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The efficacy of computer-based cognitive training for executive dysfunction in schizophrenia

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ABSTRACT

The purpose of this study was to assess the effect of computer-based cognitive training on executive dysfunction in patients with schizophrenia. Sixty-five patients with schizophrenia were randomly assigned to a training group (n = 33) or a non-training group (n = 32), and compared in terms of executive performance to a healthy control group (n = 33). Executive function was assessed using the Trail Making Test, the Stroop Color and Word Test, and the Wisconsin Card Sorting Test (computer version). Cognitive training was performed using RehaCom software over a course of 16 individual sessions. Primary outcomes were training (performance at three different timepoints) and neuropsychological components (flexibility and cognitive inhibition, high executive processing, and processing speed). In both clinical groups, all aspects of executive function were found to be deficient. In the patient training group, the use of computer-based training alongside pharmacological treatment was more effective in terms of cognitive improvement than pharmacological treatment alone. However, there was no significant effect of cognitive training on processing speed. Cognitive training in schizophrenia patients was effective at improving several aspects of executive function, but did not improve processing speed.

1. Introduction

Apart from positive, negative and disorganization symptoms, cognitive deficits, such as attention, memory, language and executive function impairment, constitute key psychopathological symptoms in schizophrenia (Palmer et al., 2009). Several meta-analyses suggest that, in most cases, these deficits are more than one standard deviation below average (Dickinson et al., 2007; Fioravanti et al., 2005, 2012). There is also clear evidence that such deficits are among the key sources of difficulties in social and occupational functioning, and have a major impact on patients' quality of life (Bell et al., 2008; Fett et al., 2011).

Executive dysfunction, stemming from abnormalities in the structure and activity of prefrontal and thalamic networks, has been recognized as the most characteristic neuropsychological symptom of schizophrenia (Giraldo-Chica et al., 2018; Orellana and Slachevsky, 2013). Based on a review of 41 studies using functional magnetic resonance imaging, Minzenberg et al. (2009) demonstrated that executive function deficit in schizophrenia is linked with decreased activity in the left dorsolateral prefrontal cortex, rostral/dorsal anterior cingulate cortex, left thalamus, and inferior/posterior cortical areas. The dysfunction is believed to relate to monitoring, inhibition, attention shifting, planning, rule generation, and abstract thinking; thus it hinders the implementation of purposive actions, especially those related to everyday activities (Bulzacka et al., 2016; Kerns et al., 2008).

Various forms of therapeutic interventions, including pharmacological treatment and cognitive training, are used to reduce cognitive deficits. Both conventional and second-generation antipsychotics have a negligible effect on such deficits (Woodward et al., 2005). Different pharmacological interventions to enhance cognition and executive function have been evaluated, including the use of dopaminergic antagonists (Bellack et al., 2004), acetyl-cholinesterase inhibitors (Keefe et al., 2008), glutamatergic agents (Buchanan et al., 2007), and nicotinic agonists (Freedman et al., 2008), but with no particularly encouraging results (Harvey, 2009). Due to the low efficacy of pharmacological treatment, interventions based on cognitive training, including cognitive remediation (i.e., curative treatment and compensatory strategies) and cognitive rehabilitation (i.e., restoration of premorbid levels), are becoming increasingly popular among both

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researchers and clinicians (Kluwe-Schiavon et al., 2013; Wykes et al., 2011).

Over the past several years, various programs have been developed to support the cognitive training of patients with schizophrenia, especially programs which aim to improve impaired executive function. These programs vary in terms of their theoretical underpinnings, applied methods, and main approaches. There are two basic types of methods: (a) computer-based and (b) paper-and-pencil tasks (Medalia and Choi, 2009; Twamley et al., 2003). The main approaches include: (a) functional adaptation (daily life activities), (b) general stimulation (non-specific training involving multiple cognitive abilities), and (c) process-specific approaches (directly strengthening the appropriate cognitive skills; Bryce et al., 2016a; Kluwe-Schiavon et al., 2013).

Still, findings regarding the effects of using computer-assisted interventions to improve executive function in persons with schizophrenia are inconsistent. On one hand, their efficacy has been demonstrated in a comparison of various test conditions: (a) "active - training" vs. "control - not training" (d'Amato et al., 2011), (b) "baseline - first testing" vs. "endpoint - second testing" (Sartory et al., 2005), and (c) "active - training" vs. "passive - training" (Fisher et al., 2009). Elsewhere, however, the effects of such methods have not been observed in a comparison of (a) "active - training" vs. "control - not-training" (Hodge et al., 2008) and (b) "active - training" vs. "passive - training" (Dickinson et al., 2009). Similar inconsistencies exist in reports on the use of paper-and-pencil methods. Some authors suggest their efficacy in improving executive function, e.g., comparing: (a) "active - training" with "control - not training" (Ojeda et al., 2012; Wykes et al., 2007), or "active - training" with "passive - training" (Katz and Keren, 2011), while others fail to report significant differences between "active - training" and "control - not-training" (López-Luengo and Vázquez, 2003). In addition, comparisons of various forms of training demonstrate that computer-assisted techniques are more effective at improving certain domains of executive function (Royer et al., 2012; Vita et al., 2011). Research on the follow-up effect seems to generate equally inconsistent data, as some findings suggest the persistence of positive effects for at least six months after completing computer-based training (Bell et al., 2007; Poletti et al., 2010) or paper-and-pencil training (Matsui et al., 2009; Penadés et al., 2006), while other reports demonstrate different results (Greig et al., 2007; Hodge et al., 2008).

In the aforementioned research, the most common tools used to measure executive function were the classic Wisconsin Card Sorting Test (WCST), the Trail Making Test (TMT), and the Stroop Color Word Test (SCWT; Kluwe-Schiavon et al., 2013; Wykes et al., 2011). However, due to the fact that patient scores are often interpreted based on response time measures (especially for TMT and SCWT), it is difficult to draw conclusions concerning executive function that are relatively independent of speed of information processing. In addition, available remediation programmes are very heterogeneous and most studies are of poor methodological quality; large randomised controlled trials remain scarce.

Given the above findings and inconsistencies, we formulated and tested the hypothesis that cognitive remediation would improve executive performance in patients with schizophrenia. Moreover, we hypothesized that patients with schizophrenia (from both groups) would exhibit executive dysfunction and reduced processing speed. We also used a broadly targeted computer-based cognitive remediation program for a large group of patients.

2. Material and methods

2.1. Clinical trial design

The study was conducted in Poland. Participants were randomly assigned to one of the study groups according to random permuted blocks (blocks of four - AABB, ABBA, BBAA, ABAB, BAAB, BABA) using the strata procedure (Stout et al., 1994). Sex (male/female) and age (20–29 years = 1, 30–39 years = 2, 40–49 years = 3, and 50–60 years = 4) were used as stratification variables. The training group patients (SPTG) received standard treatment and participated in a cognitive remediation program, while the non-training group patients (SPNTG) received standard pharmacological treatment only. Clinical and cognitive assessments were carried out at baseline (first testing, up to one week before the start of training) and at the end (second testing, up to one week after the end of training). Follow-up assessment was not conducted. Training included 16 sessions administered twice a week over a period of two months (average of 10.70 h). The results of our computer-assisted training were recorded at three time points: during the first session (baseline), the mean of the eighth and ninth sessions (middle), and the sixteenth session (endpoint).

2.2. Participants

A total of 65 patients with paranoid schizophrenia (35 women and 30 men) were recruited at psychiatric wards in the local district and from the local patient association. The diagnosis was made by properly licensed psychiatrists prior to the start of the study based on a structured clinical interview in line with the International Statistical Classification of Diseases and Related Health Problems (ICD-10, World Health Organization, 1992). The same clinical interview was used by all psychiatrists. The inclusion criteria were understanding the test procedure, being aged from 20 to 60 years, and having a stable clinical status (i.e., < 3 points on P2: “Conceptual disorganization” and G9: “Unusual thought content” from the Positive and Negative Syndrome Scale). The exclusion criteria were concomitant mental or neurological diseases, dementia, craniocerebral injuries, severe somatic diseases (e.g., cancer), addiction to alcohol or other substances, and intellectual disability (diagnosed by a neuropsychologist based on the ICD-10). All patients gave their written consent to participate in the study, in accordance with the protocol approved by a local ethics committee. All participants received antipsychotic medication before and throughout the study. A total of 21.20% of the SPTG group and 28.10% of the SPNTG group were on typical antipsychotics only, while the remaining 78.80% and 71.90%, respectively, received atypical antipsychotics (Danivas and Venkatasubramanian, 2013; Samara et al., 2016).

A healthy control group (HCG) of 33 persons (16 women and 17 men) without mental or neurological diseases, matched for gender, age, and number of years of education, were recruited through information spread by students of the local university. The inclusion and exclusion criteria for healthy controls were the same as those for patients (except for the diagnosis of schizophrenia). In addition, two other inclusion criteria in this group were: absence of mental health disorders, i.e., < 92 points on the General Health Questionnaire (GHQ-30; Frydecka et al., 2010), and < 12 points on the Beck Depression Inventory (BDI; Parnowski and Jernajczyk, 1977).

2.3. Clinical assessments

The Positive and Negative Syndrome Scale (PANSS) was used to measure the severity of psychopathological symptoms (positive, negative, and general symptoms) in schizophrenia patients (Kay et al., 1987). In addition, the General Health Questionnaire (GHQ-30; Goldberg, 1972) was used to screen for mental health problems and the Beck Depression Inventory (BDI; Beck et al., 1961) was used to assess depression in the healthy controls.

2.4. Neuropsychological assessments

The study used a computer version of the Wisconsin Card Sorting Test (WCST; Heaton et al., 1993). Following previous research using factor analysis in patients with schizophrenia, concept formation was measured based on the percentage of perseverative errors (WCST PPE),

while the percentage of non-perseverative errors (WCST NPE) was used to assess problem solving (Polgár et al., 2010). The task consists of classifying cards according to different criteria (color, shape, or number) by pressing a button from 1 to 4 on the keyboard, based on feedback appearing on a 15-inch computer screen. Beforehand, all participants received verbal instructions from a licensed psychologist. The Trail Making Test (TMT; Reitan, 1958) was used to measure cognitive flexibility. TMT A consists of drawing a continuous line sequentially connecting 25 numbered circles from 1 to 25, arranged irregularly on a white A4 sheet of paper. In TMT B, the test taker is to connect the circles, alternating between numbers and letters (1-A, A-2, etc.), completing the task with the number 13 and the letter L. Prior to the proper task, a trial run was carried out to ensure that the participants understand the instructions. The instructions were presented verbally by a psychologist twice: before the trial and before the proper task. Due to the reduced speed of information processing reported in schizophrenia patients, three different measures were used in the study (Knowles et al., 2010; Morrens et al., 2006). Response time on TMT A was used to measure speed of information processing. Response time on TMT B was used to measure cognitive flexibility dependent on processing speed. To measure cognitive flexibility independent of processing speed, we used the derived index B-A/A (TMT DI; Stuss et al., 2001). The study also used the Stroop Color Word Test (SCWT; Stroop, 1935). Given the reduced processing speed in schizophrenia patients (Knowles et al., 2010; Morrens et al., 2006), three different measures were used to assess cognitive inhibition. Response time on part 1 - congruent (SCWT 1) was used to measure processing speed. Response time on part 2 - incongruent (SCWT 2) was used to assess cognitive inhibition dependent on processing speed. To measure cognitive inhibition independent of processing speed, we used a derived index calculated using the formula: (time in incongruent - time in congruent) / time in incongruent (SCWT DI; Denney and Lynch, 2009). In part 1 (congruent), the subjects are asked to read color names printed in black font on a white A4 sheet of paper. The second trial (incongruent) consists of reading aloud a word printed in an inconsistent color font on a white A4 sheet of paper (color names are printed in colors different from those denoted by the names - e.g., the word “blue” printed in yellow).

2.5. Computer-based training

SPTG participants underwent computer-based training using the RehaCom® software package (SCHUHFRIED, GmbH), including various procedures enabling improvement in selected areas of cognitive functioning in which deficits have been diagnosed. Participants are provided with feedback about their progress in the form of a graph. Training was carried out by two experienced psychologists. The subjects used a desktop computer (with a 15-inch screen) and a special ergonomic keyboard. Currently, RehaCom is the only such software available on the local market and it has been shown to benefit persons with brain damage (Fernández et al., 2012) as well as schizophrenia patients (Cochet et al., 2006; d'Amato et al., 2011). For more details, see the Rehacom website at http://www.hasomed.de. Two of the available procedures were selected to be used in this project, and are described below.

2.5.1. Attention and concentration

The main module of interest was the Attention and Concentration module, which is used to improve sustained attention on a task, but it also improves executive function and organization of activities (van de Ven et al., 2016). A picture (symbol, item, animal, or abstract figure) is presented separately from a matrix of pictures. The patient is then asked to select the one picture from the matrix that most resembles the isolated picture.

2.5.2. Memory

The Topological Memory module is mainly used for training visual and spatial memory, as well as executive function and working memory (van de Ven et al., 2016). The procedure used in the study consists of memorizing the position and content of presented pictures, the number and complexity of which depend on the level of difficulty. After the acquisition phase, the pictures are turned face down to hide the image. A picture matching one of those facing down is then presented separately and the patient must match the pair. If chosen correctly, the picture is removed from the matrix. Incorrectly selected pictures are displayed for 5 s and then hidden again. The task ends when all the pictures are matched.

2.6. Statistical analysis

Statistical analyses were performed using the IBM SPSS 24 Statistical package. Continuous variables are presented in the form of means (*M*) and standard deviations (*SD*). The normality of the distributions of the variables was verified using the Shapiro-Wilk test. Student's *t*-test was used to check the differences between the two groups. A parametric one-way ANOVA was used to determine the differences between the three groups. To determine the differences between the mean scores, we used the Games-Howell *post hoc* test. To determine the magnitude of effect size, Cohen's *d* or η^2 effect size was used (Cohen, 1992). For multiple comparisons, Bonferroni correction was used. In order to evaluate the four effects of cognitive remediation therapy on the patients’ neuropsychological performance, we used a multivariate two-way repeated measures/mixed model MANOVA.

3. Results

3.1. Participant characteristics

Statistical analyses did not show any differences between participants in terms of gender, age, or years of education. In addition, there were no differences between the two clinical groups (SPTG and SPNTG) in terms of age of onset, number of psychotic episodes, duration of illness, chlorpromazine equivalent, or symptom severity (positive, negative, or general). All demographic and clinical characteristics are presented in Table 1.

3.2. Executive performance at first testing

There was a significant effect of the variable "performance of executive function" for all its measured aspects: (a) executive function dependent on speed of information processing in TMT B ($F_{(2, 95)} = 5.88$; $p = 0.004$; $\eta^2 = 0.11$) and SCWT 2 ($F_{(2, 95)} = 27.88$; $p < 0.001$; $\eta^2 = 0.37$); (b) executive function independent of speed of information processing in TMT DI ($F_{(2, 95)} = 4.37$; $p = 0.015$; $\eta^2 = 0.08$) and SCWT DI ($F_{(2, 95)} = 4.45$; $p = 0.014$; $\eta^2 = 0.09$); and (c) high executive processing in WCST PPE ($F_{(2, 95)} = 9.61$; $p = 0.001$; $\eta^2 = 0.17$) and WCST PNE ($F_{(2, 95)} = 12.53$; $p < 0.001$; $\eta^2 = 0.21$). The effect size (η^2) was found to be 0.08–0.37 (a medium to large effect size). A *post hoc* analysis indicated that the patients in both clinical groups (SPTG and SPNTG) scored lower than the HCG on all measured cognitive processes ($0.001 > p < 0.042$). However, no differences were found between the SPTG and SPNTG groups. In addition, a significant main effect was demonstrated for speed of information processing on SCWT 1 ($F_{(2, 95)} = 29.64$; $p < 0.001$; $\eta^2 = 0.38$), but not on TMT A. A *post hoc* analysis showed that the patients in both clinical groups (SPTG and SPNTG) scored lower than the HCG in this respect ($p < 0.001$). However, no differences were found between the SPTG and SPNTG groups. Descriptive statistics are presented in Table 2.

3.3. Effects of type of training and time of testing

To test the effects of the treatment on executive function and speed of information processing, a multivariate two-way repeated measures/

Table 1
Demographic and clinical characteristics of schizophrenia patients training group (SPTG), schizophrenia patients non-training group (SPNTG) and healthy control group (HCG) in first testing.

Variable	SPTG	SPNTG	HCG
Gender: female / male	18 / 15	17 / 15	16 / 17
Age: *M* (*SD*)	32.91 (8.83)	35.19 (10.76)	32.27 (12.65)
Years of education: *M* (*SD*)	14.33 (2.73)	13.28 (2.71)	14.18 (2.14)
Age at first episode: *M* (*SD*)	23.33 (4.38)	24.55 (5.43)	–
Number of psychotic episodes: *M* (*SD*)	2.91 (1.33)	3.21 (1.42)	–
Duration of illness: *M* (*SD*)	8.11 (7.22)	9.21 (7.45)	–
Positive symptoms (in PANSS): *M* (*SD*)	12.42 (3.20)	13.47 (6.38)	–
Negative symptoms (in PANSS): *M* (*SD*)	18.30 (5.08)	18.94 (5.26)	–
Global symptoms (in PANSS): *M* (*SD*)	29.58 (6.69)	31.34 (7.69)	–
General health (in GHQ-30): *M* (*SD*)	–	–	51.32 (3.50)
Depressiveness (in BDI): *M* (*SD*)	–	–	5.66 (2.84)
Antipsychotic medications			
Atypical			
Olanzapine: *n* /%	18 / 54.55	11 / 34.40	
Ziprasidone: *n* /%	5 / 15.15	12 / 37.50	
Clozapine: *n* /%	3 / 9.10	0 / 0.00	
Typical			
Perazine: *n* /%	7 / 21.20	9 / 28.10	
Chlorpromazine equivalent (mg): *M* (*SD*)	269.24 (95.48)	267.31 (59.94)	

Note. BDI = Beck Depression Inventory; GHQ-30 = General Health Questionnaire; PANSS = Positive and Negative Syndrome Scale.

mixed 2 × 2 MANOVA with "type of training" (training group vs. non-training group) as a between-subject factor and "time of testing" (first testing vs. second testing) as within-subject factor was computed for the dependent variable "type of executive function or speed of information processing". Complementary analysis using Student's *t*-test (between two groups) was performed if there was a significant main effect, regardless of the interaction.

3.3.1. Executive function dependent on speed of information processing

In TMT B, the main effect of "type of training" was non-significant, indicating that patients from both groups did not vary in terms of cognitive flexibility dependent on speed of information processing, regardless of time of testing. The main effect of "time of testing" was medium and significant ($F_{(1,\ 63)} = 9.75$; $p = 0.003$; $\eta^2 = 0.13$), indicating that patients from both groups improved, regardless of type of training. Furthermore, the interaction between "type of training" and "type of testing" was medium and significant ($F_{(1,\ 63)} = 7.58$; $p = 0.008$; $\eta^2 = 0.11$). Pairwise comparisons showed that only SPTG patients improved in terms of the measured cognitive process ($p < 0.001$). Descriptive statistics are presented in Table 2 and Fig. 1(A).

In SCWT 2, the main effect of "type of training" was non-significant, indicating that patients from both groups did not vary in terms of cognitive inhibition dependent on speed of information processing, regardless of the time of testing. The main effect of "time of testing" was medium and significant ($F_{(1,\ 63)} = 7.24$; $p = 0.009$; $\eta^2 = 0.10$), indicating that patients from both groups improved, irrespective of the type of training. Furthermore, the interaction between "type of training" and "type of testing" was non-significant. Descriptive statistics are presented in Table 2 and Fig. 1(B).

3.3.2. Executive function independent of speed of information processing

As regards TMT DI, the main effect of "type of training" was medium and significant ($F_{(1,\ 63)} = 5.43$; $p = 0.023$; $\eta^2 = 0.08$), indicating that patients from both groups differed in terms of cognitive flexibility independent of speed of information processing, regardless of the time of testing. The main effect of "time of testing" was medium and significant ($F_{(1,\ 63)} = 5.53$; $p = 0.022$; $\eta^2 = 0.08$), indicating that patients from both groups improved, irrespective of the type of training. Furthermore, the interaction between "type of training" and "type of testing" was non-significant. Descriptive statistics are presented in Table 2 and Fig. 1(C).

As regards SCWT DI, the main effect of "type of training" was non-significant, indicating that patients from both groups did not differ in terms of cognitive inhibition independent of speed of information processing, regardless of the time of testing. The main effect of "time of testing" was medium and significant ($F_{(1,\ 63)} = 6.52$; $p = 0.013$; $\eta^2 = 0.09$), indicating that patients from both groups improved, regardless of the type of training. Furthermore, the interaction between "type of training" and "type of testing" was non-significant. Descriptive statistics are presented in Table 2 and Fig. 1(D).

3.3.3. High executive processing

As regards WCST PPE, the main effect of "type of training" was non-significant, indicating that patients from both groups did not differ in terms of concept formation, irrespective of the time of testing. The main effect of "time of testing" was medium and significant ($F_{(1,\ 63)} = 5.61$; $p = 0.021$; $\eta^2 = 0.08$), indicating that patients from both groups improved, regardless of the type of training. Furthermore, the interaction between "type of training" and "type of testing" was non-significant. Descriptive statistics are presented in Table 2 and Fig. 1(E).

As regards WCST PNE, the main effect of "type of training" was non-significant, indicating that patients from both groups did not vary in terms of concept formation, regardless of the time of testing. The main

Table 2
Comparison of executive performance and processing speed in schizophrenia patients training group (SPTG), schizophrenia patients non-training group (SPNTG) and healthy control group (HCG) in first and second testing.

Variable		Indicator	SPTG First testing *M* (*SD*)	SPTG Second testing *M* (*SD*)	SPNTG First testing *M* (*SD*)	SPTG Second testing *M* (*SD*)	HCG First testing *M* (*SD*)
Dependent on the processing speed	Cognitive flexibility	TMT B	72.15 (31.17)	60.21 (29.48)	75.69 (20.59)	74.94 (29.07)	53.91 (20.95)
	Cognitive inhibition	SCWT 2	73.70 (22.86)	65.82 (20.95)	71.09 (30.42)	66.34 (19.49)	35.27 (8.03)
Independent of the processing speed	Cognitive flexibility	TMT DI	1.40 (0.90)	0.89 (0.62)	1.51 (0.70)	1.44 (0.78)	0.89 (0.68)
	Cognitive inhibition	SCWT DI	1.62 (0.66)	1.19 (0.69)	1.53 (1.41)	1.36 (1.14)	0.94 (0.42)
High executive processing	Concept formation	WCST PPE	20.30 (10.16)	14.27 (12.95)	19.63 (12.80)	17.25 (9.21)	11.05 (2.84)
	Problem solving	WCST PNE	19.09 (11.90)	12.09 (11.95)	16.13 (12.06)	17.65 (14.40)	7.21 (4.04)
Speed of information processing	Connecting circles	TMT A	31.70 (13.89)	31.58 (9.55)	32.59 (14.51)	31.47 (9.17)	29.91 (9.55)
	Reading	SCWT 1	28.55 (7.16)	30.85 (7.19)	29.41 (8.22)	31.00 (8.93)	18.33 (2.79)

Note. SCWT = Stroop Color Word Test: 1 = reaction time in congruent part; 2 = reaction time in incongruent part; DI = derived index (time incongruent - time congruent) / time congruent; TMT = Trail Making Test: A = reaction time in part A; B = reaction time in part B; DI = derived index: (time in part B - time in part A) / time in part A; WCST = Wisconsin Card Sorting Test: PPE = percent of perseverative errors; PNE = percent of non-perseverative errors.

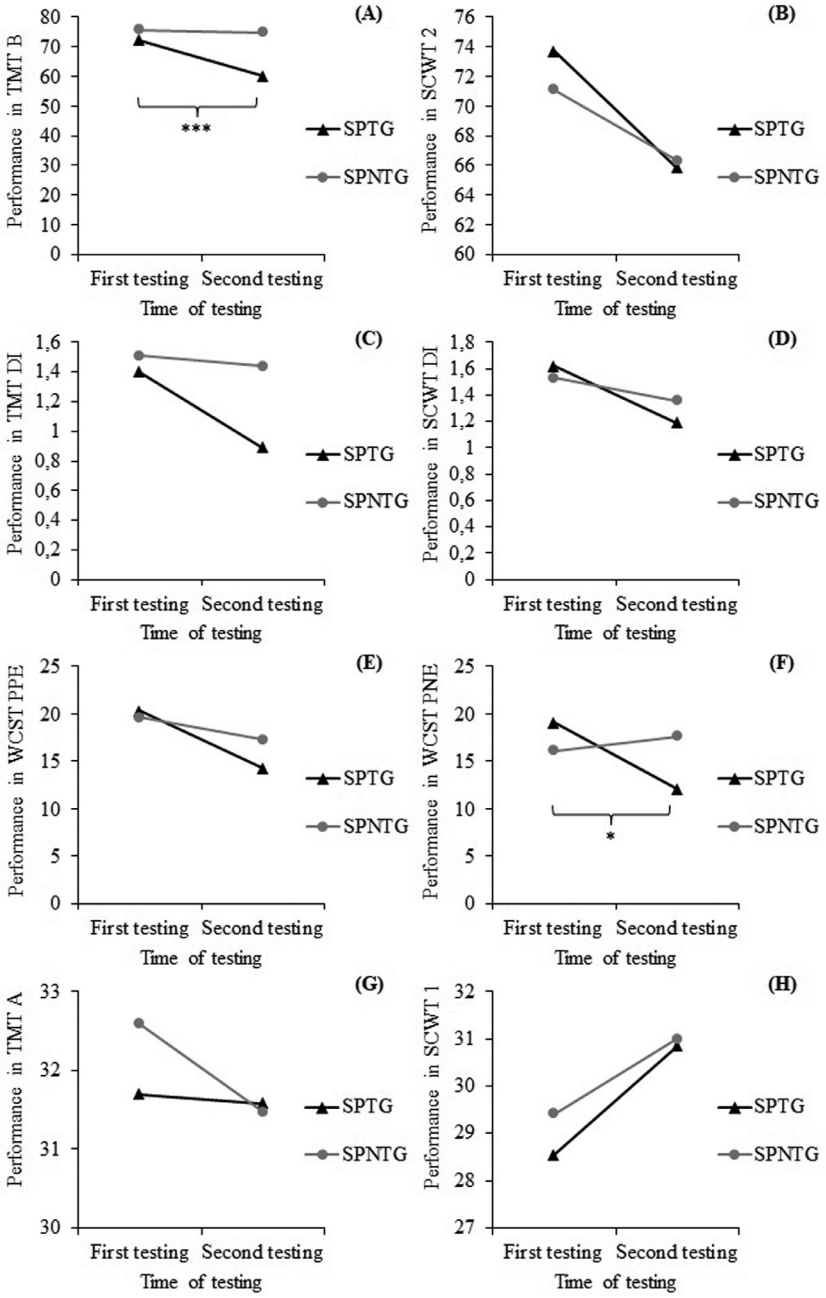

Fig. 1. Mean scores for indicators of executive functions (A, B, C, D, E, and F) and speed of information processing (G and H) in the schizophrenia patient training group (SPTG; $n = 33$) and the schizophrenia patient non-training group (SPNTG; $n = 32$), before (first testing) and after (second testing) computer-based training with RehaCom. Significant differences between pre- and post-intervention assessment are marked.
* $p < 0.05$. *** $p < 0.001$.

effect of "time of testing" was non-significant, indicating that patients from both groups did not improve, regardless of the type of training. However, the interaction between "type of training" and "type of testing" was medium and significant ($F_{(1,\ 63)} = 4.96$; $p = 0.030$; $\eta^2 = 0.07$). Pairwise comparisons showed that only SPTG patients improved ($p = 0.012$). Descriptive statistics are presented in Table 2 and Fig. 1(F).

3.3.4. Speed of information processing

The main effect of "type of training" was non-significant for both TMT A and SCWT 1, indicating that patients from both clinical groups did not vary in terms of their performance (speed of connecting circles or reading), regardless of the time of testing. The main effect of "time of testing" was non-significant, indicating that patients from both groups did not improve, irrespective of the type of training. Furthermore, the interaction between "type of training" and "type of testing" was non-significant. Descriptive statistics are presented in Table 2 and Fig. 1 (G and H).

3.4. Effect of computer-based training

To test the "effect of computer-based training", a one-way repeated measures ANOVA was used, where the independent variable was time of measurement - baseline (session 1), the middle (the mean of session 8 and 9), and the endpoint (session 16) - and the dependent variable was patient performance on each procedure separately.

Table 3
Comparison of results in three sessions in computer-based training with RehaCom in schizophrenia patient training group (SPTG).

Procedure in RehaCom	Baseline[a]	Middle[b]	Endpoint[c]
	M (*SD*)	*M* (*SD*)	*M* (*SD*)
Attention and Concentration	7.24 (2.83)	20.80 (3.37)	22.21 (2.79)
Topographical Memory	5.30 (1.68)	8.34 (2.67)	8.84 (3.16)

[a] Results in RehaCom at baseline session (first session).
[b] Results in RehaCom at middle session (mean of the eighth and ninth session).
[c] Results in RehaCom at endpoint session (sixteenth session).

3.4.1. Effect of attention and concentration training

The main effect of "training of attention and concentration" was large and significant ($F_{(2,\ 64)} = 694.26$; $p < 0.001$; $\eta^2 = 0.96$), indicating that SPTG patients got significantly different scores at the three training sessions that were assessed. Next, a *post hoc* analysis indicated that patients scored higher at sessions 8/9 compared to session 1 ($p < 0.001$), at session 16 compared to sessions 8/9 ($p < 0.001$), and at session 16 compared to session 1 ($p < 0.001$). Descriptive statistics are presented in Table 3 and Fig. 2(A).

3.4.2. Effect of memory training

The main effect of "memory training" was large and significant ($F_{(2,\ 64)} = 55.24$; $p < 0.001$; $\eta^2 = 0.63$), indicating that SPTG patients got significantly different scores at the three training sessions that were assessed. Next, a *post hoc* analysis indicated that patients got higher scores at sessions 8/9 compared to session 1 ($p < 0.001$) and at session 16 compared to session 1 ($p < 0.001$); however, there were no significant differences observed between sessions 16 and 8/9. Descriptive statistics are presented in Table 3 and Fig. 2(B).

4. Discussion

The present study was designed to test whether 16 sessions of computer-based training could enhance executive functioning and speed of information processing in patients with schizophrenia. The training involved the use of two modules of the RehaCom software (Attention and Concentration and Topological Memory). To date, the program has been successfully applied, with significant efficacy, in the training of cognitive dysfunction in patients with schizophrenia (d'Amato et al., 2011), stroke, and multiple sclerosis (Filippi et al., 2012; van de Ven et al., 2016).

In our study, cognitive flexibility and cognitive inhibition (both dependent on and independent of speed of information processing) and high executive processing (like concept formation and problem solving) were found to be deficient in schizophrenia patients (SPTG and SPNTG). This is in-line with the results of several meta-analyses comparing schizophrenia patients with healthy control groups (Fioravanti et al., 2005, 2012; Henry and Crawford, 2005). However, differences in performance on the Wisconsin Card Sorting Test (WCST) between the patients (SPTG and SPNTG) and healthy controls in our study could be due to decreased efficiency of working memory (responsible for holding information in temporary storage, manipulating it, and using it to guide subsequent behavior), which has been reported by, e.g., Park and Gooding (2014). In both groups of schizophrenia patients in this study, speed of information processing on the reading task on the Stroop Color Word Test (SCWT 1) was slower, which is consistent with the results presented by other authors (Dickinson et al., 2007; Morrens et al., 2006). In our study, however, patients did not exhibit significant dysfunctions in terms of speed of information processing on the Trail Making Test (TMT), which is not in line with the results reported in a meta-analysis by Knowles et al. (2010). Moreover, according to a recent meta-analysis by Laere et al. (2018), schizophrenia patients exhibit poorer performance on TMT A, which suggests diminished information processing abilities. These results could be useful for the clinical diagnosis of various problems with executive domains and processing speed in schizophrenia and suggest that it is important to use several indicators from the TMT, SCWT, and WCST to measure cognitive performance in this patient population.

In our study, both clinical groups exhibited similar executive performance (in terms of cognitive flexibility, cognitive inhibition, concept formation, and problem solving). Following computer-based training and pharmacological treatment, patients in the active group (SPTG) improved their cognitive flexibility dependent on speed of information processing and problem solving. On the other hand, patients from the passive group (SPNTG), receiving only pharmacological treatment, did not improve in terms of their executive function. Nevertheless, patients from both clinical groups improved in other executive domains - cognitive inhibition (dependent on and independent of speed of information processing) and concept formation. Thus, our results were consistent with the findings of d'Amato et al. (2011), who used two identical computer-based training procedures in their study. In addition, our results correspond with the data reported in other works, in which different computer-assisted programs for cognitive training were used (Cavallaro et al., 2009; Dickinson et al., 2009). However, our findings are only partially consistent with the results of other studies demonstrating the effects of computer-assisted training on cognitive flexibility (measured with TMT B), but not on high executive processing (measured with the WCST; McGurk et al., 2005, 2007). Still, several meta-analyses provide evidence of the positive effect of computer-based training on some aspects of executive performance (e.g., cognitive flexibility or concept formation) in persons with schizophrenia, as well

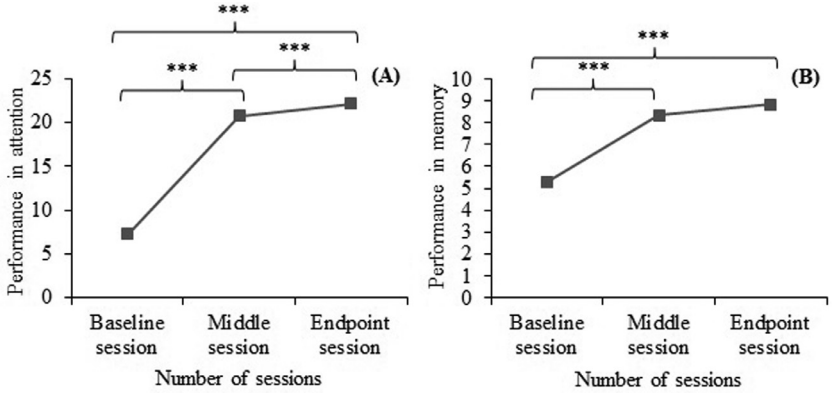

Fig. 2. Mean scores in three sessions of computer-based training with RehaCom (A = Attention and Concentration and B = Topographical Memory) in schizophrenia patient training group (SPTG, $n = 33$). Significant differences between sessions are marked above.
*** $p < 0.001$.

as sustained improvement for up to several months (the follow-up effect) following completion of training (Bryce et al., 2016b; Kluwe-Schiavon et al., 2013).

In addition, in this study, the active group participants (SPTG) displayed continuous improvement over the course of the training sessions (from baseline to the middle and endpoint) in terms of both the Attention and Concentration and Topographical Memory procedures from the RehaCom software package. No significant change in performance was observed between the middle and final session of the memory training, which could be due to the rapid early improvement plateauing during further training. Our results thus partly correspond with those presented by d'Amato et al. (2011), although that study only compared patient scores in two sessions (at baseline and endpoint). Our results suggest that both the Attention and Concentration and the Topographical Memory procedures from the RehaCom package are useful in the treatment of executive dysfunction in schizophrenia and can be used in clinical practice. It is, therefore, worth considering the use of computer-based interventions as a complementary method in the treatment of cognitive dysfunction in schizophrenia.

Our findings could be explained in several ways. Firstly, in patients with schizophrenia who suffer from executive function deficit, cognitive remediation leads to improvement of cerebral activity (Bon and Franck, 2018; Penadés et al., 2017). The changes are observed not only in the prefrontal cortex, but also in other areas of the brain that form complex networks, involving cerebral areas not related to the target functions - the lingual gyrus, for example, which governs visual attention (Penadés et al., 2013), and the superior parietal lobule, which is involved in the dorsal stream of the visual system (Vianin et al., 2014). Secondly, the observed improvement in executive performance can be a result not only of computer-based training itself, but also of non-specific factors, such as the use of electronic devices, interaction with a clinician, or cognitive challenge (Kurtz et al., 2007). Thirdly, a combination of cognitive remediation and pharmacological treatment may have a more positive effect on the functioning of the brain than pharmacological treatment alone (Bryce et al., 2016a; Kluwe-Schiavon et al., 2013).

In our study, speed of information processing (in the trail-making and reading tasks) was similar in both clinical groups (SPTG and SPNTG) and showed no improvement with either pharmacological treatment alone or combined with computer-based training. These results correspond with findings reported in other works and indicate that, as an automatic mental process, speed of information processing is difficult to improve (Bryce et al., 2016b; Hodge et al., 2008). Nevertheless, some research has demonstrated positive effects of computer training on speed of information processing (d'Amato et al., 2011; Kurtz et al., 2007). This inconsistency may be due to the use of different methods for measuring executive performance and the different clinical status of the study participants.

This study has certain limitations. First of all, the ecological validity of the applied diagnostic methods was low (in terms of, e.g., verisimilitude, i.e. the degree to which the cognitive demands of a test theoretically resemble the cognitive demands of one's everyday environment, or veridicality, i.e., the degree to which existing tests are empirically related to measures of everyday functioning; Chaytor and Schmitter-Edgecombe, 2003), which makes it difficult to draw conclusions about patients' executive performance in everyday life situations. Secondly, we did not conduct any additional assessment a few months after completion of the computer-based training, which would have allowed the confirmation of the occurrence of a follow-up effect. Thirdly, we did not evaluate social autonomy, quality of life, or daily functioning, which would show the transfer of practiced skills to other areas of social functioning. Fourthly, there was no patient group performing a different type of training (e.g., non-specific), which could help determine the strength of the effect of various types of interventions. Fifthly, the assessor was not blinded to the allocation of the patients to the two clinical groups. Sixthly, diagnosis of schizophrenia was based solely on the psychiatric evaluation conducted prior to the start of the study; no clinical measurements were used to validate the diagnosis. This is a standard procedure which has often been used in similar studies (Kluwe-Schiavon et al., 2013). Seventhly, the sample included patients with paranoid schizophrenia, which may hinder generalization of the results to the full population of people with schizophrenia. Furthermore, we did not assess participants' general intellectual level, precluding analysis of the percentage of observed variance in executive performance due to differences in intellectual abilities between the groups. Future research should, therefore, control for patients' general intellectual level.

Further studies may be necessary in order to discriminate between the effects of domain-specific, individualized cognitive remediation and more general forms of cognitive training that target all cognitive functions known to be impaired in schizophrenia patients. A longer follow-up period may help determine whether cognitive improvement can be generalized to functional outcomes. In addition, it would be worthwhile to consider the use of modern brain imaging techniques to observe potential structural and functional changes in the brains of patients undergoing such treatment.

In conclusion, our results demonstrate that persons with schizophrenia exhibit deficits in various aspects of executive function (including aspects both dependent on and independent of speed of information processing and high executive processing) and that clinical diagnosis could benefit from the use of neuropsychological indicators of executive function, in addition to time-based indicators. In this group of patients, the use of computer-based training combined with pharmacological treatment may be more effective, especially in terms of cognitive flexibility dependent on the speed of information processing and problem solving, than pharmacological treatment alone. This has the potential to significantly improve clinical management of cognitive dysfunction in schizophrenia. The efficacy of the above-mentioned computer techniques in increasing speed of information processing has not been demonstrated.

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Author contributions

All authors contributed to and have approved the final manuscript. MM was the principal coordinator of the grant, was involved in the study design, took part in patient recruitment, and wrote the first draft of the manuscript. ET took part in patient recruitment, managed literature searches and analysis, performed statistical analysis, and wrote the first draft of the manuscript. AS corrected the manuscript. EK corrected the manuscript. JS was involved in the study design and corrected the manuscript.

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