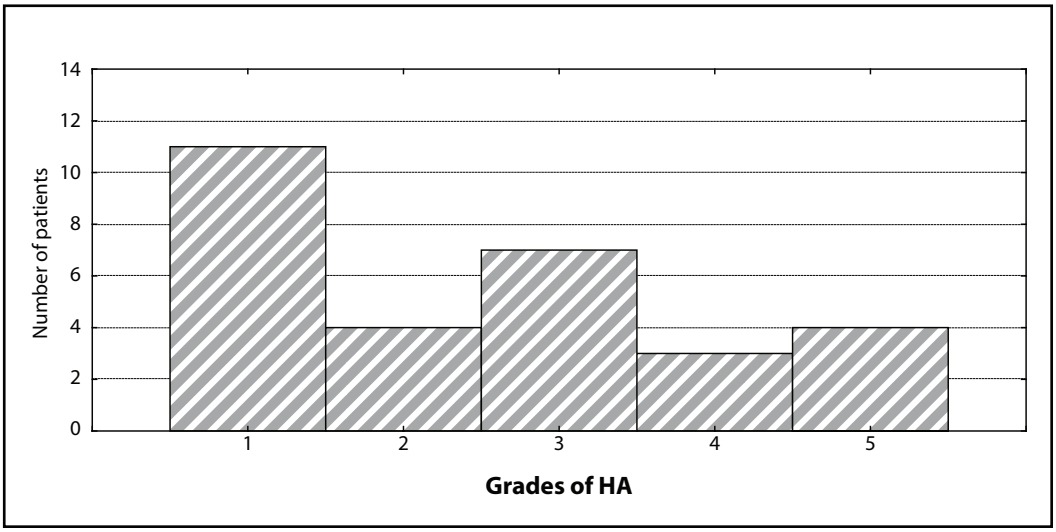

Fig. 2. Systolic blood pressure in HA group. 1 – normal; 2 – high normal; 3 – grade 1 HA; 4 – grade 2 HA; 5 – grade 3 HA; HA – arterial hypertension.

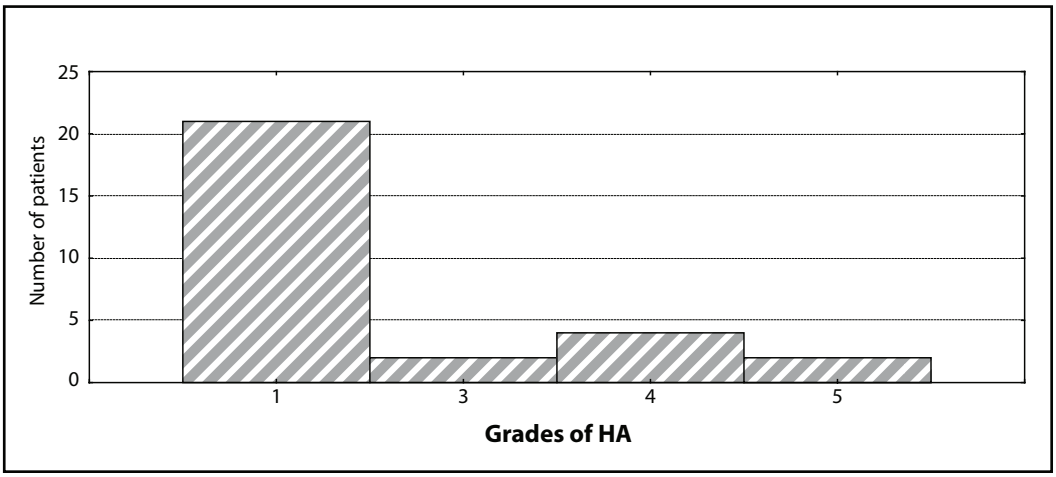

Fig. 3. Diastolic blood pressure in HA group. 1 – normal; 2 – high normal; 3 – grade 1 HA; 4 – grade 2 HA; 5 – grade 3 HA; HA – arterial hypertension.

Statistics

Statistical analysis of the collected data utilized descriptive methods, as well as a statistical inference. In order to describe the studied group of patients and HC group structural indexes were calculated in the qualitative analysis of characteristics. In order to estimate the mean values for the quantitative characteristics, arithmetic means (*M*) were calculated. Standard deviation (*SD*) was applied as the measure of scatter.

One-factor analysis of variance – ANOVA was applied to evaluate the differences between the median values, obtained by the study participants in each group. The procedure of multiple comparisons (Scheffe`s test) was applied to find out which groups were responsible for the ANOVA outcome. In all the statistical methods, p value less than 0.05 was considered significant.

RESULTS

The mean tests results for all study groups are presented in Table 3. Analysis of variances ANOVA indicated statistically significant differences of the mean values among particular groups for each of the analysed results of the Stroop Test and TMT. The Stroop Test: the time period of part RCNb performance: F=19.385, p<0.0001; the time period of part NCWd performance: F=16.264, p<0.0001; the number of errors in part NCWd: F=6.039, p=0.0001. TMT: part A/time: F=14.349, p<0.0001; part B: F=25.711, p<0.0001.

Table 4 presents multiple comparison procedures. In all performed tests, the best results, were obtained by HC and patients diagnosed with type 1 DM. The worst performance was observed among subjects with rDD and type 2 DM.

Patients with DM type 1 performed better compared to those, diagnosed with HA, considering all the variables tested. Patients with HA, however, obtained better results than patients with type 2 DM. Patients with rDD performed significantly worse than those with DM type 1 in both parts of the TMT and in the Stroop Test. They also obtained worse results than patients with DM type 2 and patients from HA group, however, the differences were not statistically significant.

DISCUSSION

The results of our study are consistent with previous reports concerning the impairment of cognitive function in patients with DM, HA and depression. Several longitudinal studies showed an association of DM2 with dementia risk over years (Yaffe *et al.* 2004; Mossello *et al.* 2011). Diabetes induces chronic vascular complications, not only macrovascular disorders, such as cardiovascular and cerebrovascular disease but also microvascular disorders (e.g. nephropathy, retinopathy and neuropathy). The prevalence of dementia, including both Alzheimer Disease (AD) and vascular dementia (VD), was higher in individuals with DM2 than in

Tab. 3. The results of tests in all groups of patients and in healthy controls.

Characteristics		TMT A / time (s)	TMT B / time (s)	Stroop Test / RCNb time (s)	Stroop Test / NCWd time (s)	Stroop Test / NCWd (errors)
rDD *n* = 99	M (±SD)	53.1 (38.9)	114.1 (70.2)	33.4 (17.6)	79.2 (46.5)	3.9 (5.38)
	Range	15–284	23–485	15–106	36–360	0–33
DM1 *n* = 31	M (±SD)	34.6 (23.1)	70.9 (31.7)	21.5 (3.9)	52.6 (11.6)	2.2 (3.1)
	Range	15–102	35–166	16–32	38–103	0–11
DM2 *n* = 31	M (±SD)	44.4 (30.11)	101.9 (57.8)	27.1 (10.7)	65.2 (15.9)	4.5 (4.1)
	Range	20–148	40–307	16–61	42–120	0–17
HA *n* = 30	M (±SD)	36.7 (11.1)	87.5 (26.8)	23.6 (3.6)	71.9 (28.4)	2.3 (3.1)
	Range	23–73	22–130	16–30	50–189	0–16
HC *n* = 109	M (±SD)	25.9 (9.5)	49.8 (16.1)	20.6 (3.3)	47.7 (10.7)	1.4 (3.6)
	Range	11–65	20–103	12–29	25–98	0–35
Total	M (±SD)	38.7 (28.6)	82.2 (54.6)	25.9 (12.3)	62.8 (32.5)	2.7 (4.3)
	Range	11–284	20–485	12–106	25–360	0–35

rDD – recurrent depressive disorders; DM1 – patients with type 1 diabetes; DM2 – patients with type 2 diabetes; HA – patients with arterial hypertension; HC – healthy controls; M – mean; ±SD–standard deviation; RcNb – reading colour names in black; NCWd – naming colour of word – different; TMT–Trail Making Test;

Tab. 4. The level of significance of the differences in Stroop Test and TMT performance in all study groups.

TMT A / time (s)					
Group	**rDD**	**DM1**	**DM2**	**HA**	**HC**
rDD		**0.022***	0.634	0.066	**0.000001***
DM1	**0.022***		0.712	0.998	0.614
DM2	0.634	0.712		0.861	**0.019***
HA	0.066	0.998	0.860		0.411
HC	**0.000001***	0.614	**0.019***	0.411	
TMT B / time (s)					
Group	**rDD**	**DM1**	**DM2**	**HA**	**HC**
rDD		**0.000779***	0.816	0.127	**0.000001***
DM1	**0.000779***		0.158	0.758	0.313
DM2	0.816	0.158		0.841	**0.00013***
HA	0.127	0.758	0.841		**0.005676***
HC	**0.000001***	0.313	**0.00013***	**0.005676***	
Stroop Test / RCNb time (s)					
Group	**rDD**	**DM1**	**DM2**	**HA**	**HC**
rDD		**0.000026***	0.095	**0.001216***	**0.000001***
DM1	**0.000026***		0.426	0.972	0.997
DM2	0.095	0.426		0.821	0.091
HA	**0.001216***	0.972	0.821		0.804
HC	**0.000001***	0.997	0.091	0.804	
Stroop Test / NCWd time (s)					
Group	**rDD**	**DM1**	**DM2**	**HA**	**HC**
rDD		**0.001032***	0.263	0.884	**0.000001***
DM1	**0.001032***		0.597	0.173	0.955
DM2	0.263	0.597		0.941	0.082
HA	0.844	0.173	0.941		**0.004192***
HC	**0.000001***	0.955	0.082	**0.004192***	
Stroop Test / NCWd errors					
Group	**rDD**	**DM1**	**DM2**	**HA**	**HC**
rDD		0.443	0.966	0.341	**0.002358***
DM1	0.443		0.316	0.999	0.947
DM2	0.996	0.316		0.245	**0.013732***
HA	0.341	0.999	0.245		0.983
HC	**0.002358***	0.947	**0.013732***	0.983	

rDD – recurrent depressive disorders; DM1 – patients with type 1 diabetes; DM2 – patients with type 2 diabetes; HA – patients with arterial hypertension; HC – healthy controls; RcNb – reading colour names in black; NCWd – naming colour of word – different; TMT – Trail Making Test; * – *p* statistically significant

those without diabetes (Biessels *et al.* 2006). Hayashi *et al.* (2011) have demonstrated that hippocampal and whole brain atrophies are more frequent in elderly patients with DM2 than in non-diabetic controls. Cognitive function impairment is significantly associated with hippocampal atrophy. Additionally, it has been observed that older nondiabetic individuals with metabolic syndrome and elevated level of inflammatory markers have an increased risk of subsequent cognitive decline (Yaffe *et al.* 2004).

A number of studies also support an association between HA, particularly in midlife, and the development of cognitive disorders and dementia, including mild cognitive impairment (MCI) (Israeli-Korn *et al.*

2011) and AD (Grassi *et al.* 2011; Wysocki *et al.* 2011). It has been found in several studies that the risk of dementia and cognitive impairment is related to high blood pressure (Verdelho *et al.* 2007). However, other studies have demonstrated that low blood pressure is associated with dementia, especially in the very old individuals (above 80 years) (Qiu *et al.* 2003; Verghese *et al.* 2003). The relationship between blood pressure and dementia risk is not yet entirely clear. Authors of recent reports have emphasized that HA leads to certain pathophysiological changes in brain, such as vascular remodeling, impaired cerebral autoregulation, small lacunar infarct, white matter lesion, microbleed and amyloid angiopathy, which may result in deterioration of the cognitive functioning (Manolio *et al.* 2003). Systolic blood pressure (SBP) and pulse pressure (PPR) are also associated with medial temporal lobe atrophy (Korf *et al.* 2004).

In the present study, patients with depressive disorders had the worst performance in all the performed tests. One of the potential causes may be the above mentioned inflammatory processes, which only in case of depressive disorder affect CNS directly. The most recent findings in neurobiological research provided an increasing evidence that inflammatory and neuroprogressive processes play a significant role in depression (Maes *et al.* 2011a). Preclinical and clinical studies on depression highlighted an increased production of inflammatory markers, such as interleukin (IL-1, IL-6), tumor necrosis factor-α (TNF-α) and interferon-α and γ. In animal models, acute and chronic administration of cytokines or cytokine inducers triggers depressive symptoms. There is now evidence that oxidative stress plays an important role in depression, i.e. increased lipid peroxidation, DNA and functional proteins damage, and decreased levels of antioxidants, such as glutathione, zinc, vitamin E and coenzyme Q10, and antioxidant enzymes, such as glutathione peroxidase (Gałecki *et al.* 2010; Gałecki *et al.* 2011; Maes *et al.* 2011c). The activation of the inflammatory and neuroprogressive pathways may induce the brain damage, observed in depression through both the reduced neurogenesis and increased neurodegeneration (Catena-Dell'Osso *et al.* 2011).

One potential confounding, or mediating factor which could explain the obtained results is action of blood-brain barrier (BBB). BBB acts as a complex cellular gate that tightly regulates the transport of molecules from and into the central nervous system (CNS). Neurodegenerative change is exacerbated by the linked process of BBB disruption and neuroinflammatory changes (Serlin *et al.* 2011). BBB breakdown is considered to be a predictor of neuronal dysfunction. In diabetic patients even after a relatively short duration of diabetes, the BBB manifests increased permeability (Mogi & Horiuchi 2011). According to Huber *et al.* (2006), changes in BBB permeability were region specific – the midbrain was most susceptible when compared with the thalamus, hypothalamus, cerebellum, cerebral cortex, hippocampus and basal ganglia. A contribution of a disrupted BBB in the basal ganglia in the pathogenesis of HIV (human immunodeficiency virus type 1) induced dementia involving dopaminergic neurons is also reported (Berger *et al.* 2000). Moreover, Bartels *et al.* (2008) have demonstrated that impaired BBB function is observed in the midbrain of patient with Parkinson's disease (PD). Furthermore, an increased intrathecal production of the proinflammatory cytokine TNF-α and a decreased production of the anti-inflammatory cytokine TGF-β (transforming growth factor beta) in the brain were observed in patients with MCI (Ray *et al.* 2007). It should be emphasized that inflammatory markers may indirectly lead to cognitive impairment via promoting vascular disease, i.e., causing stroke and transient ischemic attacks (Kuo *et al.* 2005; Zacho *et al.* 2008). Individual differences in cognitive decline are partly attributed to differences in cardiovascular risk factors, including smoking, hypertension, diabetes and vascular diseases (Rafnsson *et al.* 2010). Additionally, pathogenesis of neurodegeneration has been, at least in part, attributed to the release of proinflammatory cytokines from brain resident cells and, although less consistently, from peripheral cells (Arosio *et al.* 2011).

Our observation of the association between depressive disorder and cognitive impairment allows speculation that inflammation may contribute to cognitive decline, thus raising the possibility that cognitive function might benefit from therapies modulating the inflammatory response. The findings also suggest the potential use of biological markers in evaluating the risk of cognitive decline. Moreover, working memory deficit may be associated with loss of ability to focus attention on the essential tasks and ability to ignore irrelevant information/distractors (Pelt *et al.* 2011). Therefore, cognitive abilities (i.e., working memory, visuo-spatial/constructional abilities, attention, planning and problem solving) are associated with disease self-management behavior (Mooijaart *et al.* 2011; Primožič *et al.* 2011).

It is to be recalled that both inflammatory and oxidative and nitrosative stress (O&NS) processes can be involved in pathomechanisms of neurocognitive dysfunctions occurring in recurrent depression and in certain somatic diseases being comorbidities of depression (Maes *et al.* 2011b).

CONCLUSIONS

1. Our study confirms previous results showing association between depressive disorder and cognitive impairment.
2. Patients with rDD had worse performance on working memory tasks than the patients with DM type 1, DM type 2 and HA.
3. Further investigation is needed to clarify the role of inflammatory and O&NS processes in neurocognitive dysfunctions occurring in recurrent depression and somatic disease.

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