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Efficacy of non-computerized cognitive rehabilitation in Parkinson's disease: A one year follow up study

Vladimíra Plzáková[a,b,c], Josef Mana[a], Evžen Růžička[a] and Tomáš Nikolai[a,d]

[a]Department of Neurology and Centre of Clinical Neuroscience, First Faculty of Medicine and General University Hospital in Prague, Charles University, Prague, Czech Republic; [b]Institute of Neuropsychiatric Care, Prague, Czech Republic; [c]Rehabilitation Hospital Beroun, Beroun, Czech Republic; [d]Department of Psychology, Faculty of Arts, Charles University, Prague, Czech Republic

ABSTRACT

In this study, we explored the effect of non-computerized cognitive rehabilitation in patients with Parkinson's disease in comparison with an intervention with elements of music therapy after the completion of a three-month program and one year after the end of the intervention. After the initial neuropsychological examination, the respondents were divided into two intervention groups. The experimental group (n = 26) underwent a twelve-week program of cognitive rehabilitation at a frequency of 60 minutes once a week. The control group (n = 27) underwent an intervention program with elements of music therapy at the same frequency. Respondents who underwent the cognitive rehabilitation program improved in the delayed recall from visual memory in the follow-up examination after the end of the cognitive intervention. One year after the end, the effect of cognitive rehabilitation persisted in delayed recall from visual memory and in executive mental flexibility. Cognitive rehabilitation is an effective approach to compensate for cognitive deficits in P D, but other approaches to cognitive stimulation may be equally effective.

KEYWORDS
Cognitive impairment; cognitive training; Parkinson's disease

Introduction

Parkinson's disease (PD) is a neurodegenerative disease affecting approximately 2-3% of the world's population over the age of 65 (Riboldi & Di Fonzo, 2019). This disease is characterized by the loss of dopaminergic neurons in the substantia nigra (Uhrová & Roth, 2020). As a consequence of dopamine loss, motor and non-motor symptoms are manifested in PD (Evlice et al., 2021). Non-motor symptoms are present in up to 88% of PD patients (Gallagher, 2013) and include depressive disorder, anxiety disorders, impulsive disorders, cognitive deficits and visual hallucinations (Chaudhuri, 2009).

Cognitive deficits can range in severity from mild cognitive impairment (PD-MCI) to dementia syndrome (PD-D) (Aarsland et al., 2000; Nikolai et al., 2012). Cognitive deficits in PD are heterogeneous, characterized by deficits in executive function, psychomotor slowing, memory, sustained attention, abstract reasoning and language skills (Dubois & Pillon, 1996; Goldman et al., 2014; Vlagsma et al., 2016). Anticipation and self-regulation may be impaired (Vlagsma et al., 2016).

Cognitive rehabilitation (CR) is characterized as a non-pharmacological intervention aimed at compensating cognitive deficits in PD. The aim of CR is to improve self-sufficiency, social activation (Válková, 2015) and overall improvement of the patient's quality of life (Haskins et al., 2012). CR is based on the concepts of neuroplasticity (Kays et al., 2012) and cognitive reserve (Stern & Konno, 2009). Studies of non-computerized CR in PD show effects on attention, information processing speed, visual memory (París et al., 2011; Peña et al., 2014), visuoconstruction skills, executive functions (Mohlman et al., 2011; Nombela et al., 2011; París et al., 2011; Sammer et al., 2006), logical reasoning (Nombela et al., 2011), semantic verbal fluency (París et al., 2011). Some recent studies show the effect of CR on social cognition (Hindle et al., 2018; París et al., 2011), functional disability (París et al., 2011), self-efficacy and mood (Hindle et al., 2018). Some studies show a long-term positive effect of CR especially in quality of life and health status (Hindle et al.,2018). Most current cognitive intervention programs focus on structured cognitive training, but with minimal transfer of cognitive training into the individual's daily activities.

The CR program in the current study was designed to be as ecologically valid as possible and to have overlap into the respondent's normal daily activities. The CR program was based on the clinical experience of psychological work with patients with neurodegenerative diseases, patient's subjective complaints about cognition, the principles of Feuerstein's approach to neurorehabilitation (Lebeer & Parente, 2016), the guidelines for cognitive rehabilitation published in the Manual of Cognitive Rehabilitation (Haskins et al., 2012), and Russell Barkley's theory of the Extended Phenotype of Executive Functions (Barkley, 2012). The CR program included education about cognitive function and cognitive deficits, which is not common for cognitive training. The

CONTACT Tomáš Nikolai tomas.nikolai@vfn.cz Department of Neurology and Centre of Clinical Neuroscience, First Faculty of Medicine and General University Hospital in Prague, Charles University, Prague, Czech Republic.

purpose of the education was for the patient to understand the nature of cognitive impairment and to increase affinity for treatment and to take their own attitude toward cognitive deficits. The CR program was composed in such a way that the difficulty and complexity of the strategies to be learned tended to increase. The emphasis in the present study was on the transfer of strategies into the daily activities of the respondents. During each session, respondents were given the opportunity to bring their own experiences, situations or contexts to which an appropriate adaptation strategy needed to be applied. In contrast to conventional cognitive training sessions, the current intervention also worked with the emotional experience of respondents in different situations, e. g. in the transfer of compensatory strategies, in problem solving, planning or social interactions.

The effect of a comprehensive outpatient CR program has not yet been tested. The hypothesis of the effectiveness of this intervention program is based on a CR study in which the intervention was targeted to train compensatory and restorative strategies to improve the respondent's spatial orientation, planning, and memory and their transfer to daily activities (Hindle et al., 2018). The results of this study showed significant improvements in mood, self-efficacy, and social quality of life two months after the intervention. After six months, a persistent effect on delayed recall from memory, health status, and quality of life was demonstrated (Hindle et al., 2018).

The primary aim of the current study is to analyze the effect of a comprehensive outpatient program of non-computerised CR compared to an intervention program with music therapy elements in respondents with PD. A secondary, complementary aim of the study is to determine whether cognitive rehabilitation can be a preventive factor for conversion from PD-MCI to PD-D in the long term.

Method

Research sample

The research study was approved by the Ethics Committee of Charles University. Respondents were informed about the study process before entering the study, with the possibility of withdrawing from the study. On the basis of the information provided, the patients expressed their voluntary written consent to participate in the study. Respondents with idiopathic PD (diagnosis according to UK PDS BB criteria) and stable antiparkinsonian medication were included in the study. Respondents who met the diagnostic criteria for dementia syndrome in PD (as assessed by the Mattis Dementia Rating Scale, DRS-2 screening test (Mattis et al., 1988)) or respondents with acute psychiatric illness were excluded from the study.

A total of 62 respondents with PD were included in the study. Four respondents were excluded from the study at the baseline because they did not meet the inclusion criteria. Three of these respondents met the diagnostic criteria for PD-D, and one respondent with PD had a comorbid stroke. The research sample ($n = 58$) was divided into two groups according to the type of intervention. A total of 28 respondents were included in the experimental group (EXP). The average age of EXP respondents was 67.8 years (SD = 7.5), average years of education was 16.1 years (SD = 2.5), and average years of illness was 7.1 years (SD = 5.8). The control group included 30 respondents with an average age of 69.1 years (SD = 6.4), average years of education of 15.5 years (SD = 2.6), and average years since diagnosis of 8.6 years (SD = 5.8). The demographic characteristics of the respondents in both intervention groups who completed the study ($n = 53$) are shown below in Table 1.

Neuropsychological assessment

Respondents underwent an initial neuropsychological examination to differentiate the severity of cognitive deficits in PD. The neuropsychological battery was administered to respondents at study entry, at the end of the three-month intervention program, and one year after the end of the intervention.

At the beginning, an initial anamnestic interview was conducted with the respondent. The anamnestic interview was aimed at mapping the health status of the respondent: the quality of hearing and vision, the presence of head injuries, psychiatric, neurological diseases in the respondent and family members, mapping other diseases, long-term medication and other issues related to health status. In addition, the respondent's psychosocial history (educational attainment, total years of education, occupation of the respondent) was briefly mapped. The STAI-X1/STAI-X2 (Müllner et al., 1980) and BDI-II depression scales (Beck et al., 1996) were administered to the respondents to determine the severity of psychiatric symptoms.

The structure of the neuropsychological examination was designed according to the recommendations of Litvan et al., 2012 (Litvan et al., 2012) for the diagnosis of PD-MCI. A neuropsychological battery including tests measuring auditory memory—Auditory Verbal Learning Test, AVLT (Bezdicek et al., 2014), visual memory—Brief Visual Memory Test Revised, BVMT-R (Benedict et al., 1996), executive functions—Phonemic Verbal Fluency Test, FAS, Letters K,P,S, (Nikolai et al., 2015), Trail Making Test, TMT (Bezdicek et al., 2012), Tower of London Test, ToL (Michalec et al., 2014), Prague Stroop Test (Bezdicek et al., 2015), Clock Test (Mazancova et al., 2016), abstract reasoning—Similarities, Wechsler Adult Intelligence Scale-III (Wechsler, 2010), visuospatial functions—Benton Judgment of Line Orientation, JLO, Form H (Benton

Table 1. Sociodemographic characteristics of participants who completed the study.

	EXP		CON	
Research group	n	sd	n	sd
Total number of respondents	26		27	
Gender				
Female	11		13	
Male	15		14	
Average age	68	±7.3	68.6	±6.7
Average length of education	16	±2.6	15.5	±2.5
Average length of illness since diagnosis	7.5	±5.9	8.5	±5.7
DRS-2 total score	139.5	±4.6	139.7	±5.1
STAI-X1	37.3	±8.8	36.9	±6.9
STAI-X2	39.9	±8.9	44.1	±9.5
BDI-II	10.2	±5.4	13.5	±8.2

Note. Experimental Group (EXP), Control Group (CON), standard deviation (sd), Dementia Rating Scale-2 (DRS-2), The State-Trait Anxiety Inventory (STAI-X1, STAI-X2), Beck Depression Inventory-II (BDI-II).

et al., 1983), verbal skills—Boston Naming Test, BNT, UDS modification (Nikolai et al., 2018), semantic fluency—categories animals, vegetables (Nikolai et al., 2015), attention and working memory (Number and Letter Order, Wechsler Adult Intelligence Scale-III (Wechsler, 2010).

Development of the cognitive rehabilitation program

The background for the development of a comprehensive CR program was clinical experience with patients with neurodegenerative diseases and mapping their subjective cognitive complaints. Subjective cognitive complaints about memory represent a significant proportion of the subjective cognitive complaints of patients with PD (Lehrner et al., 2014). The basic principles underlying the CR program are Feuerstein's approach to neurocognitive rehabilitation (Lebeer & Parente, 2016), the general principles of cognitive rehabilitation outlined in the Manual of Cognitive Rehabilitation, and Russell Barkley's Theory of The Extended Phenotype of Executive Function (Barkley, 2012). Feuerstein draws on the theory of structural cognitive modifiability, which is based on a person's lifelong ability to change as they interact with their environment, and on vicarious learning, which is based on the premise that an individual can effectively develop their abilities through vicarious experience in interaction with others or the environment (Lebeer & Parente, 2016). Feuerstein's Instrumental Enrichment program is an intervention program aimed at promoting cognition and metacognition through problem solving training, relearning academic skills, and practicing coping with the demands of everyday life. A key factor in the intervention is bridging, which is the transfer of the principles learned from the intervention program into the everyday life of each individual (Lebeer & Parente, 2016). The Feuerstein's approach in neurocognitive rehabilitation is followed in the design of a CR program by the general principles of progressive achievement of long-term goals based on the Cognitive Rehabilitation Manual (Haskins et al., 2012): a) gaining insight and orientation to the problem, b) selecting appropriate compensatory strategies, c) internalizing compensatory strategies, and d) transferring compensatory strategies to activities of daily living. The Extended Phenotype Theory of Executive Function is based on the thesis that each component of executive function represents a specific type of self-regulation of an individual leading to the achievement of set goals (Barkley, 2012). The theory promotes a hierarchical division of executive functions. It consists of two levels: pre-executive and executive. The pre-executive level includes central nervous system functions such as automatic activities, operant conditioning, neuropsychological functions such as memory, attention, visuospatial and motor functions, primary emotions and motivation.

The executive level is divided into instrumental, methodical, tactical-reciprocal and strategic-cooperative levels. Each level is specified by executive components that lead to the achievement of particular goals ranging from the internalization of the individual's mental processes, self-regulation, social behavior, and social cooperation in the environment (Barkley, 2012). In the cognitive rehabilitation program, individual sessions are composed on the principle of increasing complexity of cognitive processes, emotionality, behavioral and interpersonal aspects.

The course of the study

This was a blinded clinical trial with randomly assigned intervention (see below) and time comprising exposures and test scores on all neuropsychological tests comprising outcomes. After completing the initial neuropsychological assessment, respondents were randomly divided into two intervention groups. Randomization was performed by an employee of the Laboratory of Neuropsychology of the General University Hospital in Prague, and this employee did not actively participate in the study. Randomization into intervention groups was carried out by the assessor to ensure that each intervention group had as equal a number of male and female respondents as possible. Other respondent data were blinded by the assessor. Randomization of respondents was based on the principle of pulling numbers out of a hat. More specifically, the assessor was given two envelopes where one envelope contained female respondents and the other contained male respondents. The envelope contained only the codes that were assigned to the respondents during the initial neuropsychological assessment. The evaluator gradually pulled respondent codes from the envelopes and assigned them to intervention groups until all respondents were assigned to groups.

The purpose of the CON was to examine whether other types of intervention that do not directly target cognitive function have an effect on cognitive performance and, if so, in which cognitive domains this effect is evident compared to targeted CR. To this goal, the CON underwent an intervention program with music therapy elements. The program of the CON was composed in such a way that it did not emphasize enhanced cognitive performance, the respondents were not purposely cognitively stimulated, nor were they guided to develop compensatory cognitive strategies. The CON's program focused on relaxation and leisure activities using elements and techniques of music therapy that did not purposefully stimulate cognitive function.

At the baseline of the study, the cognitive performance of both EXP and CON respondents was consistent with mild cognitive impairment in PD. EXP respondents had a mean score of 139.4 (SD = 4.9) on the DRS-2 neuropsychological screening test. CON respondents had a mean score of 139.4 (SD = 5.1). The cutoff score for mild cognitive impairment on the DRS-2 was determined by a score of 136. Cognitive decline corresponding to PD-MCI was clinically and statistically significant in respondents of both intervention groups. Cognitive decline was evidenced in respondents in the DRS-2 screening or from anamnestic interviews with respondents who were found to have impaired coping with activities of daily living that did not meet the DSM-V criteria for dementia syndrome. In a clinical study of 92 respondents with idiopathic PD without depressive symptoms, the total score on the MMSE cognitive screening test at baseline was 27.8 (SD = 3.4), and at retest after one year the total score was 26.9 (SD = 3.5). The difference in scores at baseline and after one year was not statistically significant (Starkstein et al., 1992). In a clinical population

Table 2. Description of the cognitive rehabilitation program.

Session	*Type of intervention*	*Specific activities*
1.	Education	Brain anatomy, cognitive functions, memory
2.	Mnemonics	Categorization
3.	Mnemonics	Categorization in iADL
4.	Mnemonics	Memory for numbers - theory
5.	Mnemonics	Memory for numbers
6.	Mnemonics	Memory for numbers in iADL
7.	Planning	Orientation in space, route planning, visual-spatial memory
8.	Planning	Planning the daily program, use of maps
9.	Social intelligence	Emotion, relationships, communication
10.	Executive function training	Mind maps (Buzan & Buzan, 2012)
11.	Mnemonics	Memory for names
12.	Other compensation strategies	Other external and internal compensation strategies

Note. Cognitive rehabilitation program (EXP), iADL (instrumental activities of daily living).

of 145 patients with PD, the MMSE total score at baseline was 25.6 (SD = 6.2), and in the retest after one year, the MMSE total score was 25.4 (SD = 7.9); the difference of the scores at baseline and in the retest after one year was not statistically significant (Schrag et al., 2007). In a community-based sample of PD patients, there was a statistically significant difference ($p = 0.01$) between subjective memory complaints at baseline (21%) and at one year (40%) follow-up (Schrag et al., 2007). In a study of 62 respondents with PD, the total score in the DRS-2 baseline screening test was 131.63 (SD = 9.02), and in the retest after 17 months, the total score was 129.34 (SD = 14.37). The difference between measurements was −2.29 (SD = 10.69). There was no statistically significant difference ($p = 0.63$) at the p ‘ 0.001 significance level between the measurements at baseline and after 17 months (Tröster et al., 2007).

Respondents assigned to the experimental group (EXP) underwent an outpatient CR program at a frequency of once a week, 60 minutes, for a total of 12 weeks. Respondents assigned to the control group (CON) underwent an intervention program with elements of music therapy at the same frequency and duration as the EXP respondents.

Both intervention groups were led by psychologists and supervised by the clinic's lead clinical psychologist.

The CR program (Table 2) was aimed at training compensatory, restorative, and adaptive strategies for coping with activities of daily living. The training program included training in coping strategies and relaxation techniques, as well as training in communication techniques and psychological support for respondents in coping with everyday activities and support in relation to coping with the changes brought about by the illness. After completing the comprehensive CR program, respondents were neuropsychologically examined to determine the effect of the individual intervention programs. A follow-up neuropsychological examination was repeated one year after completion of the intervention. The CON respondents were also examined at the same time interval.

Statistical analysis

All continuous variables were described by their means and standard deviations, count variables were described by medians and interquartile ranges and categorical variables were described by number of subjects belonging to each category for EXP and CON groups separately. To evaluate change in cognitive scores between each assessment (baseline, 3-months retest immediately after intervention and 1 year retest) and efficacy of EXP intervention compared to CON, we fitted a series of univariate Generalized Linear Mixed Models (GLMMs) separately for each cognitive outcome. We used Gaussian likelihood for continuous outcomes, Binomial likelihood for bounded counts and Poisson likelihood for unbounded counts (see Table 3 for the exact mapping of likelihoods to single outcome variables). Because we expected response times to be approximately follow LogNormal distribution, all response times variables were transformed via natural logarithm before entering the analysis. Each outcome was predicted by assessment (categorical variable), intervention group (categorical variable) and assessment/group interaction at group level (comprising "fixed effects") as well as patient-specific intercepts on individual level (comprising "random effects"). To ensure models identification, we did not use other patient-specific terms. No covariates were included. All models were fitted via Maximum Likelihood method using lme4 package (Bates et al., 2015) in R computing environment (R Core Team, 2022) with *p*-values derived via Satterthwaite method as implemented in lmerTest package (Kuznetsova et al., 2017). Subsequently, simple effects of intervention group at each assessment, simple effects of assessment in each intervention group and assessment/intervention group interactions were extracted separately for each outcome by statistically comparing estimated marginal means in emmeans R package (Lenth, 2022). Effects with uncorrected[1] $p < 0.05$ were considered in interpretation of the results. The full statistical analysis code is available at https://www.github.com/josefmana/pd_cogREH

Results

The current study analyzes the effect of a comprehensive outpatient CR program compared to an intervention program with music therapy elements in respondents with PD, after the intervention and after one year. A total of 26 EXP respondents completed the CR program, and a total of 27 respondents completed the intervention program with CON music therapy elements. The overall dropout rate at the end of both intervention programs was 3.1% (EX $p = 2$, CON = 3). A follow-up neuropsychological examination, which took place one year after the end of the intervention program, was completed by 12 EXP respondents, 8 CON respondents.

1. Since the goal of the article was to explore domains that could be potentially targeted by CR, we did not adjust the inference for multiple comparisons to maximise statistical power for our data set. Consequently, the results should not be interpreted as confirmatory. Note that after adjusting for 5% False Discovery Rate via Benjamini-Hochberg correction, none of discussed results remain statistically significant implying that the reader should expect that more than 5% of the results are likely to prove to be false positives.

Table 3. Statistical analysis: univariate Generalized Linear Mixed Models (GLMMs)—significant results in neuropsychological asessment.

<table>
<tr><th>Outcome</th><th>EXP_1baseline (sd)</th><th>EXP_2retest (sd)</th><th>EXP_3followup (sd)</th><th>CON_1baseline (sd)</th><th>CON_2retest (sd)</th><th>CON_3followup (sd)</th><th>sig_results</th></tr>
<tr><td>AVLT_T7</td><td>6.50 (3.50)</td><td>8.50 (5.00)</td><td>7.50 (3.25)</td><td>8.00 (3.50)</td><td>9.00 (5.00)</td><td>8.00 (3.25)</td><td>2retest > 1baseline | CON
2retest > 1baseline | EXP
3followup < 2retest | EXP</td></tr>
<tr><td>AVLT_T8</td><td>7.00 (3.75)</td><td>8.00 (4.50)</td><td>7.00 (4.25)</td><td>7.00 (5.00)</td><td>9.00 (5.00)</td><td>9.00 (4.50)</td><td>2retest > 1baseline | CON
2retest > 1baseline | EXP
3followup < 2retest | EXP</td></tr>
<tr><td>AVLT_correct</td><td>13.00 (2.00)</td><td>14.00 (1.00)</td><td>14.00 (2.50)</td><td>12.00 (3.00)</td><td>14.00 (1.00)</td><td>12.50 (2.25)</td><td>2retest > 1baseline | CON
3followup < 2retest | CON
3followup < 2retest | EXP</td></tr>
<tr><td>AVLT_false</td><td>3.50 (3.75)</td><td>2.50 (4.00)</td><td>3.50 (6.00)</td><td>3.00 (5.00)</td><td>3.00 (5.00)</td><td>1.00 (5.00)</td><td>EXP > CON | 3followup
3followup > 2retest | EXP
[(EXP − CON) * (3followup − 1baseline)] > 0
[(EXP − CON) * (3followup − 2retest)] > 0</td></tr>
<tr><td>BMVTR_delayed_recall</td><td>8.50 (4.00)</td><td>11.00 (4.50)</td><td>10.00 (2.50)</td><td>10.00 (5.00)</td><td>10.00 (3.75)</td><td>9.50 (4.50)</td><td>2retest > 1baseline | EXP
[(EXP − CON) * (2retest − 1baseline)] > 0
[(EXP − CON) * (3followup − 1baseline)] > 0</td></tr>
<tr><td>Stroop_points</td><td>16.41 ± 3.48</td><td>15.89 ± 3.15</td><td>20.62 ± 13.46</td><td>15.88 ± 3.50</td><td>16.39 ± 3.18</td><td>25.37 ± 16.19</td><td>3followup > 1baseline | CON
3followup > 2retest | CON
[(EXP − CON) * (3followup − 1baseline)] < 0</td></tr>
<tr><td>Stroop_neutral_words</td><td>18.43 ± 4.10</td><td>18.28 ± 3.35</td><td>24.09 ± 16.97</td><td>19.23 ± 5.37</td><td>18.58 ± 4.39</td><td>27.25 ± 17.58</td><td>3followup > 1baseline | CON
3followup > 2retest | CON</td></tr>
<tr><td>S_mistakes</td><td>1.12 ± 1.28</td><td>0.77 ± 1.03</td><td>0.67 ± 0.78</td><td>1.78 ± 3.25</td><td>1.56 ± 1.83</td><td>0.38 ± 1.06</td><td>3followup < 1baseline | CON
3followup < 2retest | CON
[(EXP − CON) * (3followup − 2retest)] > 0</td></tr>
<tr><td>TOL_HS</td><td>24.81 ± 6.04</td><td>23.48 ± 6.39</td><td>23.08 ± 6.57</td><td>22.50 ± 6.48</td><td>23.12 ± 6.86</td><td>11.88 ± 7.41</td><td>EXP > CON | 3followup
3followup < 1baseline | CON
3followup < 2retest | CON
[(EXP − CON) * (3followup − 1baseline)] > 0
[(EXP − CON) * (3followup − 2retest)] > 0</td></tr>
<tr><td>TMT_A_s</td><td>55.30 ± 18.40</td><td>61.75 ± 34.63</td><td>51.22 ± 16.60</td><td>54.83 ± 25.60</td><td>54.10 ± 26.75</td><td>106.43 ± 109.82</td><td>EXP < CON | 3followup
3followup > 1baseline | CON
3followup > 2retest | CON
[(EXP − CON) * (3followup − 1baseline)] < 0
[(EXP − CON) * (3followup − 2retest)] < 0</td></tr>
<tr><td>TMT_B_s</td><td>150.95 ± 79.64</td><td>154.51 ± 108.27</td><td>131.03 ± 62.95</td><td>142.46 ± 96.02</td><td>141.02 ± 104.73</td><td>278.50 ± 211.01</td><td>EXP < CON | 3followup
3followup > 1baseline | CON
3followup > 2retest | CON
[(EXP − CON) * (3followup − 1baseline)] < 0
[(EXP − CON) * (3followup − 2retest)] < 0</td></tr>
<tr><td>Similarities</td><td>23.77 ± 2.97</td><td>25.38 ± 3.50</td><td>24.58 ± 2.84</td><td>22.07 ± 4.99</td><td>23.46 ± 4.81</td><td>25.25 ± 3.01</td><td>3followup > 1baseline | CON
2retest > 1baseline | EXP</td></tr>
<tr><td>Clock_test_total</td><td>15.46 ± 1.50</td><td>16.23 ± 1.53</td><td>15.75 ± 1.66</td><td>14.64 ± 2.60</td><td>15.63 ± 1.64</td><td>15.88 ± 1.25</td><td>2retest > 1baseline | CON</td></tr>
<tr><td>BNT_correct</td><td>27.50 (3.00)</td><td>28.50 (2.00)</td><td>27.00 (2.25)</td><td>27.00 (2.00)</td><td>28.50 (3.00)</td><td>29.00 (1.75)</td><td>2retest > 1baseline | CON</td></tr>
</table>

Note. Cognitive performance of respondents in the initial neuropsychological examination before the start of the intervention (EXP_1baseline, CON_1baseline). Cognitive performance of the respondents in the follow-up neuropsychological examination after the end of the intervention programs (EXP_2retest, CON_2retest). Cognitive performance of the respondents in the follow-up neuropsychological examination one year after the end of the intervention programs (EXP_3followup, CON_3followup).

Significant changes in neuropsychological assessment battery: Auditory Verbal Learning Test - recall from auditory memory after interference (AVLT_T7), delayed recall from auditory memory (AVLT_T8), correct answers in recognition from auditory memory (AVLT_correct), false answers in recognition from auditory memory (AVLT_false). Brief Visual Memory Test Revised—delayed recall from visual memory (BVMTR_delayed_recall). Prague Stroop Test: (Stroop_points)—total time, (Stroop_neutral_words)—total time, (S_mistakes) - the total number of incorrect responses in the item Stroop color words. Tower of London Test (TOL_HS)—total score. Trail Making Test: (TMT_A_s)—total time, (TMT_B_s)—total time. Similarities (Similarities) - total score. Clock test (Clock_test_total)—total score. Boston Naming Test, UDS modification: (BNT_correct)—total number of spontaneous responses.

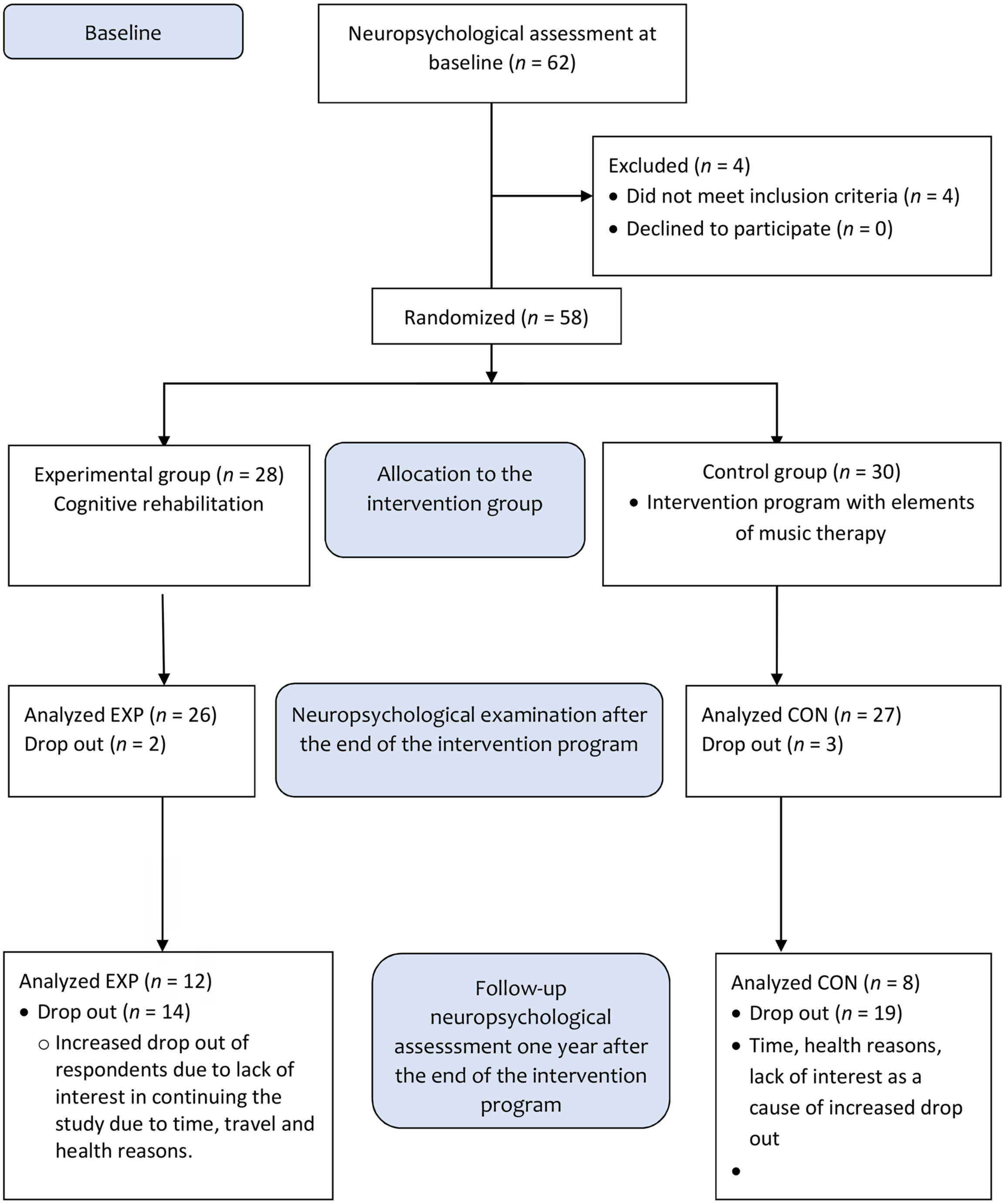

Figure 1. Consort flowchart of respondents.

The reason for the high dropout rate in the neuropsychological examination was the covid-19 pandemic and associated government restrictions (Figure 1).

In the baseline neuropsychological examination before the start of the study, no statistically significant difference was detected in the individual domains of cognitive function or in the level of depressive and anxiety symptoms between EXP and CON. Table 3 provides a description of the performance of EXP and CON respondents (mean ± standard deviation for continuous variables and median (interquantile variance) for integer counts)) and statistically significant differences at the 5% significance level without correction for multiple comparisons. In the next section we will more closely describe results for statistically significant effects. Effect sizes are described by their raw estimate for Gaussian models, log estimate for reaction times (both denoted $b_{xy,grop}$ where x and y denote which assessment are being compared, e.g., $b_{21,EXP}$ denotes difference in the second-minus-first testing in the EXP group) and odds ratios ($OR_{xy,group}$ with $OR_{21,CON}$ denoting odds ratio of the second divided by the first testing in the CON group) for Binomial models, and their respective standard errors of estimation (SE) (see below in Appendix). Clinical significance was in some cognitive domains established by comparing differences observed in test/retest previous studies (Combs et al., 2021; Stepkina et al., 2010; Tröster et al., 2007). Results were also considered clinically significant if the raw difference between means (for continuous variables) or medians (for count variables) in our sample were at least as big as standard deviations of differences reported in above mentioned studies.

Memory

Significant improvement was detected in both intervention groups (EXP, CON) in specific memory domains. In the quality of recall from verbal memory after interference (AVLT_T7), significant improvement was observed in both groups after the intervention. In EXP, performance in AVLT_T7 at baseline was Md = 6.50 (IQR = 3.50), in the post-intervention retest was Md = 8.50 (IQR = 5.00), the difference in performance is 2 points. In CON, performance in AVLT_T7 at baseline was Md = 8.00 (IQR = 3.50), in the post-intervention retest performance was Md = 9.00 (IQR = 5.00), the difference between baseline and post-intervention retest was 1 point. The difference in scores does not indicate a clinically significant change. Compared to the retest at 3 months, EXP respondents at the control examination at 1 year experienced a deterioration in performance on the verbal memory recall after interference (AVLT_T7), but cognitive performance on this quality did not fall below EXP performance at baseline. In EXP, performance in AVLT_T7 in the post-intervention retest was Md = 8.50 (IQR = 5.00), in the follow-up measurement after one year, performance was Md = 7.50 (IQR = 3.25), a performance difference of −1 point. The difference in scores does not indicate a clinically significant change. The same pattern of results was observed in delayed recall (AVLT_T8)- measurement on baseline AVLT_T8 (Md = 7.00, IQR = 3.75), follow-up measurement after one year (Md = 7.00, IQR = 4.25). On the delayed recall in the Hopkins Verbal Learnirng Test (HVLT), respondents with PD had a score of 9.80 (SD = 2.56) on the baseline measure, and had a score of 9.84 (SD = 1.25) on the retest five months later; the difference between baseline and retest scores was −0.03 (SD = 2.26) (Combs et al., 2021). The difference in scores and compared with the study by Combs et al. (2021), does not suggest a clinically significant change. An improvement was detected in CON in retrieval from verbal memory in the number of words correctly fitted (AVLT_correct) after the intervention, but this effect was no longer present at the follow-up examination after one year.

The difference between AVLT_correct performance in CON at post-intervention (Md = 12.00, IQR = 3.00) and at follow-up measurement after one year (Md = 12.50, IQR = 2.25) is −0.05 points; this difference is not clinically significant. CON respondents showed a significant deterioration in cognitive performance in the quality of recognition of correct words recalled from verbal memory after one year compared to performance in this quality after the intervention, EXP respondents also showed a deterioration in this quality. Differences between performances over time do not indicate a clinically significant outcome. There was a significant increase in the number of false positive responses in the verbal memory retest (AVLT_false) in EXP respondents compared to CON respondents at post-intervention and at retest one year later. In other words, there was a significant interaction between time of assessment and intervention group with EXP showing larger increase in false positives at one year follow-up compared to CON. The difference between the false positive EXP and CON scores at the one-year follow-up was 2.5 points. This difference may indicate a clinically significant change.

EXP respondents improved significantly compared to CON in delayed recall from visual memory (BVMTR_delayed_recall) both at post-intervention and at post-test one year. The difference in scores between the visual memory delayed recall of EXP and CON was 1 point at post-intervention and 0.5 points at 1-year follow-up. This difference does not indicate a clinically significant change. CON respondent's performance on delayed recall from visual memory remained unchanged from baseline on all subsequent measures.

Attention

In both attentional subtests of the Stroop task (Stroop_points, Stroop_neutral_words) we observed a deterioration of the CON group in the retest after one year compared to baseline and in the post-test compared to EXP performance. The difference in CON scores in Stroop_points in the retest after intervention and follow-up at one year is − 8.91 sec, the difference between baseline and follow-up at one year is − 9.49 sec. These differences suggest a clinically significant change. The performance of an outlier may intervene in the deterioration of CON performance in the control assessment after one year in the attentional subtests of the Stroop task. In the speed of the distribution of focused attention, as estimated by performance on the TMT_A, EXP respondents were statistically significantly faster in the control examination at one year compared to performance at baseline and compared to CON respondents. CON respondents significantly slowed the rate of distribution of focused visual attention in the retest at one year compared to performance in the post-intervention testing. The difference in scores of CON in TMT_A at post-intervention and control testing at one year was −55.33 sec, indicating a clinically significant change in the distribution of focused visual attention. This attentional quality may be influenced by outlier performance in the retest after one year.

Executive functions

The ability to inhibit interfering stimuli (S_mistakes) improved statistically significantly in CON respondents compared to performance at baseline and compared to EXP at post-intervention follow-up and at one year. Outlier effects may also intervene in this domain. The difference in CON respondent's scores on the Stroop_miskates at baseline and in the control at one year was 1.4 points, indicating a clinically significant change in inhibition of interfering stimuli. CON respondents performed statistically significantly worse in the planning and problem-solving domain (TOL_HS) at the follow-up examination after one year, compared with performance at baseline and at the follow-up examination after the intervention. The difference in CON respondent's TOL scores at baseline and at control testing after one year was −10.62 points, indicating a clinically significant change planning and problem solving. Compared to EXP, CON respondents significantly worsened in planning and problem solving at the follow-up examination after one year. Performance of EXP respondents in this domain of executive function was stable compared to performance at baseline after the intervention and at the follow-up examination after one year.

In mental flexibility (TMT_B_s), EXP respondents were statistically significantly faster than CON respondents in the mental flexibility domain at the control examination after one year. The difference in scores between TMT_B EXP and CON was −147.47 seconds at 1-year follow-up. This difference suggests a clinically significant change in executive mental flexibility.

CON respondents were statistically significantly slower in the mental flexibility domain at the control examination after one year compared to the retest after the intervention. The difference in scores for CON respondents on the TMT_B in the post-intervention retest and in the control at one year was −137.48 sec, indicating a clinically significant change in mental flexibility. Statistically significant improvement in abstract reasoning (Similarities) was evident in the post-intervention retest for EXP respondents compared to performance at baseline. The difference in scores for EXP respondents in Similarities at baseline and after the intervention was 1.61 points, a difference not indicating a clinically significant change. Statistically significant improvement in the abstract reasoning domain was detected in the control examination at one year for CON respondents compared to performance at baseline. The difference in scores for CON respondents in Similarities at baseline and at follow-up after one year was 3.18 points, a difference not indicating a clinically significant change.

Visuospatial functions

In the visuospatial function domain (Clock_test_total), CON respondents showed statistically significant improvement in retest performance after the intervention compared to performance in this domain at baseline (Md = 14.64, IQR = 2.60). The difference in scores at baseline and at retest after the intervention is not clinically significant in CON respondents. For respondents with PD ($n = 508$), the initial Clock test score was 8.3 ± 1.4 points, and the retest score at six months was 8.3 ± 1.4 points. There was no significant change in the Clock test at six months (Stepkina et al., 2010). For EXP respondents, there was no statistically significant effect in this domain.

Verbal skills

In the naming domain (BNT_correct), CON respondents improved statistically significantly on the post-intervention retest (Md = 28.50, IQR = 3) compared to performance in this domain at baseline (Md = 27.00, IQR = 2). In a study by Tröster et al. (2007), a difference score of −2.42 (SD = 7.89) was found in the BNT at baseline and at retest after 17 months. The difference between scores at baseline and at retest was not statistically significant at $p = 0.73$, at the p′0.001 level of statistical significance. The difference in scores at baseline and at retest after the intervention is not clinically significant in CON respondents. No statistically significant advances in the naming domain were present for EXP respondents.

The effect of the intervention over time

A follow-up neuropsychological assessment one year after the end of the intervention program was attended by 12 EXP respondents, 8 CON respondents. The average score of EXP respondents on the DRS-2 screening test one year after completing the CR program was 139 (SD = 5). One year after completing the intervention program with music therapy elements, CON respondents had an average DRS-2 score of 138.1 (SD = 10.1). The cutoff score for PD-D was determined by a DRS-2 total score of ≤ 123 (Llebaria et al., 2008). In the EXP group, none of the respondents converted to PD-D one year after completing the CR program. In the CON group, only one respondent converted to PD-D one year after completing the intervention program with music therapy elements. This respondent had a DRS-2 total score of 112 one year after the end of the intervention (cutoff score ≤ 123).

Discussion

The study analyzed the effect of non-computerized CR in respondents with PD who were randomized into two intervention groups at the beginning of the study. EXP respondents received CR, and CON respondents received an intervention program with elements of music therapy.

The basic premises for the design of the CR program were Feurestein's Instrumental Enrichment, basic principles based on the Manual of Cognitive Rehabilitation (Haskins et al., 2012), Barkley's Theory of The Extended Phenotype of Executive Function (Barkley, 2012), as well as a mapping of subjective cognitive complaints in PD patients. The CR program was designed to cover as comprehensively as possible the broadest possible range of cognitive domains, interventions targeting experience, emotion and behavior. The CR program's focus on training in compensatory, restorative and adaptive strategies is supported by a study (Cicerone et al., 2011) that suggests that cognitive interventions including training in metacognitive strategies, problem solving training, and training in compensatory mechanisms and strategies may be more effective than structured training.

Some studies characterize that memory impairment is considered a nonspecific manifestation of the development of cognitive deficits in PD, which develops in the majority of patients, with 78% of patients developing cognitive deficits eight years after the onset of the disease (Bezdíček, 2017). Deficits in memory and visuospatial functions appear to be a possible cognitive predictor of conversion to PD-D (Biundo et al., 2017; Tröster, 2008, 2011). The CR program in the current study included training in compensatory strategies, particularly mnemonics that operate primarily on the principle of visual imagination. Systematic visualization training had a significant effect on delayed recall from visual memory in EXP compared to CON who did not train visualization purposefully.

Some other studies also show the effect of non-computerized CR on attention, information processing speed, and visual memory in respondents with PD (París et al., 2011; Peña et al., 2014). In EXP, the effect of CR in delayed recall from visual memory was evident even one year after the intervention ended. CON respondent's performance was comparable to performance at baseline after the intervention and at the 1-year follow-up examination. The effect of mnemonics and other compensatory techniques was not sustained in EXP respondents. EXP improved in post-intervention retest on post-interference recall, delayed recall, and recall of correct words from verbal memory. This effect was not long-lasting, and there was a deterioration in performance in the aforementioned verbal memory qualities compared to performance in the retest at one year. The number of false-positive responses increased for EXP in both the retest and the follow-up examination after one year. In CON, post-intervention performance in verbal memory improved in post-interference recall and in delayed recall. One year after the intervention ended, CON deteriorated in recall. It is evident that the effect of CR on the verbal memory domain is short-term and nonspecific in terms of duration, and thus it is likely that other types of interventions will have the same effect on verbal memory in PD. A larger effect may be found in the current studies when CR is combined with physical exercise (Sinforiani et al.,2004). CR was effective for speeding up the distribution of focused visual attention compared to the CON, which is supported by other CR studies in which the effect of CR on attention was also detected. The effect of CR in the present study was sustained and was still demonstrated in EXP one year after the examination. CON deteriorated in attentional subtests in the post-intervention control examination and at one year, both at baseline and compared to EXP performance. In attentional distribution, CON respondents deteriorated in the post-intervention control examination at one year compared to the post-intervention retest. Outlier performance may have interfered with performance in these domains in CON. Given that PD-MCI patients are more likely to convert to PD-D (Pedersen et al., 2013), it is likely that the outlier in the current study also showed progression of cognitive deficits in attention and executive functions that are typically impaired in PD (Goldman et al., 2014; Vlagsma et al., 2016). If there is a correction in outlier performance, it is likely that an intervention with elements of music therapy could also have an effect for attentional domains. Clinical change in the quality of attention distribution in CON respondents may affect the quality of movement in new, unfamiliar environments, may have an impact on impaired stability and freezing of the gait in PD, but also on the ability to orient oneself in the text, in reading or in completing important documents.

In executive functions, CR had a significant effect on mental flexibility of respondents with PD, this effect was sustained over time and was detected even one year after the end of the study. This result correlates with studies of CR in PD in which the authors also detected improvements in executive function domains after CR (Mohlman et al., 2011; Nombela et al., 2011; París et al., 2011; Sammer et al., 2006). Neuropsychological studies have reported that cognitive deficits are heterogeneous, characterized by deficits in working memory, planning, mental flexibility, inhibition, delayed recall, verbal fluency, and psychomotor speed (Goldman et al., 2014). CR has a specific, positive effect on mental flexibility, which may intervene in other cognitive domains (attention, memory, verbal abilities, visuospatial functions). Improvements in executive mental flexibility in PD respondents correlate with effective training of mnemonics and induce significant improvements in delayed recall from visual memory. By improving specific domains of executive function that are part of the gangliothalamocortical circuits of the brain, we can indirectly influence other components of these circuits such as the motivational, visual, and motor components. Clinical change in mental flexibility in EXP respondents may indicate more flexible planning and problem solving, better ability to reevaluate and correct thoughts and behaviors, and more appropriate choice of strategies for different types of activities.

The improvement in the EXP, which was still detected one year after the end of the study, was also evident in abstract reasoning. CON improved in inhibition ability compared to the EXP, this improvement being biased by the outlier performance at baseline. CON showed deterioration in problem solving, planning, and mental flexibility. No effect of CR was detected in other cognitive domains. The control group showed improvement in visuospatial functions and in verbal skills at the post-intervention follow-up, but this effect was not sustained and was no longer detected at the retest one year later.

In the current study, none of the respondents from the EXP group converted to PD-D in the control neuropsychological examination one year after the end of the cognitive rehabilitation program. Only one respondent from the CON group developed PD-D one year after the end of the music therapy intervention, the total score of the respondent in DRS-2 was 112 (cutoff score for PD-D $\leq$ 123 in DRS-2). The EXP group respondent's mean DRS-2 score at baseline was 139 (SD = 4.6), and at the neuropsychological follow-up examination at one year, their mean DRS-2 total score was 139 (SD = 5). The CON group respondents had a mean DRS-2 total score of 139.7 (SD = 5.1) at baseline, and at one year after the end of the intervention program, they had a mean DRS-2 total score of 138.1 (SD = 10.1). The differences between mean total DRS-2 scores at baseline and at one-year follow-up were not significant in either study group. In a study of 62 respondents with PD, the total score in the DRS-2 baseline screening test was 131.63 (SD = 9.02), and in the retest after 17 months, the total score was 129.34 (SD =14.37). The difference between measurements was −2.29 (SD = 10.69). There was no statistically significant difference ($p = 0.63$) at the $p < 0.001$ significance level between the measurements at baseline and after 17 months (Tröster et al., 2007). This study also shows that differences in performance even more than one year later on the DRS-2 in respondents with PD are not significant. Other studies that have measured cognitive performance of respondents with PD using the MMSE screening test have also found no significant differences between performance at baseline and at the 1-year follow-up (Schrag et al., 2007; Starkstein et al., 1992).

The current study suggests that specific and nonspecific intervention programs for PD may be a useful protective factor in preventing conversion to PD-D. Some meta-analytic studies have shown that within three years, 25% of people with PD developed PD-MCI and 2% developed PD-D, and conversion rates to MCI and PD were higher when follow-up lasted ≥ 3 years (Saredakis et al., 2019). Given that the conversion from PD-MCI to PD-D is research-estimated to take several years, long-term follow-up is needed to confirm the effect of intervention programs as a preventive factor of cognitive decline in respondents with PD. The effect of cognitive rehabilitation as a protective factor would need to be examined in a separate study.

Limits of the study

The current study was limited by the small number of respondents, particularly in the psychological follow-up examination after one year, which was affected by the global pandemic of covid-19. Respondents who did not participate in the follow-up examination were not interested in participating further in the study after the covid-19 restrictions ended due to time, travel or health reasons (development of acute mental illness, death). Compared to respondents who participated in the follow-up examination, they did not differ significantly in any aspects. The results may also be influenced by intervening variables such as unstructured cognitive stimulation of respondents in the home environment during and after the ongoing study.

Conclusion

The present study analyzed the effect of non-computerised CR, which was carried out on an outpatient basis at a frequency of once a week for a total of twelve weeks. Compared to another intervention program, CR had an effect on executive mental flexibility and delayed recall from visual memory in respondents with PD. CR is an effective approach to compensate for cognitive deficits in PD, but other approaches to cognitive stimulation may be equally effective. In a future study, it would be appropriate to target the CR program primarily to executive function training. Specific cognitive rehabilitation of executive functions targeting strategy training, planning, problem solving, organization of activities, inhibition skills, and mental flexibility may better support the transfer effect to other cognitive domains; thus, patients may benefit more from a specific program than from broad-based cognitive rehabilitation.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Ethical aspects

The study was conducted in accordance with the Helsinki Declaration of 1975 (and its revisions in 2004 and 2008). The study (No.113/6 Grant GAUK 1-LF UK) was approved by the Ethics Committee of the General University Hospital in Prague, Na Bojišti 1, 128 98, Prague 2. All patients voluntarily signed an informed consent to participate in the study.

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Appendix 1. Generalized linear mixed model's results.[a]

	Descriptive statistics[b]							
	CON			EXP			CON	
	Baseline	Re-test	Follow-up	Baseline	Re-test	Follow-up	Re-test-minus-Baseline	Follow-up-minus-Re-test
STAI_X1_HS	36.88 ± 6.88	41.00 ± 9.15	41.86 ± 17.40	37.27 ± 8.75	37.92 ± 9.30	37.33 ± 6.62	b = 0.37 (0.18), t(75.04) = 2.054, p = 0.107	b = 0.43 (0.31), t(82.83) = 1.423, p = 0.334
STAI_X_2_HS	44.08 ± 9.49	44.73 ± 8.51	41.43 ± 12.75	39.88 ± 8.43	40.04 ± 8.65	42.17 ± 7.61	b = −0.07 (0.13), t(74.20) = −0.554, p = 0.845	b = −0.10 (0.21), t(76.74) = −0.460, p = 0.890
BDI_II_total_score	13.54 ± 8.16	13.50 ± 11.88	12.43 ± 8.66	10.16 ± 5.38	9.88 ± 6.15	9.25 ± 5.67	b = −0.12 (0.14), t(73.46) = −0.820, p = 0.692	b = 0.04 (0.24), t(76.80) = 0.170, p = 0.984
MDRS_total	139.70 ± 5.14	139.52 ± 4.26	141.43 ± 2.70	139.46 ± 4.58	140.65 ± 3.52	139.00 ± 5.03	b = −0.04 (0.22), t(76.55) = −0.165, p = 0.985	b = 0.17 (0.36), t(90.20) = 0.470, p = 0.885
Total_.AVLT.1_5	42.41 ± 10.10	45.11 ± 11.76	42.38 ± 18.26	39.23 ± 9.29	44.54 ± 9.86	39.33 ± 14.49	b = 0.24 (0.18), t(77.11) = 1.299, p = 0.400	b = −0.07 (0.30), t(87.15) = −0.233, p = 0.971
AVLT_T6	4.00 (2.00)	4.00 (2.00)	4.50 (2.00)	4.00 (2.00)	5.00 (2.00)	4.00 (1.50)	OR = 1.07 (0.17), Z = 0.403, p = 0.914	OR = 1.03 (0.25), Z = 0.122, p = 0.992
AVLT_T7	8.00 (3.50)	9.00 (5.00)	8.00 (3.25)	6.50 (3.50)	8.50 (5.00)	7.50 (3.25)	OR = 1.50 (0.23), Z = 2.706, p = 0.019	OR = 1.05 (0.25), Z = 0.214, p = 0.975
AVLT_T8	7.00 (5.00)	9.00 (5.00)	9.00 (4.50)	7.00 (3.75)	8.00 (4.50)	7.00 (4.25)	OR = 1.54 (0.24), Z = 2.744, p = 0.017	OR = 1.25 (0.31), Z = 0.879, p = 0.654
AVLT_correct	12.00 (3.00)	14.00 (1.00)	12.50 (2.25)	13.00 (2.00)	14.00 (1.00)	14.00 (2.50)	OR = 2.00 (0.42), Z = 3.293, p = 0.003	OR = 0.61 (0.18), Z = −1.691, p = 0.209
AVLT_false	3.00 (5.00)	3.00 (5.00)	1.00 (5.00)	3.50 (3.75)	2.50 (4.00)	3.50 (6.00)	OR = 0.79 (0.11), Z = −1.717, p = 0.199	OR = 0.74 (0.18), Z = −1.259, p = 0.419
BMVTR_Total_1_3	20.00 ± 7.79	23.31 ± 7.92	20.88 ± 6.98	21.23 ± 8.09	24.50 ± 6.98	24.33 ± 5.26	b = 0.44 (0.20), t(76.17) = 2.179, p = 0.081	b = 0.04 (0.32), t(88.25) = 0.135, p = 0.990
BMVTR_delayed_recall	10.00 (5.00)	10.00 (3.75)	9.50 (4.50)	8.50 (4.00)	11.00 (4.50)	10.00 (2.50)	OR = 1.24 (0.24), Z = 1.095, p = 0.517	OR = 0.78 (0.24), Z = −0.810, p = 0.697
BVMTR_correct	6.00 (1.00)	6.00 (0.00)	6.00 (0.25)	6.00 (1.00)	6.00 (0.00)	6.00 (1.00)	OR = 2.39 (1.16), Z = 1.783, p = 0.175	OR = 2.00 (1.64), Z = 0.845, p = 0.675
BVMTR_false	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	OR = 0.64 (0.43), Z = −0.656, p = 0.789	OR = 0.55 (0.64), Z = −0.509, p = 0.867
Stroop_points	15.88 ± 3.50	16.39 ± 3.18	25.37 ± 16.19	16.41 ± 3.48	15.89 ± 3.15	20.62 ± 13.46	b = 0.13 (0.21), t(77.11) = 0.590, p = 0.826	b = 1.39 (0.34), t(95.56) = 4.109, p < 0.001
Stroop_neutral_words	19.23 ± 5.37	18.58 ± 4.39	27.25 ± 17.58	18.43 ± 4.10	18.28 ± 3.35	24.09 ± 16.97	b = −0.10 (0.20), t(77.05) = −0.500, p = 0.872	b = 0.90 (0.32), t(91.32) = 2.778, p = 0.018
Stroop_color_words	37.39 ± 13.45	35.94 ± 13.92	58.30 ± 74.00	34.20 ± 11.45	33.42 ± 10.29	48.90 ± 61.48	b = −0.13 (0.19), t(77.07) = −0.670, p = 0.782	b = 0.31 (0.31), t(88.30) = 1.014, p = 0.570
S_mistakes	1.78 ± 3.25	1.56 ± 1.83	0.38 ± 1.06	1.12 ± 1.28	0.77 ± 1.03	0.67 ± 0.78	OR = 0.87 (0.18), Z = −0.632, p = 0.802	OR = 0.17 (0.10), Z = −2.901, p = 0.010
TOL_HS	22.50 ± 6.48	23.12 ± 6.86	11.88 ± 7.41	24.81 ± 6.04	23.48 ± 6.39	23.08 ± 6.57	b = 0.09 (0.21), t(75.18) = 0.413, p = 0.910	b = −1.46 (0.33), t(92.92) = −4.409, p < 0.001
number_letter_sequencing	8.00 (3.00)	7.00 (2.00)	7.50 (1.50)	8.00 (2.75)	8.00 (3.75)	7.50 (2.25)	OR = 1.01 (0.13), Z = 0.065, p = 0.998	OR = 0.82 (0.16), Z = −0.989, p = 0.584
TMT_A_s	54.83 ± 25.60	54.10 ± 26.75	106.43 ± 109.82	55.30 ± 18.40	61.75 ± 34.63	51.22 ± 16.60	b = −0.00 (0.23), t(76.60) = −0.016, p = 0.000	b = 0.90 (0.36), t(92.95) = 2.516, p = 0.036
TMT_B_s	142.46 ± 96.02	141.02 ± 104.73	278.50 ± 211.01	150.95 ± 79.64	154.51 ± 108.27	131.03 ± 62.95	b = −0.03 (0.17), t(76.01) = −0.165, p = 0.985	b = 0.86 (0.27), t(82.22) = 3.204, p = 0.005
JLO	21.64 ± 6.42	21.50 ± 6.13	15.75 ± 8.31	20.42 ± 6.63	20.42 ± 6.29	20.42 ± 5.38	b = −0.03 (0.18), t(76.02) = −0.180, p = 0.982	b = −0.54 (0.28), t(82.66) = −1.945, p = 0.133
Similarities	22.07 ± 4.99	23.46 ± 4.81	25.25 ± 3.01	23.77 ± 2.97	25.38 ± 3.50	24.58 ± 2.84	b = 0.26 (0.16), t(77.00) = 1.641, p = 0.235	b = 0.67 (0.26), t(82.99) = 2.619, p = 0.028
Clock_test_total	14.64 ± 2.60	15.63 ± 1.64	15.88 ± 1.25	15.46 ± 1.50	16.23 ± 1.53	15.75 ± 1.66	b = 0.52 (0.21), t(77.65) = 2.429, p = 0.045	b = 0.58 (0.33), t(89.62) = 1.736, p = 0.197
VF_K	15.35 ± 6.78	15.96 ± 6.48	14.50 ± 7.67	17.27 ± 4.74	17.65 ± 5.04	14.92 ± 7.46	b = 0.10 (0.17), t(76.86) = 0.561, p = 0.841	b = −0.30 (0.27), t(82.72) = −1.120, p = 0.504
VF_P	14.23 ± 5.26	15.00 ± 6.72	13.88 ± 8.49	15.46 ± 5.29	16.04 ± 3.94	13.00 ± 7.82	b = 0.13 (0.18), t(77.00) = 0.728, p = 0.748	b = −0.20 (0.28), t(83.84) = −0.692, p = 0.769
VF_S	13.23 ± 4.86	14.23 ± 5.67	10.88 ± 7.22	14.15 ± 4.23	13.85 ± 3.73	11.92 ± 7.14	b = 0.20 (0.18), t(77.01) = 1.140, p = 0.493	b = −0.37 (0.28), t(83.88) = −1.316, p = 0.390
KF_animals_total	20.73 ± 6.69	20.65 ± 7.18	17.88 ± 8.20	21.04 ± 8.41	20.96 ± 7.86	20.08 ± 10.15	b = −0.03 (0.18), t(76.93) = −0.147, p = 0.988	b = −0.44 (0.28), t(83.30) = −1.562, p = 0.268
KF_vegetables_total	12.12 ± 4.14	11.42 ± 5.46	10.38 ± 7.27	12.12 ± 4.58	12.54 ± 4.10	13.08 ± 8.43	b = −0.15 (0.20), t(77.29) = −0.763, p = 0.727	b = −0.40 (0.31), t(86.55) = −1.291, p = 0.404
BNT_correct	27.00 (2.00)	28.50 (3.00)	29.00 (1.75)	27.50 (3.00)	28.50 (2.00)	27.00 (2.25)	OR = 1.64 (0.33), Z = 2.472, p = 0.036	OR = 1.94 (0.62), Z = 2.067, p = 0.097
BNT_semantic	29.00 (2.00)	30.00 (1.00)	29.00 (1.00)	29.00 (2.00)	30.00 (1.75)	30.00 (1.00)	OR = 1.80 (0.51), Z = 2.068, p = 0.097	OR = 2.11 (1.00), Z = 1.580, p = 0.254
BNT_phonemic	30.00 (1.00)	30.00 (0.00)	30.00 (1.00)	30.00 (0.00)	30.00 (0.00)	30.00 (0.00)	OR = 2.22 (1.11), Z = 1.592, p = 0.249	OR = 1.59 (1.10), Z = 0.677, p = 0.777

Group simple contrasts[c]						
	EXP			Occasion simple contrasts		
Follow-up-minus-Baseline	Re-test-minus-Baseline	Follow-up-minus-Re-test	Follow-up-minus-Baseline	Baseline	Re-test	Follow-up
b = 0.06 (0.31), t(82.83) = 0.198, p = 0.979	b = 0.06 (0.18), t(73.56) = 0.316, p = 0.946	b = 0.02 (0.24), t(79.87) = 0.073, p = 0.997	b = −0.04 (0.25), t(80.81) = −0.163, p = 0.985	b = −0.02 (0.27), t(88.39) = −0.071, p = 0.944	b = −0.34 (0.28), t(89.65) = −1.213, p = 0.228	b = −0.44 (0.40), t(128.13) = −1.081, p = 0.282
b = −0.03 (0.21), t(76.74) = −0.134, p = 0.990	b = 0.06 (0.13), t(73.39) = 0.508, p = 0.868	b = 0.12 (0.17), t(75.73) = 0.722, p = 0.751	b = 0.06 (0.17), t(76.09) = 0.338, p = 0.939	b = −0.55 (0.28), t(67.81) = −1.943, p = 0.056	b = −0.42 (0.29), t(68.45) = −1.472, p = 0.146	b = −0.33 (0.35), t(114.43) = −0.947, p = 0.346
b = 0.16 (0.24), t(76.80) = 0.654, p = 0.791	b = −0.13 (0.15), t(73.11) = −0.871, p = 0.660	b = −0.10 (0.19), t(75.35) = −0.526, p = 0.859	b = 0.03 (0.19), t(76.19) = 0.131, p = 0.991	b = −0.44 (0.29), t(72.03) = −1.516, p = 0.134	b = −0.45 (0.29), t(71.94) = −1.549, p = 0.126	b = −0.58 (0.37), t(120.74) = −1.560, p = 0.121
b = 0.21 (0.36), t(89.16) = 0.568, p = 0.838	b = 0.27 (0.22), t(74.34) = 1.265, p = 0.419	b = −0.22 (0.29), t(84.37) = −0.775, p = 0.720	b = −0.50 (0.29), t(84.37) = −1.726, p = 0.202	b = −0.06 (0.28), t(102.71) = −0.198, p = 0.843	b = 0.25 (0.28), t(104.78) = 0.891, p = 0.375	b = −0.45 (0.45), t(127.29) = −1.002, p = 0.318
b = −0.31 (0.30), t(87.15) = −1.034, p = 0.558	b = 0.47 (0.19), t(77.11) = 2.503, p = 0.038	b = −0.09 (0.25), t(84.21) = −0.349, p = 0.935	b = −0.55 (0.25), t(84.21) = −2.214, p = 0.075	b = −0.28 (0.28), t(91.05) = −1.011, p = 0.314	b = −0.05 (0.28), t(91.05) = −0.182, p = 0.856	b = −0.30 (0.40), t(132.31) = −0.747, p = 0.456
OR = 0.97 (0.24), Z = −0.140, p = 0.989	OR = 1.17 (0.19), Z = 0.975, p = 0.593	OR = 0.95 (0.20), Z = −0.258, p = 0.964	OR = 0.81 (0.17), Z = −1.007, p = 0.573	OR = 1.00 (0.18), Z = −0.024, p = 0.981	OR = 1.09 (0.19), Z = 0.515, p = 0.606	OR = 0.91 (0.27), Z = −0.309, p = 0.757
OR = 0.70 (0.17), Z = −1.474, p = 0.304	OR = 1.81 (0.28), Z = 3.867, p < 0.001	OR = 1.00 (0.20), Z = 0.004, p = 0.000	OR = 0.55 (0.11), Z = −2.882, p = 0.011	OR = 0.85 (0.22), Z = −0.627, p = 0.531	OR = 1.02 (0.27), Z = 0.085, p = 0.932	OR = 0.81 (0.28), Z = −0.611, p = 0.541
OR = 0.81 (0.20), Z = −0.842, p = 0.677	OR = 1.93 (0.30), Z = 4.179, p < 0.001	OR = 1.14 (0.24), Z = 0.612, p = 0.813	OR = 0.59 (0.12), Z = −2.536, p = 0.030	OR = 0.73 (0.24), Z = −0.973, p = 0.330	OR = 0.91 (0.30), Z = −0.277, p = 0.782	OR = 0.66 (0.27), Z = −1.012, p = 0.312
OR = 0.31 (0.09), Z = −3.857, p < 0.001	OR = 1.50 (0.32), Z = 1.863, p = 0.149	OR = 0.75 (0.20), Z = −1.104, p = 0.511	OR = 0.50 (0.14), Z = −2.508, p = 0.032	OR = 1.23 (0.35), Z = 0.714, p = 0.475	OR = 0.92 (0.29), Z = −0.265, p = 0.791	OR = 1.49 (0.59), Z = 1.004, p = 0.316
OR = 0.94 (0.23), Z = −0.251, p = 0.966	OR = 0.75 (0.11), Z = −1.962, p = 0.122	OR = 1.51 (0.30), Z = 2.059, p = 0.099	OR = 2.02 (0.42), Z = 3.390, p = 0.002	OR = 1.07 (0.34), Z = 0.211, p = 0.833	OR = 1.02 (0.33), Z = 0.053, p = 0.958	OR = 2.19 (0.87), Z = 1.967, p = 0.049
b = −0.40 (0.32), t(88.25) = −1.239, p = 0.433	b = 0.43 (0.20), t(76.17) = 2.153, p = 0.086	b = 0.27 (0.27), t(84.85) = 1.006, p = 0.575	b = −0.16 (0.27), t(84.85) = −0.606, p = 0.817	b = 0.16 (0.28), t(96.97) = 0.587, p = 0.559	b = 0.16 (0.28), t(96.97) = 0.568, p = 0.571	b = 0.39 (0.41), t(130.03) = 0.946, p = 0.346
OR = 0.63 (0.19), Z = −1.505, p = 0.289	OR = 2.51 (0.52), Z = 4.473, p < 0.001	OR = 1.85 (0.50), Z = 2.267, p = 0.060	OR = 0.74 (0.21), Z = −1.060, p = 0.539	OR = 0.78 (0.29), Z = −0.661, p = 0.509	OR = 1.59 (0.60), Z = 1.224, p = 0.221	OR = 1.86 (0.89), Z = 1.293, p = 0.196
OR = 0.84 (0.73), Z = −0.202, p = 0.978	OR = 1.74 (0.93), Z = 1.031, p = 0.558	OR = 1.08 (0.70), Z = 0.123, p = 0.992	OR = 0.62 (0.43), Z = −0.683, p = 0.773	OR = 1.48 (0.76), Z = 0.760, p = 0.447	OR = 1.08 (0.69), Z = 0.113, p = 0.910	OR = 0.80 (0.78), Z = −0.231, p = 0.817
OR = 0.86 (1.03), Z = −0.125, p = 0.991	OR = 0.48 (0.35), Z = −1.017, p = 0.566	OR = 0.36 (0.41), Z = −0.889, p = 0.647	OR = 0.76 (0.92), Z = −0.224, p = 0.973	OR = 1.01 (0.75), Z = 0.015, p = 0.988	OR = 0.75 (0.67), Z = −0.325, p = 0.745	OR = 0.66 (1.04), Z = −0.264, p = 0.792
b = 1.27 (0.34), t(95.56) = 3.737, p < 0.001	b = −0.11 (0.22), t(77.11) = −0.499, p = 0.872	b = 0.46 (0.29), t(89.91) = 1.599, p = 0.251	b = 0.57 (0.29), t(89.91) = 1.977, p = 0.124	b = 0.12 (0.26), t(113.73) = 0.437, p = 0.663	b = −0.12 (0.26), t(113.73) = −0.456, p = 0.650	b = −0.82 (0.42), t(130.61) = −1.962, p = 0.052
b = 1.00 (0.32), t(91.32) = 3.089, p = 0.007	b = −0.01 (0.21), t(77.05) = −0.034, p = 0.999	b = 0.58 (0.27), t(87.04) = 2.141, p = 0.087	b = 0.59 (0.27), t(87.04) = 2.167, p = 0.083	b = −0.12 (0.27), t(103.69) = −0.429, p = 0.669	b = −0.02 (0.27), t(103.69) = −0.080, p = 0.936	b = −0.43 (0.41), t(131.37) = −1.041, p = 0.300
b = 0.44 (0.31), t(88.30) = 1.428, p = 0.331	b = −0.05 (0.19), t(77.07) = −0.277, p = 0.959	b = 0.31 (0.26), t(84.99) = 1.190, p = 0.463	b = 0.36 (0.26), t(84.99) = 1.396, p = 0.347	b = −0.20 (0.28), t(94.87) = −0.720, p = 0.473	b = −0.13 (0.28), t(94.87) = −0.453, p = 0.652	b = −0.20 (0.41), t(132.16) = −0.498, p = 0.619
OR = 0.20 (0.12), Z = −2.670, p = 0.021	OR = 0.69 (0.20), Z = −1.278, p = 0.407	OR = 0.59 (0.25), Z = −1.252, p = 0.422	OR = 0.86 (0.37), Z = −0.349, p = 0.935	OR = 0.76 (0.28), Z = −0.745, p = 0.456	OR = 0.60 (0.24), Z = −1.304, p = 0.192	OR = 2.62 (1.99), Z = 1.273, p = 0.203
b = −1.54 (0.33), t(92.92) = −4.674, p < 0.001	b = −0.20 (0.21), t(75.89) = −0.955, p = 0.608	b = −0.31 (0.28), t(88.17) = −1.100, p = 0.517	b = −0.10 (0.28), t(89.87) = −0.364, p = 0.930	b = 0.33 (0.26), t(111.40) = 1.273, p = 0.206	b = 0.04 (0.26), t(112.48) = 0.137, p = 0.891	b = 1.48 (0.40), t(127.85) = 3.645, p < 0.001
OR = 0.81 (0.16), Z = −1.032, p = 0.556	OR = 1.08 (0.14), Z = 0.627, p = 0.805	OR = 0.87 (0.14), Z = −0.850, p = 0.672	OR = 0.80 (0.13), Z = −1.325, p = 0.381	OR = 1.14 (0.17), Z = 0.877, p = 0.381	OR = 1.22 (0.18), Z = 1.360, p = 0.174	OR = 1.21 (0.29), Z = 0.783, p = 0.434
b = 0.90 (0.36), t(93.63) = 2.533, p = 0.034	b = 0.14 (0.23), t(75.38) = 0.630, p = 0.804	b = −0.10 (0.30), t(88.16) = −0.331, p = 0.941	b = −0.24 (0.30), t(88.16) = −0.809, p = 0.699	b = 0.12 (0.28), t(112.56) = 0.426, p = 0.671	b = 0.27 (0.28), t(111.76) = 0.964, p = 0.337	b = −0.88 (0.43), t(127.90) = −2.018, p = 0.046
b = 0.89 (0.27), t(82.59) = 3.313, p = 0.004	b = −0.03 (0.17), t(75.18) = −0.177, p = 0.983	b = −0.13 (0.23), t(80.42) = −0.562, p = 0.841	b = −0.10 (0.23), t(80.42) = −0.431, p = 0.903	b = 0.15 (0.28), t(81.97) = 0.538, p = 0.592	b = 0.15 (0.28), t(80.83) = 0.536, p = 0.593	b = −0.84 (0.38), t(127.98) = −2.203, p = 0.029
b = −0.51 (0.28), t(83.05) = −1.834, p = 0.165	b = 0.00 (0.17), t(75.16) = 0.000, p = 0.000	b = 0.04 (0.23), t(80.74) = 0.171, p = 0.984	b = 0.04 (0.23), t(80.74) = 0.171, p = 0.984	b = −0.20 (0.28), t(83.68) = −0.706, p = 0.482	b = −0.17 (0.28), t(82.51) = −0.598, p = 0.552	b = 0.38 (0.39), t(128.51) = 0.982, p = 0.328
b = 0.41 (0.26), t(82.67) = 1.600, p = 0.251	b = 0.39 (0.16), t(76.25) = 2.466, p = 0.042	b = 0.24 (0.22), t(80.93) = 1.104, p = 0.514	b = −0.16 (0.22), t(80.93) = −0.721, p = 0.752	b = 0.41 (0.28), t(78.98) = 1.491, p = 0.140	b = 0.55 (0.28), t(80.03) = 1.958, p = 0.054	b = −0.02 (0.37), t(128.84) = −0.057, p = 0.955
b = 0.06 (0.33), t(90.80) = 0.185, p = 0.981	b = 0.41 (0.21), t(75.40) = 1.962, p = 0.129	b = 0.17 (0.28), t(85.81) = 0.614, p = 0.813	b = −0.24 (0.28), t(85.81) = −0.862, p = 0.666	b = 0.43 (0.28), t(106.31) = 1.548, p = 0.125	b = 0.32 (0.27), t(104.27) = 1.193, p = 0.236	b = 0.02 (0.42), t(129.20) = 0.049, p = 0.961
b = −0.40 (0.27), t(82.72) = −1.474, p = 0.309	b = 0.06 (0.17), t(75.15) = 0.376, p = 0.925	b = −0.39 (0.23), t(80.50) = −1.729, p = 0.201	b = −0.45 (0.23), t(80.50) = −2.009, p = 0.117	b = 0.33 (0.28), t(83.50) = 1.198, p = 0.234	b = 0.30 (0.28), t(83.50) = 1.082, p = 0.282	b = 0.24 (0.38), t(129.52) = 0.638, p = 0.525
b = −0.33 (0.28), t(83.84) = −1.152, p = 0.485	b = 0.10 (0.18), t(75.15) = 0.557, p = 0.843	b = −0.40 (0.24), t(81.29) = −1.676, p = 0.221	b = −0.50 (0.24), t(81.29) = −2.090, p = 0.098	b = 0.22 (0.28), t(87.30) = 0.787, p = 0.433	b = 0.19 (0.28), t(87.30) = 0.672, p = 0.503	b = 0.02 (0.39), t(130.18) = 0.039, p = 0.969
b = −0.58 (0.28), t(83.88) = −2.036, p = 0.110	b = −0.06 (0.18), t(75.16) = −0.339, p = 0.939	b = −0.46 (0.24), t(81.32) = −1.934, p = 0.136	b = −0.40 (0.24), t(81.32) = −1.682, p = 0.218	b = 0.19 (0.28), t(87.38) = 0.703, p = 0.484	b = −0.07 (0.28), t(87.38) = −0.253, p = 0.801	b = 0.11 (0.39), t(130.19) = 0.275, p = 0.784
b = −0.41 (0.28), t(83.30) = −1.469, p = 0.311	b = −0.01 (0.17), t(75.13) = −0.057, p = 0.998	b = −0.14 (0.23), t(80.90) = −0.596, p = 0.823	b = −0.13 (0.23), t(80.90) = −0.554, p = 0.845	b = 0.04 (0.28), t(85.53) = 0.137, p = 0.891	b = 0.05 (0.28), t(85.53) = 0.195, p = 0.846	b = 0.33 (0.39), t(129.96) = 0.864, p = 0.389
b = −0.25 (0.31), t(86.55) = −0.807, p = 0.700	b = 0.08 (0.20), t(75.18) = 0.415, p = 0.910	b = 0.21 (0.26), t(83.19) = 0.809, p = 0.698	b = 0.13 (0.26), t(83.19) = 0.499, p = 0.872	b = 0.00 (0.28), t(95.88) = 0.004, p = 0.997	b = 0.23 (0.28), t(95.88) = 0.841, p = 0.403	b = 0.62 (0.41), t(130.05) = 1.510, p = 0.133
OR = 1.18 (0.39), Z = 0.508, p = 0.868	OR = 1.50 (0.29), Z = 2.081, p = 0.094	OR = 1.07 (0.27), Z = 0.278, p = 0.958	OR = 0.71 (0.19), Z = −1.265, p = 0.415	OR = 1.10 (0.30), Z = 0.351, p = 0.725	OR = 1.01 (0.30), Z = 0.027, p = 0.979	OR = 0.61 (0.26), Z = −1.177, p = 0.239
OR = 1.18 (0.58), Z = 0.327, p = 0.943	OR = 1.61 (0.46), Z = 1.662, p = 0.220	OR = 2.88 (1.34), Z = 2.276, p = 0.059	OR = 1.79 (0.86), Z = 1.206, p = 0.450	OR = 1.11 (0.37), Z = 0.322, p = 0.747	OR = 1.00 (0.39), Z = −0.006, p = 0.995	OR = 1.52 (1.00), Z = 0.636, p = 0.525
OR = 0.72 (0.54), Z = −0.439, p = 0.899	OR = 3.41 (2.26), Z = 1.849, p = 0.154	OR = 117904989728.18 (85372395146456.53), Z = 0.035, p = 0.999	OR = 34589286267.36 (25045354063191.75), Z = 0.034, p = 0.999	OR = 1.42 (0.79), Z = 0.621, p = 0.534	OR = 2.18 (1.74), Z = 0.974, p = 0.330	OR = 104653712612.96 (75777440084207.91), Z = 0.035, p = 0.972

[a]Results indicate expected difference (b) or odds ratio (OR) with resulting test statistic (t-statistic with degrees of freedom in brackets or Z statistic) and *p*-values.
[b]Data are presented as mean ± standard deviation for continuous variables and as median (interquantile range) for count variables.
[c]EXP-minus-CON.