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Specificity of attention and cognitive inhibition processes in relapsing-remitting multiple sclerosis patients with consideration of their mood level

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Summary

The results of contemporary neuropsychological analyses lay foundation for a broad discussion of the nature and causes of cognitive deficits in MS patients.

Aim. The aim of this study was to determine the level of alternating attention and dominant reaction inhibition in relapsing-remitting multiple sclerosis patients, with consideration of their mood level, age and disease duration.

Method. Experimental group consisted of 43 adults (30 women and 13 men) diagnosed with relapsing-remitting multiple sclerosis, with Extended Disability Status Scale (EDSS) results ranging between 2.5-6.5. Control group comprised 38 healthy adults (26 women and 12 men) selected according to sex, age and education. The following tasks were used in the study: the Trail Making Test A and B (TMT), Stroop Colour-Word Test (SCWT), and Beck Depression Inventory (BDI).

Results. Experimental group was characterized by significantly worse performance in TMT ($p<0.001$) and SCWT ($p<0.001$) than the control group. No differences were observed in performance of TMT ($p>0.05$) and SCWT ($p>0.05$) in the experimental group between subjects with depressed and neutral mood. Disease duration proved significantly related to the level of dominant reaction inhibition ($p<0.001$).

Conclusions. Cognitive impairments within areas of concentration, attention shifting and dominant reaction inhibition were all revealed in the experimental group.

Key words: multiple sclerosis, alternating attention, cognitive inhibition, lowered mood

Introduction

Attention is construed to be a heterogenous system responsible for information selection, which prevents negative effects of cognitive system overload [1]. Top-down attention assumes the following functions: selectivity, sustained concentration, divisibility, shifting, vigilance, and search [2, 3]. Cognitive inhibition processes, on the other hand, described in terms of cognitive control, i.e. cognitive system's capacity to monitor and regulate its own cognitive processes, is a non-uniform notion [1]. Depending on a theoretical approach, various kinds of cognitive inhibition are distinguished. One of the available theories identifies its three fundamental types: dominant reaction inhibition, resistance to distraction and resistance to proactive interference [4]. Cognitive inhibition is often tested by means of the so-called Stroop effect, in which inhibition of dominant reaction and automatic verbal reaction are observed [4, 5].

The conceptualization of neural basis underlying attention processes makes use of various theoretical approaches, based upon the role of functional systems, cortical-subcortical interactions and complex networks linked to attention [2, 6]. The processes of cognitive inhibition of dominant reaction have been described more precisely. Namely, cingulate cortex is assumed to detect, monitor and process interference conflict, while the dorsolateral prefrontal cortex is engaged in conflict resolution [7, 8].

Deficits within different functions of top-down attention and cognitive inhibition are researched in Multiple Sclerosis patients (Lat. Sclerosis Multiplex, SM) [9]. MS is a degenerative demyelinating disease of the central nervous system (CNS), the etiology of which is still not fully understood [10]. Its neurological symptoms are disseminated in space (depending on the location of the pathology) and time (relapses) and may assume various degrees of severity and different courses [11]. Cognitive dysfunctions are present in 43-70% of the patients [12]. Results reported by numerous authors as well as certain metaanalyses point out to the existence of non-uniform deficits as regards attention, executive functions and cognitive inhibition in MS patients [13, 14]. In its relapsing-remitting form, the most frequent deficits include decline in information processing speed, sustained focus, vigilance, selectivity and shifting of attention, cognitive control dysfunctions, decrease in short-term memory function and working memory disorders [15]. The nature of the symptoms is linked to the location of the atrophy, which most commonly appears in the frontal, occipital and temporal portions of both hemispheres and demyelinating plaques (caused by the loss of the myelin sheath insulating the nerves and axon degeneration) in the white matter, particularly in the corpus callosum [16, 17]. The predictors of attention and cognitive inhibition deficits are still searched for. It has been found that factors such as age, time since diagnosis, years of schooling, fatigue, depression, location and number of demyelinating plaques as well as the picture of cortical losses all highly correlate with the aforementioned cognitive impairments [18, 19, 20]. Metaanalyses of the research on cerebral activity in relapsing-remitting MS (RRMS) patients completing assignments which engage attention and working memory show a distinct pattern of activation in their left prefrontal cortex and right pre-motor area [21].

Aims of the paper

The results of contemporary neuropsychological analyses lay foundation for a broad discussion of the nature of attention and cognitive inhibition deficits in MS patients, as well as their links to the level of depressiveness and depressed mood observed in MS.

The objectives of this paper are to:

1. Determine the level of attention shifting and dominant reaction inhibition in MS patients as compared to the control group.
2. Assess differences in the level of attention shifting and dominant reaction inhibition in MS patients with depressed and neutral mood.
3. Determine the relationship between age, disease duration and the level of attention shifting and dominant reaction inhibition in MS patients.

Material

In the study an experimental and a control group were created. 43 adults with diagnosed relapsing-remitting MS with Expanded Disability Status Scale (EDSS) scores 2.5 – 6.5 points were selected for the experimental group (RRMS). MS diagnosis was made by a neurologist, based on a clinical examination comprising interview, neurological status assessment with neuroimaging (NMR, CT, evoked potentials), cerebrospinal fluid and ophthalmologic examination. The relapsing-remitting form (RRMS) was diagnosed based on revised McDonald's criteria [22]. The recruitment took place in The John Paul Multiple Sclerosis Rehabilitation Centre in Borne Sulinowo and EuroMedis Medical Centre in Szczecin. Excluded from the study were patients with a disability hindering performance on neuropsychological tests (dominant limb motor deficits, optic neuritis) and persons with mental illnesses and / or addiction to alcohol or psychotropic drugs, as well as those with other chronic diseases (parenchymal organ diseases and/or cancer).

The control group (CG) comprised 38 healthy adult subjects, matched for age, sex and number of years of schooling. They were recruited through an advertisement from various institutions, i.a. research and education facilities, and examined at the Institute of Psychology at the University of Szczecin. A purposeful selection of participants was used in this study. All subjects had been familiarized with the aim of the study and had given their written consent to participate, in compliance with the resolution approved by the Bioethical Committee at the Regional Medical Chamber in Szczecin (ref. no OIL-Sz/KB/452/05/2011).

Method

The methods used in the study were the Trail Making Test A and B (TMT), Stroop Colour-Word Test (SCWT) and Beck Depression Inventory (BDI).

The TMT is a tool designed to assess executive functions, flexible attention switching or mental set shifting abilities, the speed of recognition of numbers and letters and working memory [23]. The method is composed of two separately evalu-

ated parts (A and B). Part A consists in connecting 25 circles containing numbers from 1 to 25, arranged irregularly on an A4 sheet of paper. In part B, the subject is to alternate between irregularly arranged circles containing numbers from 1 to 13 and letters from A to I, connecting them with a continuous line. In the study, performance times for each of the two parts (Time A and Time B) and the B to A difference score (B-A Index), are regarded as the measures of the method, thus eliminating the impact of speed component (work rate). Errors were rare and therefore were not treated as indicators of reaction quality.

The SCWT is applied to assess cognitive inhibition of the prepotent automatic reading response's distracting influence and measure inhibitory control in a conflict situation [23]. In the study, an experimental procedure was administered, involving performance of three tasks: a) speed reading of names of colours printed in black on an A4 white sheet of paper; b) speed naming of colours presented in the form of rectangles printed on an A4 white sheet of paper; c) speed naming of colour words printed in ink of different colour on an A4 white sheet of paper (e.g. the word "red" printed in yellow). The parameters measured were time of the task and the number of errors. In the present analyses, the following indices were adopted: single trial time (Time 1, Time 2, Time 3), time interference index, trial 3-2 (Interference A), number of errors in each trial (Errors 1, Errors 2, Errors 3), error interference index, trial 3-2 (Interference B).

The BDI is a popular self-report inventory administered for assessment of mood level and symptoms of depression in clinical trials, recommended for use in MS patients [24]. The tool is based on A. Beck's cognitive approach, according to which patients focus mainly on the cognitive aspects of their depressive beliefs. The questionnaire consists of 21 questions to which there are four answer choices, ranging in intensity, which reflects the severity of depressive thoughts (0 - lack of symptoms, 3 - severe symptoms). The interpretation of the total score is as follows: 0-9 points - lack of depressive symptoms, 10-19 - mild depression; 20-25 - moderate depression, 26-63 - severe depression [25]. In the present study, a BDI total score exceeding 10 points is considered an indicator of depressed mood [26].

Statistical analyses of the obtained results were performed by means of SPSS statistical software package, version 21. Continuous variables were expressed as mean (M) and standard deviation (SD). The normal distribution of variables was checked using the Kolmogorov-Smirnov test. In order to verify the differences between the groups for variables with normal distribution, Student's t-test was applied.

Alternatively, nonparametric Mann-Whitney U test was used. In order to determine the strength of the relationship between the chosen variables, the Pearson parametric or Spearman nonparametric correlation coefficients were employed. The analyses were performed adopting also a single variable regression model for variables with normal distribution.

Results

Presented below are the results of the research project. The age of RRSM patients ranged between 23 and 63 years (M = 38.44; SD = 10.12), whereas that

of their CG counterparts ranged between 23 and 63 years (M = 36.28; SD = 12.74). Mean age of the subjects in both groups did not differ significantly (t = 0.846; df = 79; p = 0.40). The number of years of schooling in RRMS group extended from 8 to 21 (M = 15.04; SD = 3.30), and in CG it extended from 10 to 19 (M = 14.47; SD = 2.53). The mean number of years of schooling in both groups did not differ significantly either (t = 0.867; df = 79; p = 0.38). In RRMS group there were 30 women (69,8%) and 13 men (30,2%), while in CG there were 26 women (68,4%) and 12 men (31,6%). The two groups did not differ in terms of gender ($\div^2$ = 0.24; p > 0.05). In RRSM group time since diagnosis ranged from 1 to 18 years (M = 6.27; SD = 4.32), whereas the subjects' EDSS score varied between 2.5 and 6.5 points (M = 4.01; SD = 1.15). In RRSM group there were 14 subjects with depressed mood (M = 13.00; SD = 1.79; Min = 10; Max = 16) and 29 with neutral mood (M = 4.72; SD = 2.73; Min = 0; Max = 9).

The experimental and control groups were compared in terms of their TMT results (Table 1). RRMS patients, in comparison to their CG counterparts, obtained higher scores on Time A (Z = -4.89; p<0.001), Time B (Z = -5.81; p < 0.001) and B-A (t = 5.58; p < 0.001).

Table 1. The significance of differences in TMT test performance indexes between the experimental group (RRSM) and control group (GKR) - comparison by means of Student's t-test, or Mann-Whitney U test.

Type of index		RRSM	GRK	t/Z	p
Time A	M	55.74	30.84	-4.89	0.000***
	SD	38.09	7.32		
Time B	M	105.53	54.63	-5.81	0.000***
	SD	55.68	11.74		
Index B-A	M	49.79	23.78	5.58	0.000***
	SD	28.51	10.25		

*** p < 0,001; underlined U Mann–Whitney test results

Compared were also the subjects' SCWT scores. Compared with their healthy counterparts, RRSM patients' results were higher in value as regards indexes: Time 2 (t = 2.00; p < 0.05), Time 3 (t = 4.37; p < 0.001), Interference A (t = 4.87; p < 0.001), Errors 3 (Z = -5.56; p < 0.001), Interference B (Z = -5.25; p < 0.001). The results are presented in Table 2.

Table 2. The significance of differences in SCWT test performance indexes between the experimental group (RRSM) and control group (GKR) - comparison by means of Student's t-test or Mann-Whitney U test.

Type of index		RRSM	GRK	t/Z	p
Time 1	M	23.58	22.89	0.44	n.s.
	SD	7.56	6.06		

table continued on the next page

Time 2	M	29.83	25.97	2.00	0.049*
	SD	10.91	5.97		
Time 3	M	51.51	37.84	4.37	0.000***
	SD	19.00	7.16		
Interference A	M	21.67	11.86	4.87	0.000***
	SD	11.70	5.72		
Errors 1	M	0.06	0.07	-0.15	n.s.
	SD	0.25	0.27		
Errors 2	M	0.06	0.05	-0.31	n.s.
	SD	0.25	0.22		
Errors 3	M	2.74	0.23	-5.56	0.000
	SD	3.18	0.48		
Interference B	M	2.67	0.18	-5.25	0.000
	SD	3.21	0.56		

* $p < 0.05$, *** $p < 0.001$, n.s. – not significant; underlined U Mann–Whitney test results

There was a comparison conducted between the experimental group subjects with depressed and neutral mood as regards their TMT and SCWT results. What follows is that both RRSM patients with depressed and neutral mood do not differ in terms of any TMT or SCWT measures. The results are presented in Tables 3 and 4 respectively.

In table 5 are presented correlations between age, disease duration and neuropsychological test results in the experimental group. There was a positive correlation between age and the following SCWT indices: Time 1 ($r = 0.35$; $p < 0.05$), Time 2 ($r = 0.40$; $p < 0.01$), Time 3 ($r = 0.40$; $p < 0.01$), Errors 1 ($R = 0.37$; $p < 0.05$) and Errors 3 ($R = 0.34$; $p < 0.05$). Time since diagnosis positively correlated with the following SCWT indices: Time 1 ($r = 0.39$; $p < 0.01$), Time 2 ($r = 0.48$; $p < 0.01$), Time 3 ($r = 0.44$; $p < 0.01$), Errors 3 ($R = 0.46$; $p < 0.01$), Interference B ($r = 0.54$, $p < 0.01$) and TMT indices: Time A ($R = 0.39$; $p < 0.01$) and Time B ($R = 0.32$; $p < 0.05$).

As the next step, a single variable regression analysis was performed, where the explained variable was Interference B, and the explanatory variable was time since diagnosis (expressed in years). The proposed regression model turned out to be well suited for the data $F(1, 41) = 17.62$, $p < 0.05$. On the basis of R2 coefficient, it is possible to explain 30% of the dependent variable variance. The dependency between predictor and dependent variable is strong and positive (Beta = 0.548). Hence, what follows is a conclusion that the longer the duration of the disease, the higher Interference B coefficient is.

Table 3. The significance of differences in TMT test performance indexes between the experimental group (RRSM) with lowered and balanced mood – comparison by means of Student's t-test or Mann-Whitney U test.

Type of index		RRSM with lowered mood	RRSM with balanced mood	Z	p
Time A	M	50,44	66,71	0,000	n.s.
	SD	19,24	60,82		
Time B	M	102,03	112,78	-0,23	n.s.
	SD	40,99	79,46		
Index B-A	M	51,58	46,07	-0,50	n.s.
	SD	30,14	25,43		

n.s.– not significant

Table 4. The significance of differences in SCWT test performance indexes between the experimental group (RRSM) with lowered and balanced mood –comparison by means of Mann-Whitney U test.

Type of index		RRSM with lowered mood	RRSM with balanced mood	Z	p
Time 1	M	22.62	25.57	-1.49	n.s.
	SD	7.38	7.82		
Time 2	M	29.58	30.35	-0.42	n.s.
	SD	11.08	10.94		
Time 3	M	50.13	54.35	-0.05	n.s.
	SD	15.21	25.60		
Interference A	M	20.55	24.00	-0.24	n.s.
	SD	8.28	16.91		
Errors 1	M	0.03	0.14	-1.29	n.s.
	SD	0.18	0.36		
Errors 2	M	0.10	0.00	-1.23	n.s.
	SD	0.30	0.00		
Errors 3	M	2.31	3.64	-0.23	n.s.
	SD	2.15	4.63		
Interference B	M	2.20	3.64	-0.34	n.s.
	SD	2,21	4,63		

n.s. – not significant

Table 5. Correlations between age and time from diagnosis and TAT and SCWT test indexes in the experimental group (RRSM) – parametric r-Pearson and nonparametric Spearman R correlations were performed

Type of index	Age		Time from diagnosis	
	r/R	p	r/R	p
Time A	0.152	n.s.	0.397	0.008**
Time B	0.246	n.s.	0.320	0.036*
Index B-A	0.295	n.s.	0.246	n.s.
Time 1	0.357	0.019*	0.393	0.009**
Time 2	0.402	0.008**	0.480	0.001**
Time 3	0.403	0.007	0.446	0.003**
Interference A	0.279	n.s.	0.277	n.s.
Errors 1	0.372*	0.014*	0.115	n.s.
Errors 2	0.269	n.s.	0.159	n.s.
Errors 3	0.341	0.025*	0.465	0.002**
Interference B	0.292	n.s.	0.548	0.000***

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, n.s. – not significant;
underlined R-Spearman coefficient significance

Table 6. The relationship between the time from diagnosis and the level of interference B index in the experimental group (single variable regression analysis model)

	R2	Standard estimation error	F	p	B (constant/time from diagnosis)	Beta	p
Time from diagnosis	0.301	2.75	17.62 df (1/41)	0.000***	0.11/0.41	0.548	0.879/0.000***

*** $p < 0.001$

Discussion of results

The results confirmed that RRSM patients exhibit significant cognitive function impairment, affecting the processes of concentration, attention shifting, working memory and dominant reaction inhibition, linked with prefrontal cortex and cingulate gyrus activity [13, 15]. Impaired attention and cognitive inhibition disorders may result in difficulties affecting patients' professional lives as well as their everyday activities, such as driving, quick decision making, or their ability to work under stress [9]. However, no differences in cognitive processing in MS subjects with varied mood levels (i.e. depressed vs. neutral) were reported in the study. In this study the authors used the Trail Making Test (TMT), Stroop Colour-Word Test (SCWT), and Beck Depression Inventory (BDI).

Compared to the control group, RRMS patients scored worse on TMT Part A ($Z = -4.89$; $p < 0.001$). It means that they needed more time to finish the task. Time needed to complete this part of the test is considered to be an indicator of the ability to focus attention, and therefore lower results may suggest RRMS patients' reduced capacity in this area. Similar findings were reported by other authors, thus indicating psychomotor retardation and reduced concentration as common symptoms in MS patients [9].

Part B is more demanding, as it requires more cognitive involvement, activates the process of attention switching between letters and numbers more strongly and is linked with the function of working memory. The results across RRSM group in this part of the test were lower in comparison with the control group ($Z = -5.81$; $p < 0.001$). To detect executive dysfunction more accurately, a measure eliminating the impact of speed component (mental work speed) was devised in the shape of B to A difference [27]. RRMS patients' B-A results reached higher values as compared to the control group ($Z = 5.58$; $p < 0.001$), which confirms the presence of working memory and attention shifting deficits in the experimental group subjects. Attempts have been made to account for such deficits in MS patients, particularly in respect of pathology within the frontal lobes [21, 28].

In the first part of SCWT, RRMS patients and the healthy controls had the same response times ($t = 0.44$; $p > 0.05$), which suggests preserved reading capacity in the former ones. In the second part, RRMS patients had higher response times in comparison to their healthy counterparts ($t = 2.00$; $p < 0.05$), which may indicate a greater difficulty experienced by MS patients in activating their mental lexicon. Inthe third part of SCWT, RRMS patients again had higher reaction times than the healthy subjects ($t = 4,37$; $p < 0,001$), which implies deficits in the area of dominant reaction inhibition across the group. As regards Interference A index, which ignores the time component, RRMS patients got worse scores compared to the healthy subjects, thus further confirming the presence of difficulties in dominant reaction inhibition in this group of patients. In the first and second parts of SCWT, experimental group subjects made few errors, similarly to their healthy counterparts ($Z = -0.15$; $p > 0.05$ and $Z = -0.31$; $p > 0.015$). In the third part, on the other hand, RRMS patients made more errors than the controls ($Z = -5.56$; $p < 0.001$) and scored significantly worse in Interference B index ($Z = 5.25$; $p<0.001$), which further asserts the existence of problems within the functioning of dominant reaction inhibition in MS patients. White matter atrophy was suggested as a potential reason underlying the aforementioned dysfunctions in this group of MS patients [28]. Furthermore, a link was confirmed between deficits concerning dominant reaction inhibition and a decreased cerebellar activity, cerebellum being the area which closely cooperates with prefrontal cortex, involved in cognitive control processes [29].

In the MS patients group the most common research subject seemed to be the relationship between clinically diagnosed depression and cognitive function. The relationship between depressed (lowered) mood and cognitive function, however, did not go under such scrutiny. In the present study, experimental group subjects with depressed and neutral mood did not differ in their performance on TMT or SCWT. Lubrini et al. managed to confirm a significant relationship between depression, attention disorders and psychomotor speed [30]. Randolph et al., in turn, assumed a paradigm according

to which in MS depression has a moderating nature, influencing executive dysfunctions and attention disorders [31]. Yet other conceptualizations consider cognitive dysfunctions in MS to constitute cognitive markers of depression. Julian et al. indicated anomalous activity within prefrontal cortex as a common neurofunctional basis of attention dysfunctions and executive disorders [20]. However, not all available sources confirm the above correlation, which points to the necessity of further research [32].

Age may affect psychometric test performance, especially when time is a relevant factor for assessment [27]. In this study, age was positively correlated only with SCWT time parameters in patients with MS with relapsing-remitting course. A more important parameter proved to be time since diagnosis of MS, which was positively correlated with TMT and SCWT time parameters. A particular relationship was observed between MS duration and Interference B (error) index in RRMS group, suggesting that the longer the course of the disease, the lower the capacity for cognitive inhibition in MS patients.

Results presented in this paper constitute a confirmation of the works of others and require further empirical verification. The great value of the present study lies in its consideration of measures disregarding time parameters, which contributes to a more valid assessment of the investigated processes. It is worth highlighting that the obtained data offer a wider diagnostic scope and may thus be useful in the work of a therapeutic team. The authors of the present study are also aware of its limitation in the form of low predictive power regarding MS patients' daily hardships, i.e. low ecological validity of the results. Moreover, the experimental group lacked MS patients with clinically diagnosed depression. Variables such as pharmacotherapy or psychotherapeutic treatment were not taken into account.

Conclusions

1. Deficits in both attention shifting and dominant reaction inhibition are prevalent in MS patients.
2. Age is one of the factors which have a minor influence on the level of attention shifting and dominant reaction inhibition in MS patients.
3. Time since diagnosis is highly correlated with the level of dominant reaction inhibition in MS patients.
4. Depressed mood is not correlated with the level of attention shifting or dominant reaction inhibition in MS patients

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