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SHORT COMMUNICATION

COMPUTERIZED TRAINING IMPROVES VERBAL WORKING MEMORY IN PATIENTS WITH MYALGIC ENCEPHALOMYELITIS/CHRONIC FATIGUE SYNDROME: A PILOT STUDY

Daniel Maroti, PsyD[1], Annika Fryxell Westerberg, OT[1], Jean-Michel Saury, PsyD, PhD[1] and Indre Bileviciute-Ljungar, MD, PhD[1,2]

From the [1]ME/CFS-Rehabilitation, Department of Rehabilitation Medicine and [2]Department of Clinical Sciences, Karolinska Institutet Danderyd University Hospital, Stockholm, Sweden

Objective: **Patients with myalgic encephalomyelitis/chronic fatigue syndrome experience cognitive difficulties. The aim of this study was to evaluate the effect of computerized training on working memory in this syndrome.**

Design: **Non-randomized (quasi-experimental) study with no-treatment control group and non-equivalent dependent variable design in a myalgic encephalomyelitis/chronic fatigue syndrome-cohort.**

Subjects: **Patients with myalgic encephalomyelitis/chronic fatigue syndrome who participated in a 6-month outpatient rehabilitation programme were included in the study. Eleven patients who showed signs of working memory deficit were recruited for additional memory training and 12 patients with no working memory deficit served as controls.**

Methods: **Cognitive training with computerized working memory tasks of increasing difficulty was performed 30–45 min/day, 5 days/week over a 5-week period. Short-term and working memory tests (Digit Span – forward, backward, total) were used as primary outcome measures. Nine of the 11 patients were able to complete the training.**

Results: **Cognitive training increased working memory ($p = 0.003$) and general attention ($p = 0.004$) to the mean level. Short-term memory was also improved, but the difference was not statistically significant ($p = 0.052$) vs prior training. The control group did not show any significant improvement in primary outcome measures.**

Conclusion: **Cognitive training may be a new treatment for patients with myalgic encephalomyelitis/chronic fatigue syndrome.**

Key words: myalgic encephalomyelitis; chronic fatigue syndrome; cognitive training; working memory; short-term memory; neuropsychology.

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Correspondence address: Indre Bileviciute-Ljungar, Department of Clinical Sciences, Karolinska Institutet, Danderyd University Hospital, Building 39, 3rd Floor, SE-182 88 Stockholm, Sweden. E-mail: indre.ljungar@ki.se

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INTRODUCTION

Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) is characterized by physical and mental fatigue and fatigability, which are not ameliorated by rest. In addition, patients experience widespread diffuse pain and cognitive difficulties that last more than 6 months (1). Patients often report malaise, worsening of symptoms with effort, non-restorative sleep, sore throat, swollen lymph nodes and other symptoms (2). The prevalence varies depending on the criteria used, from 1.2% when the more strict Canadian criteria are applied to 2.6% when broad Oxford criteria are used (3). Suffering is described as mild to moderate in patients who are able to maintain part-time employment, or severe to extremely severe when patients are on 100% sick leave, housebound or bedridden. At least 75% become ill after an infection (2). The cause of the illness is not known. Few patients completely recover, and there is currently no curative treatment (4).

As many as 9 out of 10 patients with ME/CFS report cognitive difficulties, and coping with cognitive symptoms is one of the main issues for those affected (2). A review of neuropsychological performance of ME/CFS patients has demonstrated impairments of simple and complex information processing speed and tasks which require working memory (5). Although some patients benefit from rehabilitation, cognitive behavioural therapy (CBT) or graded exercise therapy (GET), cognitive difficulties often persist (6, 7). Cognitive difficulties have been shown to be a predictor of reduced activity level (7) and ME/CFS patients' working memory difficulties lead to impairments in daily functioning and difficulties at school or work (8).

The aim of this study was to evaluate whether working memory deficits can be reduced in patients with ME/CFS by using a computerized training programme to improve working memory. The primary hypothesis was that consecutive daily memory training would improve cognitive performances, as measured by neuropsychological tests.

MATERIALS AND METHODS

Diagnostic procedure

Eleven patients with ME/CFS were recruited from an outpatient rehabilitation programme at the Department of Rehabilitation Medicine, Danderyd University Hospital, ME/CFS-project, Stockholm, Sweden. Diagnosis of ME/CFS was given according to Centers for Disease Control and Prevention (CDC) (1) and/or Canadian criteria (2) after medical and psychological investigations. For medical investigation, a clinician who was a specialist in rehabilitation medicine screened every patient during a 90-min visit. Fifty-five laboratory tests were

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performed to exclude ongoing inflammation, infection, metabolic and immunological disorders and other pathological conditions. Brain magnetic resonance images (MRI) were performed to exclude brain disorders. A certified psychologist screened each patient for 90 min to rule out primary psychiatric disorders and to evaluate working memory capacity using neuropsychological testing.

Neuropsychological assessment and recruitment procedure

The Digit Span subtest from the Wechsler Adult Intelligence Scale, Third edition (9), was used as outcome measure. It consists of 2 parts: the Forward Digit Span (FDS) task consists of recalling a string of numbers immediately after presentation; and the Backward Digit Span (BDS) consists of recalling a string of numbers in reverse immediately after presentation. In addition, the Wechsler Adult Intelligence Scale, Fourth edition (10), provides norms for the total score FDS+BDS, which is considered to measure general attention and will henceforth be called Global Digit Span (GDS).

Over 50% of the study participants had a higher education degree, indicating a high premorbid cognitive capacity. Patients performing less than their estimated premorbid level, often with results for the BDS 1 standard deviation (SD) below that of a reference population (10), were offered computerized working memory training and were included in the training group. The control group was provided standard rehabilitation services and did not participate in any activity known to specifically enhance working memory. Cognitive memory training lasted for 5–10 weeks and was included in the rehabilitation programme, which lasted for 17–20 weeks. Participants in the training group were assessed before and after the computerized training programme for working memory (i.e. reassessment took place 2–3 weeks after the completed training). Participants in the control group were assessed before and after rehabilitation (i.e. reassessment took place 1–3 weeks after the completed rehabilitation).

Computerized cognitive training

Cogmed QM is a computerized working memory training programme. It consists of different kinds of video game-like exercises involving both verbal and spatial short-term and working memory. The verbal exercises involve remembering the correct forward serial order of letters and digits, whereas the spatial exercises involve remembering the correct forward serial order of locations in a 2- or 3-dimensional grid. Cogmed QM is performed 5 days a week, approximately 30–45 min per day, during a 5-week period. The programme is sensitive to individual and day-to-day differences and adjusts the difficulty of the memory exercises accordingly. Patients were introduced to the programme at Danderyd University Hospital, but they continued training in their homes. They received a fixed set of 3 coaching sessions during the training period, and feedback on their performance. Despite their best intentions, 3 patients were not able to perform the training at the pre-planned level of intensity, i.e. 5 days a week for 5 weeks. Instead, they received prolonged training periods (6, 7 or 10 weeks). In addition, 2 out of the 11 patients did not complete the whole training period. One patient lost motivation and 1 patient reported elevated ME/CFS symptoms parallel with performing the computerized training. That patient's symptoms returned to their previous level after stopping the training. These 2 patients were excluded from the analysis. The study protocol was approved by the Regional Ethics Review Board in Stockholm, application no. 2012/1790-31 and 2013/2007-32.

Statistical analysis

Descriptive statistics for nominal data (genus, education, sick-leave) are presented as the number of participants/group. Baseline characteristics of nominal data (genus, education, sick-leave) were compared using the χ^2 test. The raw data of the Digit Span were converted to age-appropriate standard scores according to the tables provided by the test editors for the Wechsler scales (10). The Wechsler Adult Intelligence Scale, Fourth edition, provides norms for a normally distributed population. The Shapiro-Wilk test was used to test the normality of sample population. All variables were normally distributed except for GDS during the first testing ($p < 0.045$). Therefore we applied parametric tests for statistical analysis. Quantitative data (age, FDS, BDS and GDS) are presented by mean, SD and 95% confidence interval. The resulting data were then compared with those from the reference population by computing the 1-sample *t*-test with the mean for the healthy, normal subjects equal to 10. The results from the first testing session were compared with the second testing for both groups by computing a paired *t*-test analysis. Cohen's *d* of effect size was also calculated. Independent *t*-test was used to compare data between the groups. *p*-value < 0.05 was considered significant. Statistical package SPSS, version 21 and MS Excel were used for coding and analysing the data.

RESULTS

Characterization of participants

The background data for patients for both groups prior to rehabilitation are shown in Table I. ME/CFS patients in both groups were of middle-age with female dominance. More than half of the patients had higher education and were on sick-leave when refereed to the ME/CFS-project at Danderyd University Hospital. No differences were found between the groups for the baseline parameters (Table I).

Neuropsychological assessment and effect of cognitive training

The performance of subjects from both groups is shown in Table II. The data show that subjects in the training group performed at a mean level for FDS and significantly lower than average for BDS and GDS, i.e. below the norms of a reference population. This was expected, since this was one of the inclusion criteria for the training group.

Patients in the control group performed at the average level in all 3 variables with no significant difference compared with norms. Even if the patients in the control group performed higher than those in the training group during the first test compared with the norms, the differences between the groups were significant only for GDS (Table II).

Table I. *Baseline characteristics of participants. Nominal data (genus, education and sick leave) was compared using a χ^2 test, and interval data (age) using a t-test. No statistical difference was found between the groups*

	Training group ($n=9$)	Controls ($n=12$)
Age, years, mean (SD) [95% CI]	39.0 (9.35) [31.81–46.19]	42.08 (12.11) [34.39–49.78]
Gender, *n* (%)		
Men	4 (44)	2 (17)
Women	5 (56)	10 (83)
Education, *n* (%)		
Secondary	1 (11)	3 (25)
Professional	3 (33)	2 (17)
University	5 (56)	7 (58)
Sick leave, *n* (%)		
Yes	6 (67)	9 (75)
50%	2 (33)	3 (33)
75%	0	1 (11)
100%	4 (67)	5 (56)
No	3 (33)	3 (25)

Table II. *Pre- and post-test scaled scores of Forward Digit span (FDS), Backward Digit span (BDS) and Global Digit span (GDS) are presented as mean, standard deviations (SD) and 95% confidence interval (95% CI) both as raw and converted data. Statistics was performed by using converted data only. Comparisons were made with age-appropriate norms using 1-sample* t-*test, between the groups using independent 1-tailed* t-*test as well as within the groups using paired sample* t-*test*

	Training group ($n=9$)				Control group ($n=12$)			
Variables	Raw data Mean (SD) [95% CI]	Converted Mean (SD) [95% CI]	*p*-value compared to norms[a]	Effect size (Cohen`s d)	Raw data Mean (SD) [95% CI]	Converted Mean (SD) [95% CI]	p-value compared to norms[a]	Effect size (Cohen`s *d*)
FDS								
Pre-test	8.89 (1.05)	9.44 (1.88)	n.s.		9.91 (2.35)	11.25 (3.82)	n.s.	
	[8.08-9.70]	[8.00-10.89]		1.09	[8.42-11.41]	[8.82-13.68]		0.14
Post-test	10.56 (2.0)	12.33 (3.43)	n.s.		10.25 (2.73)	11.83 (4.22)	n.s.	
	[9.01-12.10]	[9.70-11.97]			[8.51-12.0]	[9.15-14.51]		
BDS								
Pre-test	5.89 (1.61)	6.44 (2.60)	0.003		7.50 (2.88)	8.83 (4.06)	n.s.	
	[4.65-7.13]	[4.44-8.45]		1.21[c]	[5.67-9.33]	[6.25-11.42]		0.28
Post-test	8.11 (2.09)	9.78 (2.90)	n.s.		8.42 (2.81)	9.92 (3.55)	n.s.	
	[6.51-9.72]	[7.54-12.01]			[6.63-10.20]	[7.66-12.17]		
GDS								
Pre-test	14.78 (1.92)	8.33 (1.22)[b]	0.004		17.42 (4.70)	10.5 (3.34)	n.s.	
	[13.3-16.26]	[7.39-9.27]		1.68[c]	[14.43-20.40]	[8.38-12.62]		0.21
Post-test	18.67 (3.32)	11.22 (2.22)	n.s.		18.67 (5.35)	11.25 (3.82)	n.s.	
	[16.12-21.21]	[9.51-12.93]			[15.27-22.06]	[8.82-13.68]		

[a]One sample *t*-test with 10 as mean of norms; [b]independent 1-tailed *t*-test between the groups, *$p<0.05$, and [c]paired sample *t*-test within the group, +$p<0.05$ and +++ $p<0.001$.

The training group increased their performance from the first to the second testing, and significant differences were no longer observed in FDS, BDS and GDS compared with the norms (Table II). In addition, for FDS in the training group, subjects performed slightly, but non-significantly better than the norms ($p=0.075$, 1-sample *t*-test). Comparison within the training group showed a statistically significant increase in BDS ($t=3.050$, $df=8$, $p=0.016$) and GDS scores ($t=5.640$, $df=8$, $p=0.0001$) and a statistical trend towards an increase in FDS scores ($t=2.287$, $df=8$, $p=0.052$, paired samples *t*-test). The effect sizes for FDS, BDS and GDS were also large (1.09, 1.21 and 1.68, respectively). The control group did not show any significant improvement in their performances at the end of rehabilitation period compared with their pre-measurements (Table II). No significant differences were found between the groups during the second testing (independent 1-tailed *t*-test) (Table II).

DISCUSSION

The aim of this study was to evaluate whether working memory deficits in patients with ME/CFS could be reduced using a computer-based training programme for working memory. The patients in the study increased their performance in working memory and global attention, and there was a trend towards improvement in short-term memory after training. Moreover, working memory performance was normalized after training compared with the standard norms for healthy counterparts. Therefore, this study supports the idea that working memory capacity can be increased in the subgroup of patients with ME/CFS who show signs of working memory deficit. It should also be noted that, despite the fact that computerized training to improve working memory is a rather invasive treatment method, an increase in ME/CFS symptoms was not a common side-effect in the training group. Only 1 out of 11 patients had to be excluded from the study because of increased symptoms during training. That patient's increased symptoms subsided by the time of the clinical follow-up.

The results of this study indicate that a subgroup of patients with ME/CFS perform less well in neuropsychological tests than healthy controls, as has been confirmed in a review (5). It should be stressed that the cause of cognitive complaints or working memory complaints in ME/CFS patients has not been thoroughly investigated. Neuroimaging studies of working memory have shown activation of distributed networks of cortical and subcortical areas, including regions within the frontal and parietal cortices and in the cerebellum (11, 12). More specifically, white matter regions of the cingulum, parieto-frontal pathways, thalamo-cortical projections, with a left-sided predominance, and right cerebellum, have been identified to be involved in verbal working memory in patients with multiple sclerosis (13). Consistent with positron emission tomography (PET) studies of ME/CFS patients, cognitive complaints have been associated with activated microglia or astrocytes in the amygdala, thalamus, and midbrain (14). These studies indicate a possible underlying pathology in the brain that might explain lower neuropsychological performance in a subgroup of ME/CFS patients.

Although our results should be viewed as preliminary, it is necessary to view them in the context of ME/CFS and previous research findings. Few patients affected by ME/CFS recover (4), and existing treatments, such as CBT or GET, do not seem

to enhance cognitive function (6, 7). Working memory difficulties in ME/CFS lead to impairments in daily functioning and difficulties at school or work (8). No interventions that specifically target cognitive deficits have been tested in patients with ME/CFS, while studies with other patient groups, such as those with acquired brain damage, have demonstrated that cognitive retraining can enhance cognitive performance (15). To our knowledge, this is the first investigation of cognitive training in patients with ME/CFS, despite the fact that cognitive complaints are very common and have a treatment-resistant nature. The present study features a few methodological shortcomings. First, given that cognitive training has never been tested in patients with ME/CFS, a non-randomized (quasi-experimental) design with no-treatment control was our first choice of study design. However, a larger sample with a randomized, placebo-controlled trial would be necessary to ensure the generality and to create the evidence-based treatment for cognitive difficulties in patients with ME/CFS. Secondly, the control group should be given a placebo intervention. That intervention might include the same time spent in front of the computer, but with tasks that do not increase cognitive functioning. Thirdly, the re-testing time for the control group should be performed at the same time as for the experimental group. Using objective neuropsychological instruments to evaluate the effects, as was done in this study, is uncommon in research with ME/CFS patients, and most studies rely heavily on subjective measures, such as fatigue scales, in evaluating effects (6). The use of objective and repeated neuropsychological testing is a major strength of our study. Relating neuropsychological measures and cognitive-related activities in daily life will be an important step in forthcoming research. It is not known if the increase in verbal working memory for patients in the training group will transfer to other cognitive domains or other working memory-related cognitive tasks, such as learning or sustained attention. Future studies should therefore include a more comprehensive neuropsychological battery as well as measurements of performances in activities of daily living, in order to evaluate potential transfer effects. Since no long-term follow-up was employed in the present study it is not known whether increases in cognitive performance persist and whether they affect activities of daily living. Future studies should include long-term follow-up.

In summary, this study indicates the possibility of a new treatment approach for the subgroup of patients with ME/CFS who have signs of working memory deficits. More research into the mechanisms of cognitive decline and the effects of treatments targeting cognitive difficulties is needed in patients with ME/CFS.

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