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Home-based personalized cognitive training in MS patients: A study of adherence and cognitive performance

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Abstract. *Objectives*: To explore unprompted adherence to a personalized, home-based, computerized cognitive training program in patients with multiple sclerosis (MS), and to examine the impact of training on cognitive performance.
Methods: Participants were assigned to a training ($n = 59$) or a control group ($n = 48$). Those in the training group were instructed to train three times a week for 12 weeks. The control group received no training. All participants were evaluated with a Neuropsychological Examination (N-CPC) at baseline and at the end of the study.
Results: In the training group, 42 (71.2%) participants adhered to the training schedule and 22 (37.3%) completed the entire training regimen. In the control group, 24 (50.0%) participants agreed to be retested on the N-CPC. The training group showed a significant improvement over that shown by the control group in three memory-based cognitive abilities (general memory, visual working memory and verbal working memory). Post-hoc exploration of data from the N-CPC showed that cognitive training was also associated with increased naming speed, speed of information recall, focused attention and visuo-motor vigilance.
Conclusions: The appreciable rates of adherence and cognitive improvements observed indicate that personalized cognitive training is a practical and valuable tool to improve cognitive skills and encourage neuronal plasticity in patients with MS.

Keywords: Cognitive training, multiple sclerosis, memory, personalized medicine, plasticity

1. Introduction

Multiple sclerosis (MS) is a chronic inflammatory disease characterized by the development of demyelinating lesions in the brain and spinal cord, which ultimately result in long-term disability [7]. Because neuronal damage can occur throughout the central nervous system, patients experience a wide variety of symptoms [9].

Estimates of the prevalence of cognitive impairment in patients with MS range from 43 to 65% [3, 24]. The most commonly affected domains include episodic memory, attention/concentration and processing speed [3,24]. Executive functions such as verbal fluency, concept formation, abstract reasoning, planning and monitoring are also often affected [3,24]. Cognitive impairment is associated with a poorer quality of life. Patients with MS who are cognitively impaired participate in fewer social activities, are less likely to be employed, report more sexual dysfunction, and are more likely to require personal assistance and assistance with household chores than those without cognitive impairment [25].

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No established or effective pharmacological therapies currently exist for the symptomatic treatment of MS-associated cognitive impairment described above, although limited data from clinical trials suggest that disease-modifying drugs such as interferon beta may reduce the progression of cognitive deterioration [11, 22]. Data from small pilot studies suggest that acetylcholinesterase inhibitors, used to treat Alzheimer's disease, may also have some temporary benefit for cognition in MS [1,13,17].

Although cognitive rehabilitation is recognized as an important component of the treatment strategy for cognitive impairment in MS [2], relatively few studies have investigated it. A recent review identified 16 studies of cognitive rehabilitation specific to patients with MS, of which only 9 were classified as having a high level of evidence (class I or II) [20]. None of the computer-assisted interventions discussed in this review had taken place at the patient's home, leaving open the question of whether MS patients would adhere to a systematic cognitive training regimen if left unprompted and if not reminded to use the software.

Although many studies that have investigated the efficacy of computer-assisted cognitive rehabilitation in MS have various weaknesses, such as absence of a control group, small patient numbers, short follow-up periods, insufficient outcome criteria and lack of detail on study design [15,20,23,27,28], most have reported some cognitive benefit as a result of cognitive training. In an early open study, 22 patients with MS received a computer training program that included 12 sessions concentrating on the two most impaired cognitive domains [23]. Significant improvements in performance over 9 weeks were observed only in the specifically trained functions, suggesting that the improvement could not have been due solely to practice effect, spontaneous recovery, or improved mood. Another small controlled study involving 19 MS patients with mild-to-moderate cognitive impairment reported benefits from a 4-week neuropsychological training program, with participants in the treatment group experiencing significant improvements in executive functions and spatial-constructional abilities, and improvements in verbal and nonverbal learning memory [28]. In a recent controlled study investigating a training program for memory and working memory in 42 patients with MS, the treatment group showed better verbal learning, long-delay verbal memory performance and working memory performance than the control group [15]. In contrast, a double-blind study in 82 MS patients with subjective complaints of poor attention or memory failed to support the efficacy of computer-assisted memory and attention retraining, with the study treatment being better than the control treatment only on the word list generation test [27].

Studies in healthy adults have shown that personalized adaptive feedback is an important feature of a cognitive training program [5]. The training program used in the present study, achieves this by: (i) using a baseline cognitive evaluation to individualize the training regimen (ii) continually adapting the difficulty level to the subject's performance using an interactive-adaptive system (iii) providing detailed graphic and verbal feedback after each training task. This cognitive training program has previously been shown to improve cognitive skills (focused attention, visuo-spatial learning, and short-term memory) in elderly people, both with and without mild cognitive impairment [12]. The present study sought to examine the impact of the cognitive training regimen on the cognitive performance of patients with MS. Because the cognitive training program was designed for home use, understanding patterns of unprompted adherence and establishing whether participants would voluntarily adhere to home-based computerized training was a primary goal of this study.

2. Methods

2.1. Study design

This interventional study in patients with MS included a 12-week computerized cognitive training program with assessments at baseline and at the end of the training schedule. Participants were allocated either to the training group or the control group. Because the primary goal of the study was to understand patterns of adherence, we first allocated a sufficient number of subjects for the training group. Subjects with no home internet connection and remaining subjects were allocated to the control group.

The study was conducted at the Multiple Sclerosis & Brain Research Centre, Carmel Medical Centre, Haifa, Israel between 14 November 2005 and 22 November 2006. The protocol was approved by the ethics committee of Carmel Medical Centre (number HT2917) and written informed consent was obtained from all participants prior to the baseline assessment.

2.2. Participants

Participants were selected from among the patients attending the multiple sclerosis outpatient clinics at the Carmel Medical Centre. Participants eligible for inclusion had a diagnosis of relapsing – remitting or relapsing – progressive MS, had healthy dominant hand functioning, were Hebrew speakers, owned and were able to use a home personal computer, and expressed an interest in taking part in the study.

Exclusion criteria included any other neurological disease, drug or alcohol abuse or dependence, as well as major depression and/or known conditions which required the use of psychotropic medication. MS patients categorized as primary progressive were also excluded because primary progressive MS has different clinical features, different underlying pathogenic processes and a different response to treatment compared to the more common relapsing forms of MS.

2.3. Intervention

The training program selected for this study was CogniFit Personal Coach® (CPC), a home-based, computerized, individualized cognitive training program. Training rests upon the results of a baseline cognitive evaluation, the Neuropsychological Examination – CogniFit Personal Coach® (N-CPC) [14]. This evaluation is administered before and after the training and requires two twenty-minute sessions for each administration. It is composed of 15 evaluation tasks measuring a wide range of cognitive abilities such as memory, attention and eye-hand coordination, with scores derived from response times (in milliseconds) and accuracy (%) [14]. The N-CPC has been validated in healthy younger adults (mean age 23) against several major standard neuropsychological tests, including the full Cambridge Neuropsychological Test Automated Battery (CANTAB), Raven's Standard Progressive Matrices, the Wisconsin Card Sorting Test, the Continuous Performance Test, the STROOP test, and other reading tests [14]. The reliability and validity of the N-CPC was also demonstrated in a study of 89 participants aged 50 and over, with internal consistency of 0.70 (Cronbach's alpha), and test – retest reliability of 0.80 (intra-class correlation coefficient) [14].

Raw data collected from the N-CPC evaluation tasks are reduced and scores assigned to a number of traditionally recognized cognitive abilities using weights previously derived from a factor analysis performed on normative data from a healthy population (N $=$ 861, 344 males and 517 females; average age 65.7 years $\pm$ 8.85, range 50–90). Thus, for each individual, the CPC assigns scores to 17 cognitive abilities that are subsequently trained by means of 21 different training tasks. Each training task focuses on one or two of the 17 cognitive abilities. The CPC uses an adaptive-interactive system that attempts to ensure that a subject works in his or her comfort zone and does not experience high levels of frustration. Because the choice of training tasks is determined by individual performance on the N-CPC, no two people have the same training regimen. Training consisted of 24 training sessions, each including three different tasks and requiring 20 to 30 minutes to complete.

A total of 107 individuals were enrolled and assigned to either the training (n = 59) or control (n = 48) group. The groups were well matched at baseline on their clinical and socio-demographic characteristics (Table 1).

Participants in the training group were given a computer disk containing the cognitive training program on their baseline clinic visit, and were shown how to install the program and how to send the data to a central database via the internet. Participants in the control group were informed that they would receive the training software as a gift at the end of the study. Participants in the training group were instructed to use the training package three times a week for a period of 12 weeks. The program closed automatically at the end of training or at the end of 12 weeks. Throughout this time 24-hour technical support by telephone was available to all participants in the training group. Participants who were lagging behind in their training were called once by the second author who inquired whether there were any technical reasons for the observed delay. However, in order to avoid significant prompting, the patients' personal doctor (A Miller) did not initiate any training-related contact with the participants throughout the course of the study.

2.4. Assessments

The total N-CPC [14], Zung Depression Scale [29], Expanded Disability Severity Scale (EDSS) [19] and Fatigue Severity Scale (FSS) [18] assessments were administered at the initial clinic visit and at the 12-week follow-up visit.

Table 1
Baseline characteristics of the entire study population

	Training group $n = 59$	Control group $n = 48$	Statistic	Significance (P)
Female gender n (%)	44 (74.6)	39 (81.2)	$X^2 = 3.721$	0.054
Age (mean $\pm$ SD)	43.78 ± 12.15	41.35 ± 11.23	$t = 1.06$	0.291
Zung Depression Scale	62.08 ± 7.89	61.25 ± 8.78	$t = 0.512$	0.610
FSS	43.88 ± 14.69	43.13 ± 16.10	$t = 0.254$	0.800
EDSS	3.06 ± 1.95	2.66 ± 1.73	$t = 1.12$	0.266

Table 2
Unprompted adherence to the training program in the cognitive training group

	Frequency	Cumulative frequency	Percent	Cumulative percent
Did not begin training	17	17	28.8	28.8
Completed less than 25% of training	6	23	10.2	39.0
Completed 25–50% of training (6–11 sessions)	2	25	3.4	42.4
Completed 50–75 % of training (12–17 sessions)	3	28	5.1	47.5
Completed up to 96% of training (18–23 sessions)	9	37	15.3	62.7
Completed entire training regimen (24 sessions)	22	59	37.3	100.0
Total	59		100.0	

2.5. *Statistical analyses*

Unprompted adherence to the training program was calculated using simple frequency measures. To evaluate 1) differences in the cognitive outcome measures at baseline between the two groups and the training effect in each group and 2) the post-intervention difference between the two groups adjusting for baseline scores we first used mixed effects models for repeated measures and general linear models in the SAS statistical program. Then, using SPSS, we tried a different statistical approach. We used independent samples t-tests and paired sample t-tests to assess differences in N-CPC scores between the groups at baseline and within the groups before and after the training, respectively. We used analysis of Covariance (ANCOVA) to evaluate differences in N-CPC post-training scores between the groups. Results were similar regardless of the statistical procedure used (similar effects were obtained using either approach). The results reported in the article are based on the second approach (independent samples t-tests, paired sample t-tests and ANCOVA).

3. Results

3.1. *Study population and adherence*

The unprompted adherence data for the 59 participants in the training group are shown in Table 2. Forty two (71.2%) of the participants in this group used the program at home unprompted, and, among those, 57.6% completed more than half of the prescribed number of training sessions. In the control arm, 24 participants (50%) declined to return to the clinic for the second examination when contacted at the end of the study. Forty six participants completed the entire 12-week study; 22 in the training arm, and 24 in the control group.

No differences were observed in gender distribution, EDSS, Zung Depression Scale or FSS scores between participants who did not complete training and those who remained in the study in either group. However, in the training group, non-completers (mean 40.1 years) were younger than completers (mean 49.9 years; $p = 0.001$).

The two groups completing the study were similar at baseline regarding gender, education, Zung depression scale scores, FSS and EDSS (Table 3). However, on average, training group completers (mean 49.9 years) were significantly older than control group completers (mean 42.3 years; $p < 0.01$).

In order to understand why younger participants left the training group, we looked to see whether there was any correlation between age and severity of illness (EDSS). It was found that, in the training group, but not in the control group, increasing age was significantly correlated with higher EDSS scores ($r = 0.39$, $p < 0.05$).

3.2. *Cognitive outcome measures*

Table 4 summarizes pre and posttraining scores for each of the N-CPC cognitive abilities for the two completer groups. Significant improvement was observed in seven cognitive abilities in the control group: di-

Table 3
Baseline characteristics of the study completers

	Training group $n = 59$	Control group $n = 48$	Statistic	Significance (P)
Female gender n (%)	17 (77)	19 (75)	$X^2 = 0.179$	0.0858
Age (mean ± SD)	49.9 ± 1.9	42.3 ± 10.7	$t = 2.60$	0.013
Level of education n (%)*				
University	16 (71)	17 (71)	X2 = 0.216	0.829
High school	6 (29)	7 (29)		
Zung Depression Scale	62.84 ± 9.74	58.44 ± 7.43	$t = 1.73$	0.09
FSS	40.91 ± 14.78	40.76 ± 17.26	$t = 0.051$	0.960
EDSS	2.56 ± 2.09	2.53 ± 1.66	$t = 0.082$	0.935

*Education data are available for the subjects who completed the study as it was collected on the retest visit.

vided attention, sustained attention (avoiding distractions), naming, response time, shifting attention, spatial perception and time estimation. In the training group, significant increases were observed in eleven cognitive abilities: divided attention, hand – eye coordination, general memory (a measure of memory derived from several memory constructs), naming, response time, spatial perception, time estimation, visual working memory, visual perception, visual scanning and verbal-auditory working memory. Improvement in the training group was significantly superior over that shown by the control group in general memory, visual working memory and verbal-auditory working memory.

3.3. *Other measures*

No significant differences in Zung depression scale score or EDSS were observed in either group over the course of the study. However, fatigue as (measured by FSS scores), remained stable in the control group, but increased in the trained group (F = 5.76, $p < 0.021$).

3.4. *Post-hoc evaluation of performance on memory tests*

At baseline, 15 of 22 (68.2%) completers in the training group were classified by the program as having low or intermediate scores on general memory, visual working memory or verbal working memory, and an average of 57% of their total training time (range: 35% to 69%) was dedicated to memory training in this group. (The classification into low, intermediate or high memory scores by the program is used to determine intensity of training and is not a norm-based assessment of memory. Lower memory scores do not necessarily mean that the subject has memory impairment, but rather that the memory scores are low relative to other cognitive abilities).

There was a high degree of correlation between the three memory abilities that showed an improvement in the training group beyond that of the control group (general memory and visual working memory, $r = 0.96$; general memory and verbal-auditory working memory, $r = 0.97$; verbal-auditory working memory and visual working memory, $r = 0.99$) at baseline. This is unsurprising, given that the scores draw on some of the same tests. In order to assess the specific contribution of each task to the memory improvement in the training group, the raw data (before its transformation into scores representing cognitive abilities) from the five memory tasks in N-CPC were analyzed, using paired sample t-tests to assess whether there were any differences within the two groups of completers, and ANCOVA to evaluate differences between the groups. The memory tasks were 'Flowers and Numbers', a task composed of three sub tasks using visual-spatial working memory as well as forward and backward verbal working memory for digits; 'The Letters', a task assessing speed and accuracy of naming known objects; 'Pictures and Words', a task assessing visual and auditory working memory for objects; 'Television', a time-estimation judgment task heavily involving working memory for auditory non-linguistic (tonal) stimuli; and 'Objects Seen or Heard Before', a task to evaluate the efficiency of auditory and visually based recall. The cognitive training group improved in all measures except two (Table 5). Cognitive training was shown to be related not only to improved memory but also to increased speed at which participants were able to retrieve and recall information. Improvements were observed in all speed scores in the majority of working memory and recall assessments. No improvement was apparent in naming accuracy (an expected finding, since the goal of naming tasks is to measure speed of name retrieval from memory rather than vocabulary knowledge). In contrast, in the control group, no improvements were observed on any of the measures except accuracy of recall in the 'Objects Seen or Heard Before' task (for

Table 4

Summary measures of the scores of 17 cognitive abilities in the N-CPC at baseline and post training

Domain	Training group ($n = 22$)			Control group ($n = 24$)				
	Baseline (mean score ± SD)	Post training (mean score ± SD)	P for difference between baseline and post training	Baseline (mean score ± SD)	Post training (mean score ± SD)	P for difference between baseline and post training	P values in the ANCOVA model after controlling for baseline score and age	Effect size (partial ETA^2) for the group factor in the model
Auditory (non- linguistic) working memory	0.39 ± 1.06	0.69 ± 0.78	0.107	0.42 ± 0.84	0.62 ± 0.87	0.109	0.436	0.014
Awareness	−0.19 ± 0.99	−0.09 ± 1.04	0.669	−0.31 ± 0.99	−0.13 ± 1.39	0.573	0.990	0.000
Divided attention	1.93 ± 0.73	2.37 ± 0.78	0.011	1.72 ± 1.26	2.41 ± 0.72	0.007	0.698	0.040
Avoiding distractions	−0.85 ± 0.49	−0.70 ± 0.47	0.362	−1.26 ± 1.05	−0.67 ± 0.69	0.011	0.940	0.000
Hand – eye co-ordination	−0.16 ± 1.25	0.26 ± 1.20	< 0.0001	0.29 ± 1.07	0.38 ± 0.99	0.562	0.140	0.051
General memory*	0.24 ± 1.03	1.13 ± 0.82	< 0.0001	0.63 ± 0.93	0.56 ± 1.10	0.686	0.002	0.207
Inhibition	−0.17 ± 0.55	−0.16 ± 0.62	0.935	−0.47 ± 0.26	−0.30 ± 0.59	0.172	0.830	0.010
Naming	0.42 ± 0.74	0.68 ± 0.56	0.029	0.06 ± 0.98	0.54 ± 0.85	0.004	0.851	0.001
Planning	−0.16 ± 0.72	0.07 ± 0.77	0.297	0.20 ± 0.91	0.00 ± 0.90	0.375	0.513	0.010
Response time	−0.02 ± 1.10	−0.39 ± 0.74	0.001	−0.29 ± 0.76	−0.51 ± 0.67	0.014	0.252	0.031
Shifting attention	0.22 ± 0.79	0.37 ± 0.91	0.481	0.15 ± 0.83	0.48 ± 0.62	0.004	0.529	0.010
Spatial perception	−0.03 ± 0.98	0.46 ± 0.69	< 0.0001	0.22 ± 0.97	0.54 ± 0.64	0.024	0.507	0.010
Time estimation	0.04 ± 1.13	0.62 ± 0.61	0.014	−0.03 ± 1.09	0.34 ± 1.00	0.013	0.249	0.032
Visual working memory	0.31 ± 1.07	1.15 ± 0.84	< 0.0001	0.66 ± 0.91	0.65 ± 1.03	0.935	0.003	0.196
Visual perception	0.20 ± 0.95	0.54 ± 0.58	0.006	0.29 ± 0.66	0.45 ± 0.64	0.064	0.077	0.072
Visual scanning	−0.13 ± 0.98	−0.53 ± 0.74	0.029	−0.35 ± 1.00	−0.57 ± 0.94	0.341	0.710	0.030
Verbal auditory working memory	0.18 ± 1.07	1.09 ± 0.81	0.001	0.66 ± 0.80	0.53 ± 1.02	0.463	0.003	0.191

*An average of scores from several memory constructs such as recall of names, verbal working memory and visual-spatial working memory.

Table 5

Post-hoc analysis of raw data from the memory tasks in the N-CPC

Name of the task	Cognitive ability assessed by task		Training group score (mean ± SD)	P value for difference between baseline and post-training scores in the training group	Control group score (mean ± SD)	P value for difference between baseline and post-training scores in the control group	P values in the ANCOVA model after controlling for baseline score and age	Effect size (partial ETA^2) for the group factor in the model
Flowers and numbers	Visuo-spatial working memory	Baseline	4.05 ± 1.33	0.001	5.00 ± 1.25	0.792	$P = 0.066$	0.078
		Post-training	5.41 ± 1.26		4.92 ± 1.44			
	Auditory verbal working memory (digit forward)	Baseline	4.82 ± 1.44	0.002	5.38 ± 1.01	0.450	$P = 0.011$	0.143
		Post-training	5.68 ± 1.17		5.25 ± 1.19			
	Auditory verbal working memory (digit backward)	Baseline	4.77 ± 1.80	0.023	4.96 ± 1.33	0.216	$P = 0.008$	0.157
		Post-training	5.55 ± 1.47		4.67 ± 1.34			
Letters	Naming speed	Baseline	1361.76 ± 653.20	0.016	1270.17 ± 444.91	0.272	$P = 0.050$	0.089
		Post-training	1065.62 ± 359.20		1164.79 ± 461.73			
	Naming accuracy	Baseline	96.97 ± 4.45	0.540	94.87 ± 6.41	0.147	$P = 0.670$	0.040
		Post-training	97.47 ± 3.73		96.53 ± 5.63			
Pictures and words	Working memory for objects reaction time (msecs.)	Baseline	1739.55 ± 633.50	0.010	1681.59 ± 478.10	0.056	$P = 0.316$	0.024
		Post-training	1522.65 ± 450.00		1534.61 ± 407.81			
	Working memory for objects accuracy (%)	Baseline Baseline	91.72 ± 8.91	0.697	89.24 ± 9.36	0.641	$P = 0.782$	0.020
		Post-training	90.53 ± 13.44		90.28 ± 10.62			
Television	Auditory working memory accuracy (%)	Baseline	79.05 ± 15.14	0.028	81.25 ± 18.19	0.790	$P = 0.153$	0.048
		Post-training	86.89 ± 10.89		80.14 ± 13.42			
Objects seen or heard before	Speed of recall (msecs)	Baseline	9660.55 ± 2522.78	0.004	9429.58 ± 1550.68	0.382	$P = 0.033$	0.104
		Post-training	8661.20 ± 1938.67		9154.24 ± 1488.05			
	Accuracy of recall	Baseline	76.61 ± 19.24	0.05	75.22 ± 19.58	0.005	$P = 0.731$	0.030
		Post-training	83.15 ± 16.88		82.15.46 ± 13.08			

which an improvement was also observed in the training group). The training group surpassed the control group in forward and backward working memory for digits, in object naming speed, and in working memory speed of recall.

The training intervention significantly explains 9%–21% of the observed differences between the groups after controlling for the variance due to baseline scores and to age. Before controlling for these two influences, the models explain an average of 40% (range 12%–60%) of the differences between the groups.

3.5. *Post-hoc evaluation of performance on other cognitive tests*

The detailed findings obtained from the post-hoc analysis of the memory tasks led us to reason that information about changes associated with the intervention might have been lost in the original factor analysis used for data reduction to create the participants' scores on the 17 abilities in the N-CPC. Because executive control functions (planning, scheduling, and task coordination), attention and speed of information processing are common complaints among patients with MS [3,24], we analyzed the raw data from three attention tasks in the N-CPC, including two with a strong speed component. The three tasks were 'Light Bulb', a task requiring speeded action in a high state of alertness, 'Colours', a variant on the Stroop, requiring rapid inhibition of automated knowledge, and 'Tracking the Ball', a task requiring vigilance and sustained attention in order to attain high levels of precision. ANCOVA was used to compare the groups and control for inequalities between the groups in age and in baseline scores. Improvements on the three tasks were seen in the cognitive training group but not in the control group (Table 6). In addition, after controlling for baseline score and age, the cognitive training group significantly outperformed the control group on two measures: faster action during an alert state and sustained attention in a high-vigilance visual-motor task.

4. Discussion

A key aim of this study was to establish whether patients with MS would voluntarily adhere to home-based, computerized cognitive training. Almost 60% of the participants in the training group persevered autonomously, without any prompting or reminders, in carrying out at least half of the prescribed number of sessions. This positive trend of unprompted use might be explained by the fact that the participants were free to use the program at their discretion in their home settings. Partial or total lack of adherence can be due to fatigue or other health-related limitations, lack of motivation or to lack of interest in the cognitive training program. It is thus possible that a higher level of adherence might be reached with prompting.

In order to understand why younger participants left the training group, we looked to see whether there was any correlation between age and severity of illness (as measured by the EDSS). It was found that, in the training group, but not in the control group, the older the participants were, the more severe their illness. It is possible that younger participants left the training group because they did not yet feel the urgency for cognitive training.

Although true subject randomization and the intention-to-treat principle were not adopted in this study, thus not enabling an unbiased assessment of the efficacy of cognitive training, the results suggest that personalized cognitive training using a home-based computer-assisted program is associated with improved memory skills (visual memory, general memory and working memory) in patients with MS, as well as significant improvements in processing speed. Conventional interpretations of Eta square suggest that values of 0.01, 0.06 and 0.14 represent small, medium or large effect sizes respectively [8]. The observed Eta square values indicate a large effect size in general memory, visual working memory and verbal auditory working memory, and a medium effect size in retrieval from long-term memory and in naming speed and speed of recall. Because the training tasks do not resemble the assessment tasks, and because the control group did not receive training, it appears unlikely that the observed improvements with cognitive training result from a practice effect.

It is as yet unclear why memory seemed most responsive to cognitive training in this study. Improvements in other cognitive domains (focused attention, visuo-spatial learning and visual memory) have previously been observed in healthy elderly individuals using this program [12]. However, memory is one of the most frequently impaired domains in MS [24], and thus it may have been easier to observe a greater improvement on this domain in the present study. In particular, this may have been apparent because the algorithms within the CPC provide each user with individualized training. A previous study of a computer training program in MS patients that concentrated on the most impaired

Table 6

Post-hoc analysis of raw data from the attention tasks in the N-CPC

Name of the task			Training group score (mean ± SD)	P value for difference between baseline and post-training scores in the training group	Control group score (mean ± SD)	P value for difference between baseline and post-training scores in the control group	P values in the ANCOVA model after controlling for baseline score and age	Effect size (partial ETA^2) for the group factor in the model
Light bulb								
	Focused attention	Baseline	610.87 ± 578.18	0.051	399.44 ± 183.38	NS		8.2%
		Post-training	449.64 ± 267.02		452.10 ± 278.25		$P = 0.06$	
Tracking the ball								
Visuomotor attention:								
	Vertical segments	Baseline	54.22 ± 26.48	0.004	67.82 ± 20.26	NS		
		Post-training	69.48 ± 18.98		70.76 ± 19.75			
	Horizontal segments	Baseline	49.67 ± 27.77	0.004	71.16 ± 18.38	NS		
		Post-training	68.29 ± 20.02		75.16 ± 20.45			
	Diagonal segments	Baseline	53.99 ± 32.54	< 0.001	76.14 ± 17.06	NS		10%
		Post-training	72.76 ± 20.69		73.73 ± 22.28		$P = 0.037$	
	Curve segments	Baseline	52.55 ± 32.39	0.008	71.05 ± 26.15	NS		
		Post-training	74.08 ± 22.63		76.54 ± 29.23			
Variant on the Stroop task								
	Reaction times	Baseline	1072.453 ± 251.70	< 0.001	870.47 ± 506.67	NS	NS	
		Post-training	919.675 ± 239.59		942.72 ± 232.79			
	Correct answers	Baseline	94.89 ± 5.99	NS	87.50 ± 17.87	NS	NS	
		Post-training	97.16 ± 3.19		94.27 ± 14.38			

domains observed significant improvements in performance only in the specifically trained functions [23]. In the present study, over two thirds of the participants in the training group had intermediate or low memory scores (relative to other cognitive abilities) at baseline, and more than half of the training time was dedicated to memory, suggesting that the observed improvements in memory could be explained by the program assigning a relatively large memory training component. Additional training over a longer time period may be required to observe improvements in other domains. Alternatively, some cognitive processes in MS may be less plastic than others.

Medium and small improvements were observed on focused and sustained attention measures when the raw data from three attention tasks in the N-CPC were analyzed, although no significant changes in inhibition were observed. This indicates that the improvement in memory is accompanied by a modest increase in executive control.

The two completer groups were well matched at baseline, except that the mean age of training group was greater than that of the control group. However, given that memory and executive control are frequently impaired with increasing age [21], this is unlikely to account for the improvements observed in the training group. Depression can reduce cognitive capacity in patients with MS, and in particular may exert an adverse effect on working memory [10]. However, no significant differences in depression score were observed between the groups over the course of the study, suggesting that the improvement in the training group was not due to improved mood.

The observed increase in fatigue scores in the trained group did not appear to compromise cognitive performance. A similar finding was observed in a recent study in patients with advanced MS, which reported that change in subjective fatigue did not correlate significantly with change in cognitive performance [4]. Whether a relationship exists between subjective fatigue and cognitive performance requires further investigation. In this study fatigue was assessed using the Fatigue Severity Scale, a patient-reported assessment. Other tools may be more appropriate to investigate particular dimensions of fatigue in future studies [16].

A first limitation of the study is the lack of an active comparator control group. This could be addressed in future studies with a computer program designed to be similar to the CogniFit Personal Coach® program, but which involves tasks that do not engage high-level cognitive functioning. Another limitation of the study is the absence of health and quality of life endpoints. Because cognitive impairment is associated with a much poorer quality of life for patients with MS [25], the improvements in cognitive skills from cognitive training may also be associated with improvements in aspects of quality of life. This should be addressed in future studies. A last limitation of the study is the lack of subjects' random assignment to groups. However, because this study is primarily dedicated to the exploration of voluntary, unprompted adherence to systematic cognitive training, this manner of allocation was deemed appropriate.

Recent neuroimaging studies have provided evidence for the existence of cortical plasticity in MS, with cognitively impaired patients recruiting additional brain areas to perform challenging tasks [6,26]. This provides support for the use of interventions such as cognitive training to encourage use of neuronal resources to overcome cognitive deficits. Imaging measures could be used as an additional assessment of the functional improvement from individualized, computer- based cognitive rehabilitation. Future studies should also investigate the potential of personalized cognitive training for patients with other types of MS, such as primary progressive MS, as well as for patients with other neurological disorders.

5. Conclusion

The encouraging spontaneous adherence data and cognitive improvements in the current study indicate that individualized, computer-based cognitive training in the home setting is a practical and valuable tool to improve cognitive skills in patients with MS, and that it may be a useful component of the clinical treatment strategy for cognitive rehabilitation in MS. Our findings support the undertaking of large-scale studies to explore how home-based cognitive training interventions might enhance neuronal plasticity to overcome cognitive deficits in MS.

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