Enhancing Cognitive Rehabilitation in Multiple Sclerosis with a Disease-Specific Tool

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ORIGINAL RESEARCH

Enhancing Cognitive Rehabilitation in Multiple Sclerosis with a Disease-Specific Tool

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ABSTRACT
Purpose: Computerized rehabilitation programs can be used to address cognitive deficits typically caused by multiple sclerosis (MS). However, there are still doubts on their effectiveness, due to mixed results obtained in clinical trials. The objective of this paper is to improve cognitive rehabilitation (CR) practices in MS, by presenting and assessing a MS-specific cognitive rehabilitation software.

Methods: We conducted a detailed analysis of how CR is carried out in practice in MS rehabilitation centers. From the analysis, we elicited a reference CR process, and identified the essential features a software supporting the process should have. We designed and implemented MS-rehab, a novel MS-specific computerized rehabilitation systems having the identified features. We experimented MS-rehab in a pilot study involving eight MS patients. To highlight the improvement with respect to the state of the art, we compared MS-rehab with available professional tools selected using well defined criteria.

Results: This paper has three main contributions: (1) the identification of a set of essential features a computerized tool for CR in MS should provide; (2) MS-rehab, a novel CR system designed for MS therapists and patients, which embodies innovative MS specific features; (3) the assessment of MS-rehab efficacy in a pilot study with MS patients.

Conclusions: The availability of a MS-specific CR system like MS-rehab fosters the design of more rigorous clinical studies on the effectiveness of computerized rehabilitation in MS. MS-rehab demonstrated its potential and innovativeness as a tool for cognitive rehabilitation in MS.

KEYWORDS
Cognitive Rehabilitation; Multiple Sclerosis; Computerized Tools; Home-based cognitive rehabilitation; Disease-Specific Software; Experimentation

1. Introduction

Multiple sclerosis (MS) is the most common autoimmune disease affecting the central nervous system. Cognitive impairment has been recognized as a serious consequence of MS, and cognitive problems are frequently observed in patients: from 43% to 70% of them [1]. Cognitive impairment can produce mild dysfunctions in various cognitive domains: attention [2]; memory [3]; and executive functions [4]. It may have several

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negative impacts; for example, on learning new concepts and methods [5], on visual-spatial skills, and on information processing abilities [6]. Cognitive deficits also have a detrimental effect on patients' quality of life, as people with cognitive deficits have more problems in performing common daily-life activities than patients with physical impairment only [7].

In the last few years, cognitive rehabilitation (CR) has increasingly been applied to MS patients, and promising results have been achieved in research studies (e.g., [8–13]) in which a computerized approach has been adopted. However, reviews of the published literature about the effectiveness of (computerized) CR highlight conflicting findings [14–16]. In [14], 16 studies (25% of which adopted a computer-assisted approach) were examined, concluding that more methodologically rigorous research is needed to determine the efficacy of cognitive rehabilitation. In [15], the authors assessed the effects of neuropsychological/cognitive rehabilitation on health-related factors, including cognitive performance. They examined 18 studies (83% of which adopted computer-assisted rehabilitation) conducted with randomized controlled trials and quasi-randomized trials, and found low-level evidence that neuropsychological rehabilitation reduces cognitive deficit symptoms in MS. In [16], a total of 33 studies (56% of which used computerized rehabilitation) were examined. Almost all of the studies (31) reported some improvements in cognitive abilities after the intervention. However, the review highlighted that there is inconclusive evidence about the impact of cognitive rehabilitation intervention in MS on patients' mood, quality of life, and self-perceived cognitive deficits. Among the recommendations for clarifying the efficacy of rehabilitation interventions, all of the three reviews suggest drastically reducing the heterogeneity of interventions, especially in terms of clinical experiment design and rehabilitation methodology.

As a part of the rehabilitation methodology, there is an important variable that can influence the results of the studies, i.e., the computerized tool used in the interventions. As a matter of fact, the studies adopting computer-assisted rehabilitation utilized tools having very dishomogeneous features, and not specifically tailored to MS. On the contrary, our intuition is that the availability of MS-specific features in computerized CR systems may facilitate the design of more rigorous studies, and the improvement of cognitive rehabilitation practices, optimizing them for routine clinical uses.

We addressed this challenge by highlighting a set of essential features that a MS-specific system should provide to support a standardized CR process in MS. The process has been defined by means of a thorough analysis (conducted with the help of clinicians) on how CR for MS patients is carried out in practice in some Italian specialized centers and clinics. With the contribution of the clinicians, we also identified which phases of the process should be supported by a computerized tool and how. This allowed us to derive the distinguishable features of the tool.

Based on this analysis we implemented MS-rehab, a computerized system specifically designed for cognitive rehabilitation in multiple sclerosis. We show how the system integrates all the phases of the standardized CR process and includes the essential features. The new version of MS-rehab presented in this paper extends the first prototype described in [17] with many rehabilitative exercises (52, with respect to 23 of the first prototype), and new advanced functionalities and components. It was optimized and tuned for routine clinical use thanks to a formative usability study colorred [18]. An exhaustive comparison to state-of-the-art systems for professional CR confirms that several of them do not include many of the essential features we identified.

Finally, the last contribution of this paper is a pilot study conducted at the Lab-

oratory of Cognitive Psychology of the Department of Medicine and Surgery of the University of Parma. The main goal of the study was to collect indications about the suitability of the system for the CR of MS patients. To this purpose, eight MS patients were involved into a three-week cognitive training program with MS-rehab and, despite the limited sample size, we obtained encouraging results. First, we did not find significant negative effects of the program on psychometric parameters, such as subjects' depression or anxiety, while cognitive abilities (evaluated using the main indexes of the WAIS-IV scale [19]) significantly improved after the program. As a secondary result, we collected a notable positive feedback on the usability and potential efficacy of MS-rehab by the patients involved in the study.

2. Material and Methods

2.1. Cognitive rehabilitation process

Cognitive rehabilitation is a complex process aimed at restoring impaired cognitive functions. It is usually conducted by a multidisciplinary team including neuropsychologists, occupational therapists, and speech/language pathologists. We performed a detailed analysis of how CR is carried out in practice in four Italian centers for the treatment of MS. Our analysis was conducted by interviewing the experts of these centers, by directly observing rehabilitation sessions involving clinical operators and patients, and by examining pertinent clinical documentation. From the analysis, we derived the multi-phase standardized cognitive rehabilitation process described in this section, and illustrated in Figure 1. We summarize here the process phases; a detailed description of them is presented in [17].

- **Initial Screening.** This phase identifies if a MS patient could suffer from cognitive impairment. It cannot be automatized, as the symptoms of possible cognitive deficits are noted by the physician during neurological examinations, or reported by the caregivers.
- **Multidimensional Assessment.** It consists of a comprehensive neuropsychological evaluation of the patient in order to identify the specific cognitive deficits; the assessment is generally performed by a psychologist, can be supported by a computerized tool, and results in the *cognitive profile* of the patient.
- **Definition of Rehabilitation Goals.** In this phase the CR team establishes concrete objectives aimed at improving various aspects of the patient's life. Goals are discussed with the patient, tailoring them to her/his specific needs, and therefore cannot be automatically set up by using computerized support.
- **Definition of Rehabilitation Program.** The rehabilitation program includes supervised interventions aimed at achieving the rehabilitation goals, and is prepared by the CR team considering the cognitive profile of the patient. The preparation of rehabilitation exercises can be (partially) automatized using a computerized tool.
- **Cognitive Rehabilitation Cycle.** In order to promote adherence to the treatment, the rehabilitation program consists of a series of individual or collective rehabilitation sessions carried out in the hospital, plus other sessions the patient carries out (unassisted or remotely assisted) at home. A rehabilitation session consists of graded rehabilitation exercises relative to cognitive domains as *memory*, *attention*, or *executive functions*. Rehabilitation cycles are led by the members of the CR team, and many aspects of them can be automatized using a
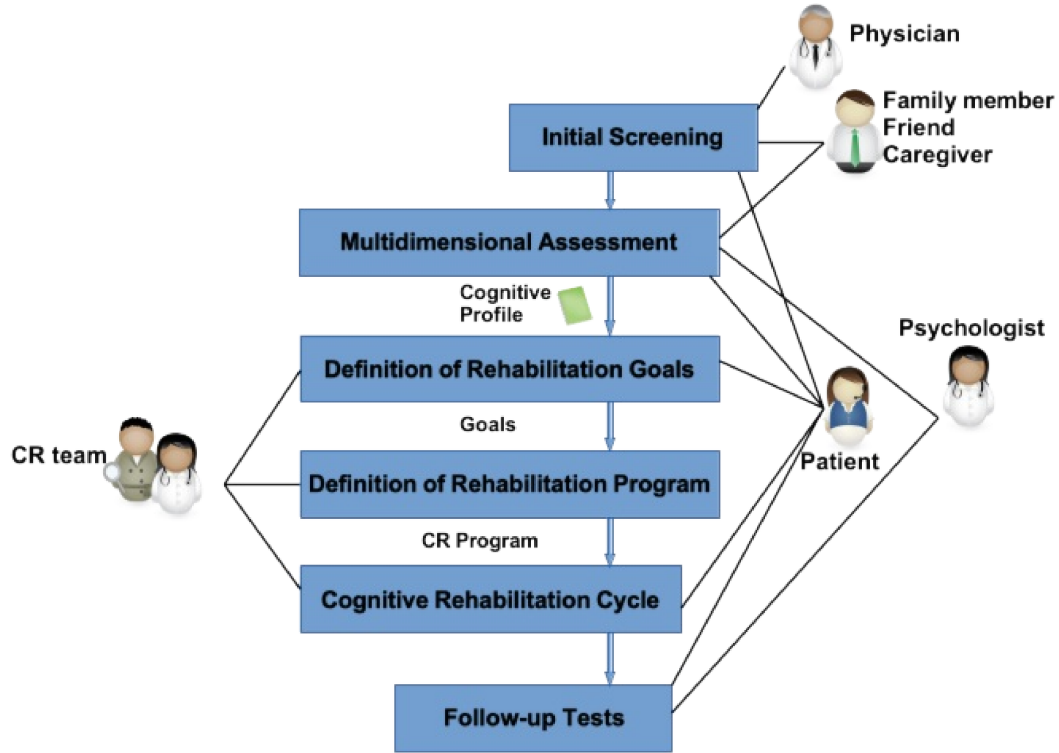
Figure 1. MS standardized cognitive rehabilitation process.

specific software.

- **Follow-up.** The last phase of the process are neuropsychological evaluations scheduled when a rehabilitation cycle terminates. It is carried out by psychologists, and can be supported by computerized tools. Successively, further rehabilitation interventions may be prepared by the CR team, in case the patient needs them.

2.2. Essential features for cognitive rehabilitation in MS

We identified a set of essential features a computerized CR system should have to support a CR team in the illustrated cognitive rehabilitation process, ideally providing functionalities for the most effective treatment of patients. As a basic feature, we postulate that a MS-specific tool should provide a set of exercises in which the difficulty is varied over time, and suitable for the treatment of mild dysfunctions in all the cognitive domains (attention, memory, and executive functions). Indeed, although the most common problems MS patients have involve memory and attention/concentration, deficits may occur in all the cognitive domains. Essential features related to *exercises* are:

- **Practice** easier versions of the rehabilitative exercises to get familiar with them before actually starting the rehabilitation sessions, thus minimizing learning effects on patient's performance.
- **Realistic contents**: availability of ecological exercises (simulating real life situations) with realistic content to improve patient involvement during treatment,

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and improve their ability to develop compensatory strategies in everyday situations.

- **Automatic variation** of the exercise difficulty according to the patients' cognitive profile and performance during rehabilitation, in order to support training at the highest level of their skills.

Considering *treatment options*, essential features include support for all the types of treatment currently used in clinical practice:

- **Individual sessions** in the hospital.
- **Collective sessions** in the hospital.
- Continuation at home of the rehabilitation sessions initiated in the hospital as **Home work**.

Other features concern the importance of having *disease-specific cognitive profiles*, which are fundamental in almost all the phases of the CR process:

- **MS-Cognitive profile**: acquisition, storage, and update of the patient's cognitive profile (including MS-specific neuropsychological data), and easy access to it when needed.
- **MS-Cognitive history**: the variation over time of the MS-specific cognitive profile assessed at the beginning of the intervention and during follow-up examinations should be stored in a persistent form.
- **Semi-automatic configuration** of rehabilitation sessions tailored to the patient's cognitive profile.

Finally, crucial features concern the ability to *monitor and control* all types of rehabilitation sessions: individual, collective, and home work:

- **Monitoring** how the patient executes the exercises, showing his/her performance, statistics over time, and other relevant data.
- **Remote control** of the exercise during the rehabilitation sessions: when necessary therapists can manually update exercise difficulty, depending on the patient's behavior and achieved performance.

2.3. MS-rehab

MS-rehab is a novel MS-specific software system designed to support the phases of the reference CR process presented in Section 2.1, and having the essential features we have highlighted in Section 2.2. Figure 2 illustrates how MS-rehab is integrated in the process. In particular, MS-rehab supports the clinical operators in: the *Multidimensional Assessment* phase (Figure 2.A), to build the cognitive profile of the patient; the *Definition of Rehabilitation Program* phase, to set up rehabilitation exercise sessions (Figure 2.B); performing live and long term monitoring of the patients in the *Cognitive Rehabilitation Cycle* (Figures 2.C and 2.D). MS-rehab also supports patients in their execution of the rehabilitation exercises (Figure 2.E). Finally, it allows therapists to insert new instances of the neuropsychological profile after follow-up tests (Figure 2.F), to measure the treatment effects, and to tune the next rehabilitation cycles. In the rest of this section, we present the cognitive profile and the exercises provided by MS-rehab, the services it offers to clinical operators, and its monitoring functionalities.
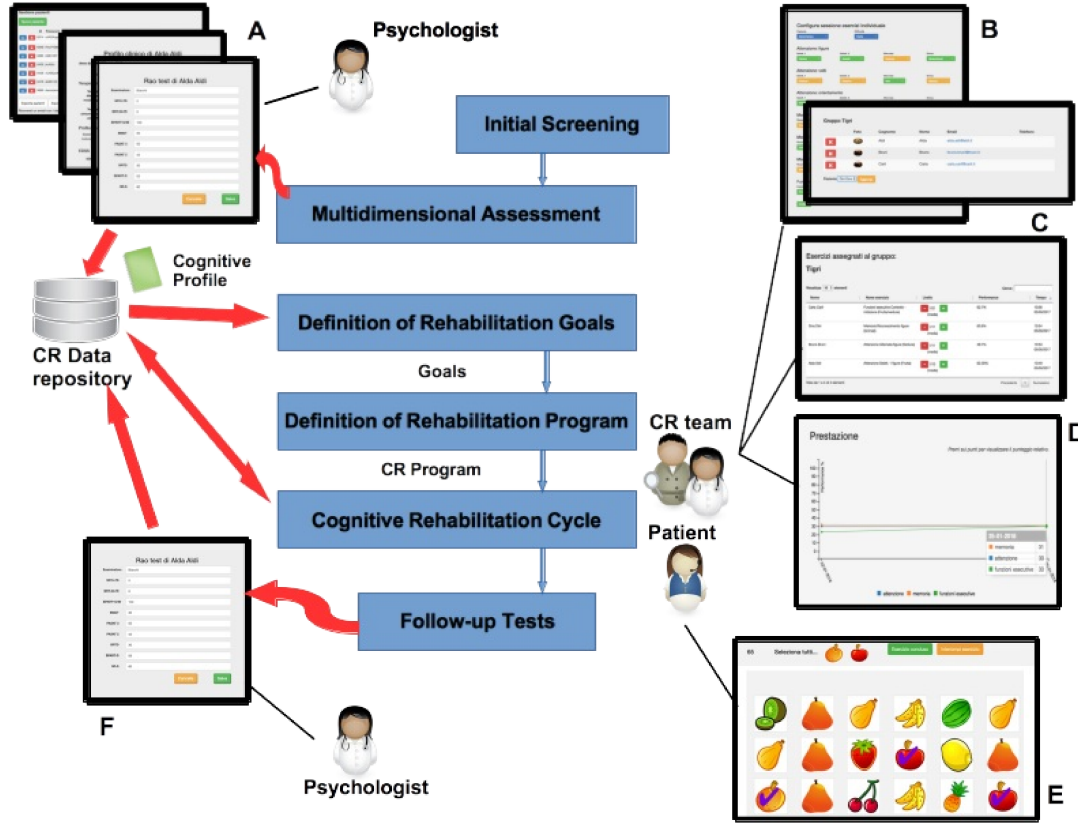
2.3.1. Cognitive profile

Figure 2. Use of MS-rehab in the MS cognitive rehabilitation process.

MS-rehab includes all the functionalities to create, update, and access an extended cognitive profile defined for clinical use with the contribution of neurologists and psychologists. The cognitive profile is composed by three sub-profiles: the *neuropsychological profile*, the *clinical profile*, and the *personal data*. The *neuropsychological* profile is the richest among the three, we present here a default version. However, given that there is no agreement on cognitive measures to be used with MS patients, additional functionalities to store the results of other test-batteries can be added, for example, the WAIS-IV [19] we used in the pilot study presented in Section 3.

The first tool administered to derive the neuropsychological profile is the Rao's *Brief repeatable battery of neuropsychological tests* [20]. By means of this battery, the specialists are able to discover whether or not the patient suffers from a cognitive impairment caused by MS, and its possible gravity. Other data included in this profile are obtained from:

- the *Trail making test* (a neuropsychological test of visual attention and task switching) of the ENB battery [21];
- the *Modified Fatigue Impact Scale* [22], a questionnaire for the subjective assessment of fatigue impact on physical conditions, cognitive functions, and psychosocial functions;
- the *State-Trait Anxiety Inventory* [23], a commonly used measure of trait and state anxiety;
- the *Beck's Depression Inventory* [24];

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- the *MSQOL-54 questionnaire*, investigating the quality of life of MS patients [25];
- the *D-KEFS* sorting test [26], for the assessment of cognitive functions, such as ability of reasoning, categorization, and problem solving;
- the *White test*, [27] a questionnaire to acquire the patient self-perception about her/his abilities, e.g., language, visual-spatial memory, or attention.

The *clinical profile* and the *personal data* integrate the neuropsychological profile with data that could help the CR team decide the rehabilitation goals and program. The clinical profile includes information on the disease, such as the diagnosis year, the MS type, the pharmacologic therapy, and the magnetic resonance reports. The personal data include information about patient's gender, birthdate, schooling, and family and work situation.

2.3.2. Exercises

MS-rehab provides exercises designed by a team of computer scientists and neuropsychologists. The exercises cover the three main cognitive domains: *attention* (12 exercises), *memory* (8), and *executive functions* (4). Each exercise has multiple versions in which the stimuli vary, for a total of 52 exercises. For most visual stimuli we adopted a set of images that has been scientifically validated [28], and is considered a standard for a wide range of experimental and clinical studies. Particular care has been devoted to the realization of novel ecological exercises for executive functions.

From their home page, patients can access the rehabilitation exercises that have been assigned to them by the CR team (see Figure 2.E). Patients can get familiar with the exercises by practicing with simplified versions of them. Patients can also stop an exercise whenever they like, and restart it later. In this case, the system is able to restart the rehabilitation with an exercise at the same difficulty level as the last one completed by the patient. A feedback pop-up is shown to the patients at the end of each exercise. Feedback generally includes the obtained performance[1], and the number of correct, wrong, and missed answers.

2.3.2.1. Exercises for attention. Attention can be defined as the ability to perform a selection of the inputs [30], and then an analysis of the information deriving from the external world. Exercises for the rehabilitation of three types of attention are available in MS-rehab: *selective attention*, *alternating attention*, and *divided attention*. Various stimuli can be used in the exercises: *images* (i.e., fruit, vegetables, animals, and chess pieces); *faces*; and *orientational stimuli* (i.e., arrows, and cardinal points). Examples of attention exercises available in MS-rehab are presented in Figure 3.

2.3.2.2. Exercises for memory. Memory is the function that allows to encode, store and retrieve information [31], even after some time. MS-rehab provides a set of exercises to train memory: exercises for recognition with *images*, *faces*, and *orientational stimuli*; exercises for visuospatial memory with *images*; exercises for working memory with *images*, *faces*, and *orientational stimuli*; and an exercise for *face-name association*. Some exercises to train memory are presented in Figure 4.

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[1]The patient performance in expressed in a scale from 0% to 100%, and is calculated with a function that combines the number of correct, wrong, and missed answers with the exercise execution time. In this paper, we do not elaborate more on this concept, explained in [29] in detail.
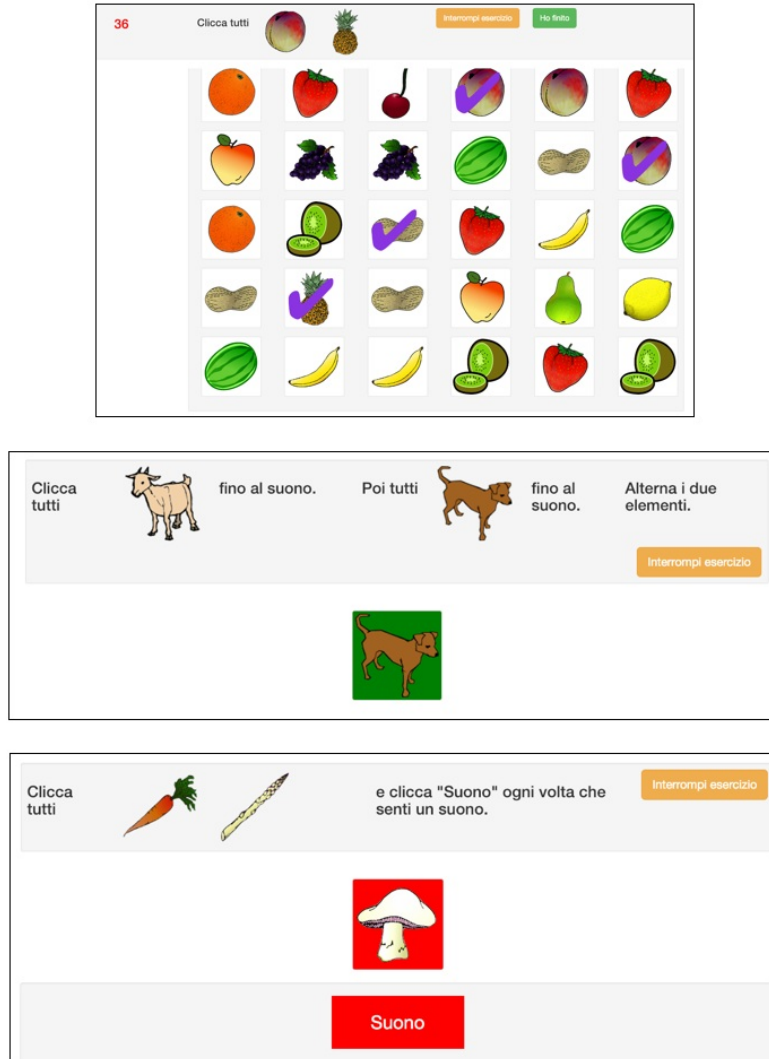
Figure 3. *top*: exercise for *selective attention* (tick all the target images shown on the upper part of the screen among those visualized in the grid below); *middle*: exercise for *alternating attention* (select one animal and then, after hearing a sound, another one, among those sliding on the screen); *bottom*: exercise for *divided attention* (select specific vegetable items and, at the same time, capture a sound whenever it is played).

2.3.2.3. Exercises for executive functions. Executive functions are higher-level cognitive processes that control other processes, in order to achieve a goal [32]. MS-rehab has two types of exercises dedicated to training executive functions (Figures 5 and 6). In the exercises to train the response–inhibition function, the patient has to discriminate between two categories of objects by pressing on different buttons, whenever an object appears on the screen. Moreover, she/he should not press on the category button (i.e, her/his actions is inhibited) if a specific instance of one of the two categories appears.

The exercises of the second type have been designed to train the planning ability of the patient. Particular care has been taken in making these exercises ecological, i.e., being based on realistic contents. MS-rehab includes three planning exercises:
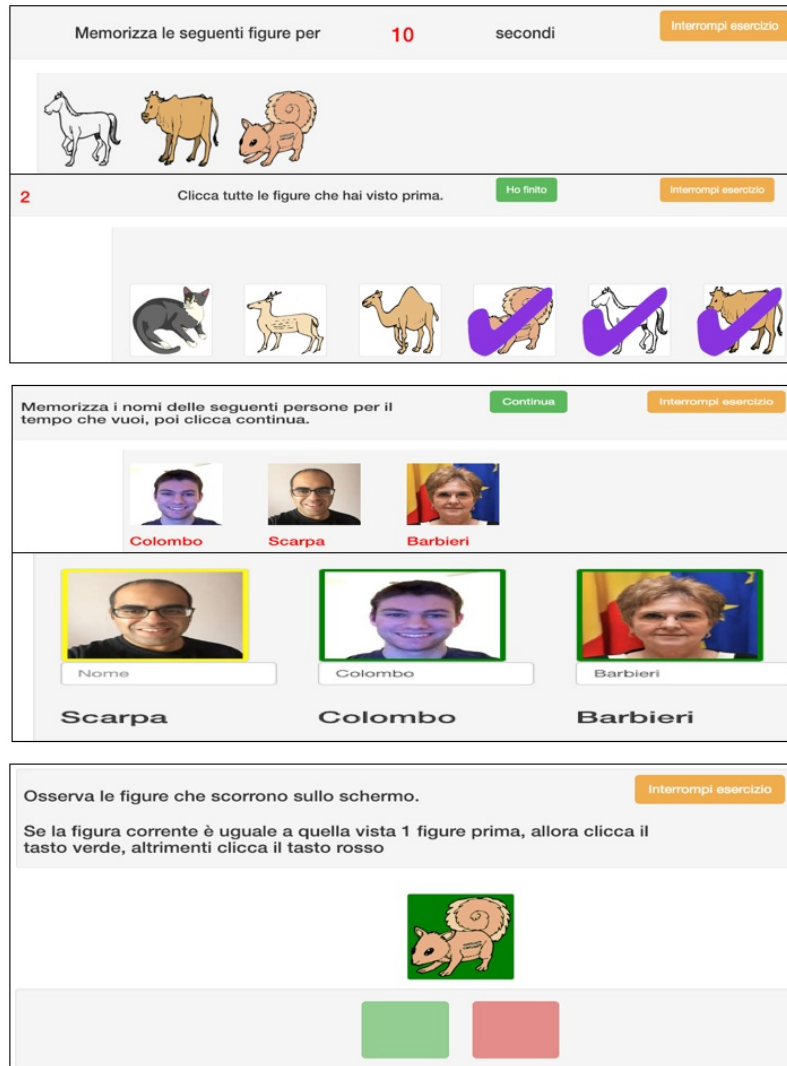
Figure 4. *top*: exercise for memory *recognition* (Memorize the target images for some time, and then, after they disappear, recognize them among others within a given time); *middle*: exercise for memory *face-name association* (Memorize people's names for a time interval, and then, after they disappear, write the correct name under each face); *bottom*: exercise for memory *Nback* (Press the green or red button according to whether or not the current figure is the same as the one appeared N figures before).

- *Day of Committments* [33,34], inspired by [35]. The patient is given a series of unordered tasks to be carried out in a day (e.g., going to the bank to withdraw money, or bringing his/her daughter to the swimming pool), a map of the city where the tasks have to be executed, and a set of time constraints for the places on the map (e.g., the bank opening hours, or the time when the daughter starts her swimming course). The patient has to find a plan that allows her/him to execute all the tasks, without violating the constraints, and optimizing the number of actions.
- *ZooSafari Visit* [36], inspired by the Zoo Map test of the BADS battery for executive functions [37]. In this exercise, the patient has to plan his/her route through a map of the ZooSafari, visiting a selection of animals and locations.

- *Weekend in Rome* [38]. In this exercise, the patient has to plan a two-day vacation in the Italian capital city. In addition to making train and hotel reservations, he/she is also given a list of tasks (such as locations to visit, or events to attend) to be accomplished, navigating all the difficulties which are typical of planning a trip in real life (e.g., reservations, bus schedules, or opening hours).
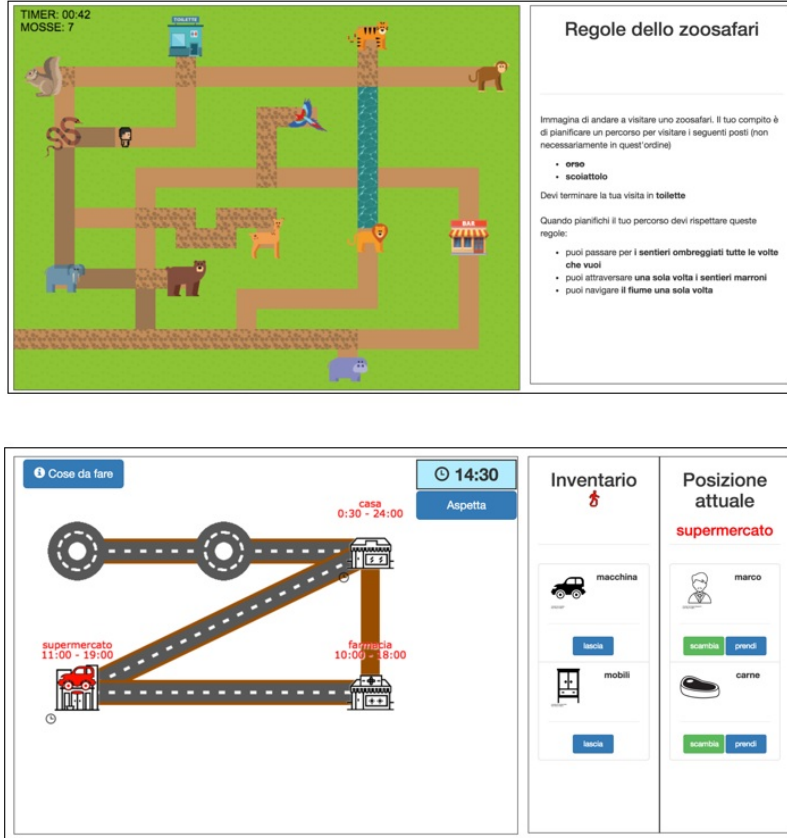
Figure 5. Exercises for executive functions: ZooSafari Visit at the top, Day of Commitments at the bottom.

2.3.2.4. Automatic difficulty variation. For each exercise, the design team has carefully identified a set of parameters that influence the difficulty, and how the values of these parameters need to be changed in order to increase the difficulty level. For example, an exercise for selective attention (Figure 3, top) has the following parameters:

- **#targets**: the number of different targets to be selected among the stimuli;
- **#stimuli**: the number of stimuli;
- **time**: the maximum time to conclude the exercise;
- **alignment**: the type of alignment (aligned, misaligned, disordered) of the stimuli;
- **distractors**: the presence of distracting animations in the background (distractors can be *absent*, *simple*, or *complex*);
- **color**: the color (full color, uniform color, black and white) of the stimuli.

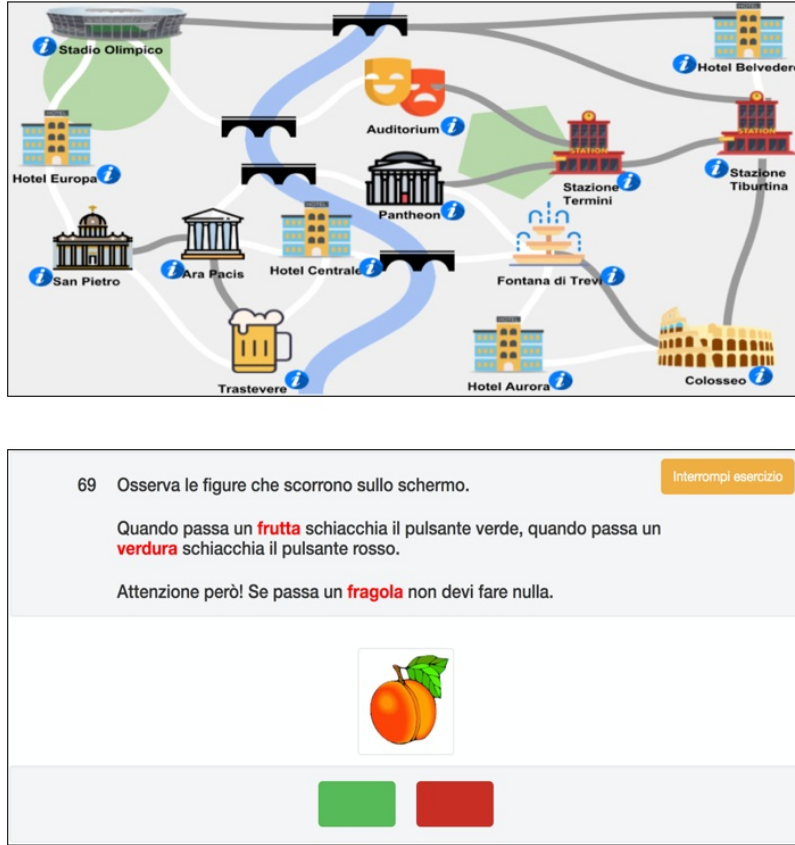**Figure 6.** Exercises for executive functions: Weekend in Rome at the top, and response–inhibition at the bottom (in the particular exercise shown above, the patient has to discriminate between fruit and vegetables by pressing the green or red button, but should not press the green button if a strawberry appears).

The difficulty level depends on the value of the parameters that characterize the exercise. For each exercise, we defined, in cooperation with the clinicians, precise rules to associate a level with a parameter value combination, and to increase the difficulty by varying specific parameters. An automatic mechanism provides variation of the exercise difficulty: it is increased whenever the patient performance on an exercise goes over the 80% of the maximum for two consecutive times[2].

2.3.3. Services for clinical operators
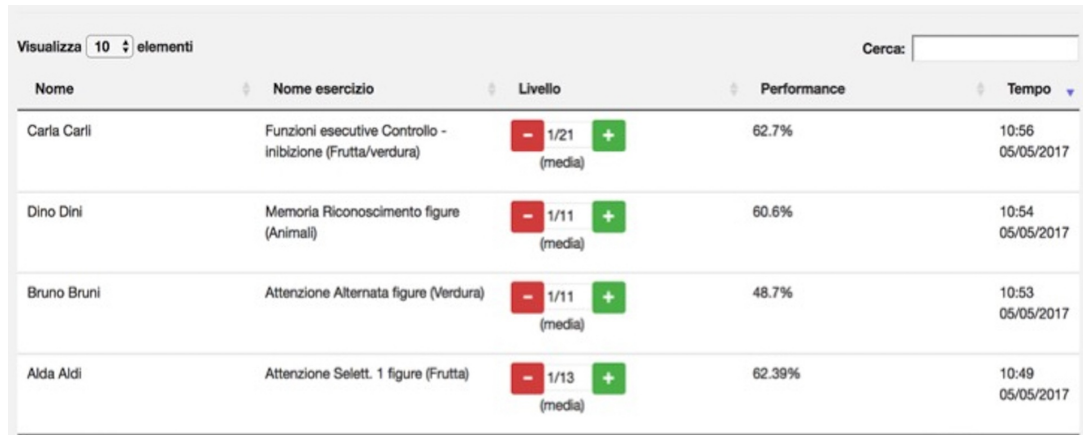
Clinical operators are in charge of managing the whole CR process for single patients and groups of patients. To this aim, MS-rehab provides operators with four different services.

2.3.3.1. Patient/Group management. Operators can register new patients to be treated in a rehabilitation process, and modify their *cognitive profile* if necessary. Operators can also add, modify, or delete groups for collective rehabilitation sessions, and insert/delete patients into/from groups.

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[2]We also experimented with promising results another adaptive difficulty variation mechanism based on Reinforcement Learning [29].

2.3.3.2. Exercise configuration. An operator selects the exercises in each session of the CR cycle by means of a semi-automatic configuration tool (Figure 2.B). The configuration procedure takes as input the desired difficulty class (chosen by the operator according to the cognitive profile of the patient) and the exercises for attention, memory, and executive functions to be configured (chosen according to the rehabilitation goals that the patients should achieve); then, it builds a set of exercises of the selected difficulty, and stores the rehabilitation session in the system database. MS-rehab also provides the operator with a service to set up collective sessions. The exercise configuration service is used to set up each rehabilitation session at the hospital. At the end of the hospital session, the operator can assign to the patients similar exercises to be done at home. In this way, the patients can further individually exercise the same cognitive domain, possibly at a higher level of difficulty.

2.3.3.3. Remote control. A remote control interface allows the operator to monitor both individual and collective sessions, in the hospital or at home. In this way, the system gives real-time feedback to clinicians on how patients are performing. For example, Figures 2.C and 7 show the monitoring of a collective session. The interface shows the names of the members of the group, the last exercise executed by them, the last level of difficulty they have faced, the obtained performance, and possibly an arrow that indicates whether the performance has increased or decreased with respect to the previous exercise of the same type. The operator can modify the difficulty (by clicking on the "plus" or "minus" buttons) so that the patient continues training at the most appropriate level. The automatic variation of the difficulty has a lower priority than the manual variation that the operator can set via the interface of the monitoring service.

Nome	Nome esercizio	Livello	Performance	Tempo
Carla Carli	Funzioni esecutive Controllo - inibizione (Frutta/verdura)	− 1/21 + (media)	62.7%	10:56 05/05/2017
Dino Dini	Memoria Riconoscimento figure (Animali)	− 1/11 + (media)	60.6%	10:54 05/05/2017
Bruno Bruni	Attenzione Alternata figure (Verdura)	− 1/11 + (media)	48.7%	10:53 05/05/2017
Alda Aldi	Attenzione Selett. 1 figure (Frutta)	− 1/13 + (media)	62.39%	10:49 05/05/2017

Figure 7. Collective session live monitoring and remote control.

2.3.3.4. Statistics. While the remote control is devoted to observe the patient performance on single exercises in quasi-real time, statistics services allow the rehabilitation team to acquire a picture of the increase or decrease of patients' performance over the long period (Figure 2.D). By using the statistics user interface, the operator can select the observation period and the performance visualization granularity (i.e., per day, week, or month). Moreover, the interface permits to aggregate the performance

per cognitive function (i.e., attention, memory, executive functions) and per exercise type (e.g., selective attention). The collective session services allow the members of the CR team to compare the global performance of the involved patients over time.

3. Results and Discussion

A pilot study involving eight patients suffering from multiple sclerosis was set up, with the goal of acquiring preliminary indications about the impact of a MS-rehab-based CR program, and on its possible side effects. In addition, a secondary goal of the study was to get feedback from the patients about the usability of the system. It is important to note that a solid clinical evaluation of the system was not in the scope of the study, due to the very limited size of the patient sample. The study was conducted by the researchers of the Laboratory of Cognitive Psychology of the Department of Medicine and Surgery of the University of Parma.

3.1. Participant selection

Eight individuals were recruited at the MS center of the Parma University Hospital taking into consideration the following inclusion criteria.

- Diagnosis of MS according to 2017 Mc Donald criteria [39];
- Age $\geq$18 years and $\leq$ 72 years;
- Schooling $\geq$ 5 years;
- Expanded Disability Status Scale (EDSS) $\leq$ 4;
- Presence of cognitive deficit, defined as at least two altered tests of the repeatable short Rao battery integrated by the Stroop Test [40]. Altered tests are those with scores lower than two standard deviations with respect to the average normative value for the Italian population;
- Patients able to read, understand, and provide written informed consent to the experimental treatment;
- Concomitant treatment with antidepressants or antipsychotics is allowed, provided that the treatment has not changed in the last 90 days prior to the start of the study, both in terms of the molecule used and the dosage.

The most important exclusion criterion was a personal history of epilepsy, head trauma or other disorder (neurological or medical), which might have impaired cognitive or psychiatric function in the course of the study.

3.2. Experiment structure

All patients underwent an evaluation of psychometric parameters and cognitive neuropsychological evaluation according to the following timeline:

$\mathbf{T_0}$ Demographic questionnaire administration and baseline evaluation within the month preceding the treatment with MS-rehab;

$\mathbf{T_1}$ Post-treatment evaluation within 7 days from the last treatment session.

The psychometric parameters evaluation was performed by administering the Beck Depression Inventory - II (BDI-II) [24], the anxiety STAI-Y1 and STAI-Y2 scales [23], the Fatigue Severity Scale (FSS) [41], and the Multiple Sclerosis Quality of Life-54 questionnaire (MSQOL-54) [25], to assess the quality of life.

The cognitive neuropsychological evaluation was performed by administering the Wechsler Adult Intelligence Scale - Fourth Edition (WAIS-IV) [19]. In particular, the following specific indexes were considered: the Verbal Comprehension Index (VCI), the Perceptual Reasoning Index (PRI), the Working Memory Index (WMI), the Processing Speed Index (PSI), and the total IQ index.

After T_1, a series of statistical test (see section 3.5 for details) were performed on the collected data to verify the presence of significant differences among the average values of the variables above at times T_0 and T_1. The tests were performed using *Apple Numbers* spreadsheet[3] and *IBM SPSS*[4].

Non-structured interviews with the patients were conducted during and at the end of the treatment, in order to retrieve their impressions about the usability of the system and their feedback on its features.

3.3. Treatment description

The cognitive training was carried out with the MS-rehab software. The rehabilitation program consisted in three weekly cycles, each including three individual sessions lasting 40 minutes each (nine sessions in total). The exercises in a session were the same for all the patients and covered the following cognitive domains: memory (recognition, visuospatial, and work), attention (selective, alternating, and divided), and executive functions. The exercises proposed in each session are listed in Table 1; for their description the reader can refer to Section 2.3.2. The difficulty of the exercises automatically increased with the progression of the training, depending on the patients' performance, using the mechanism described in Section 2.3.2.

Domain	Exercise	Duration
Attention	Selective	5/6 mins
	Alternating	5/6 mins
	Divided	6 mins
Memory	Working	6/7 mins
	Visuospatial	6/7 mins
	Recognition	6/7 mins
Executive functions	Planning (ZooSafari)	7 mins

Table 1. Exercises in a rehabilitation session.

Two ASUS PCs were used in the study to access MS-rehab, both with a screen size of 15.6 inches. In order to cope with the lack of coordination of some patients, a gaming mouse (Trust GXT 165 Celox) was adopted in the treatment, in order to ensure to the patients a firmer grip and smoother movements.

3.4. Patient sample description

The descriptive statistics of the patients involved in the pilot study for the assessment of MS-rehab are illustrated in Table 2. The sample included 8 people (5 females - 62.5%, 3 males - 37.5%) with an average age of 58.3 ± 9.4 years. The average duration of the illness had been 16.2 ± 12.7 years. The average EDSS was 3.25 ± 0.89. Four subjects (50%) suffered from Relapsing Remitting MS, two subjects (25%) from the

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[3]https://www.apple.com/numbers/
[4]https://www.ibm.com/analytics/spss-statistics-software.

Primary Progressive form, and 2 subjects (25%) from the Secondary Progressive form.

$Variable$	$Frequency$	%	$Avg \pm Stdev$
Female	5	62.5	–
Male	3	37.5	–
Age (years)	8	–	58.3 ± 9.4
Illness duration (years)	8	–	16.2 ± 12.7
EDSS	8	–	3.25 ± 0.89
Relapsing Remitting MS	4	50	–
Primary Progressive MS	2	25	–
Secondary Progressive MS	2	25	–

Table 2. Descriptive statistics of the patients involved in the study.

3.5. Experimental results

Table 3 summarizes the results of the statistical analysis performed to acquire impact indications of the cognitive training on the patient sample described above. Since we were not certain about the normality of the sampling distributions of the means of the considered variables, we performed both parametric (T-test) and non-parametric (Wilcoxon signed-rank test) 2-tailed tests[5], considering a significance level $\alpha = .05$.

	T_0 (avg $\pm$ stdev)	T_1 (avg $\pm$ stdev)	$T_0 \neq T_1$	
			T-test (p)	Wilcoxon test (p)
VCI	93.1 ± 18.7	106.1 ± 15.9	**.017**	**.025**
PRI	96.5 ± 17.2	103.0 ± 12.4	.121	.091
WMI	91.1 ± 16.8	102.4 ± 20.9	**.014**	**.028**
PSI	90.5 ± 17.4	98.8 ± 18.4	**.008**	**.018**
IQ	89.3 ± 20.4	102.9 ± 17.9	**.005**	**.012**
BDI-II	15.6 ± 12.2	10.8 ± 9.1	**.023**	**.035**
STAI-Y1	37.8 ± 10.0	42.8 ± 14.8	.256	.208
STAI-Y2	40.9 ± 13.0	40.9 ± 12.9	1.000	1.000
FSS	4.1 ± 2.3	4.3 ± 2.1	.656	.833
MSQOL-54 phys	61.4 ± 18.8	64.4 ± 20.8	.586	.779
MSQOL-54 ment	55.6 ± 19.2	61.0 ± 22.1	.090	.092

Table 3. Results of 2-tailed T and Wilcoxon signed-rank tests. In **bold** the p-values showing a significant difference between T_0 and T_1 ($\alpha = .05$).

As for the values of the WAIS-IV indicators, in the majority of the cases the T-tests showed a significant difference between the values measured immediately before the use of MS-rehab, and those measured immediately after. In all cases, the values of the indicators improved after the treatment. The Wilcoxon signed-rank test confirmed these results. As for the psychometric parameters, the BDI-II significantly decreased after the treatment, indicating a reduction of the average subjects' depression. The tests did not show a significant impact of the treatment on the other parameters, even though the improvement of mental status measured by the MSQOL-54 questionnaire should be noted.

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[5]As the T-test is generally considered robust to violations of normality and homogeneity of variance, performing Wilcoxon test might be too conservative. Indeed, it reduces the chance of type-I errors but, at the same time, increases the chance of type-II errors.

To sum up, the tests we performed on the data collected in the pilot study allows us to conclude as a preliminary result that the cognitive training performed with MS-rehab has a positive effect on the patients. In addition, since none of the psychometric indicators showed a significant degradation after the treatment, we can also accept the hypothesis that the use of MS-rehab does not have a negative impact. Of course, these results need to be confirmed in other studies involving a greater number of patients.

3.6. Patient feedback on MS-rehab usability and usefulness

The MS-rehab system presented in this paper was optimized and tuned for routine clinical use thanks to a formative usability study [18]. However, this was the first time it was adopted to perform a real cognitive training, and therefore it is worthwhile to report the impressions we collected from the patients about the usability of the system and the perceived usefulness of the training.

One of the few difficulties encountered by the patients was to fully understand the description of the exercises they had to execute. Some patients reported that these descriptions could be improved, for example by enlarging the text and the explicative images. Another way the system could be improved is replacing the exercise items that do not have an ecological value (e.g., chess images, which some of the patients did not know) with others that are more commonly known. Finally, as MS-rehab is optimized for the use on a 10 inch display tablet, it would be necessary to make the system interface more adaptable to a larger PC display.

Regarding the training impact on patients, all of them demonstrated enthusiasm and motivation about the possibility of taking advantage of a specific and effective rehabilitation instrument specifically dedicated to MS. In addition, we noticed that the presentation and organisation of the exercises led to an increase in the number of sessions, and in the willingness to continue the training beyond the time set for the pilot study.

4. Enhancement of the state-of-the-art

To evaluate the impact of MS-rehab on the state-of-the-art, we have compared our system with available professional computerized tools for CR selected using well defined criteria. We have selected available tools providing exercises for the main cognitive domains, all designed for clinical use, and adopted for cognitive rehabilitation in published studies: *Brainer* [42], *Rehacom* [12], *Erica* [43], *CogniPlus* [44,45], *Happy Neuron Pro* [46,47], *CogniFit* [48–50]. Some of them have been used for the rehabilitation of MS patients [12,43,50].

Table 4 shows a comparison considering the essential features of Section 2.2, and four additional relevant features, which MS-rehab does not currently have, provided by some of the other tools: *3D graphics*, to implement highly realistic exercises; *Special hardware*, to facilitate the human-computer interaction of patients with severe motor impairments; *Multi-language*, to support rehabilitation exercises in several languages; and *Test-batteries*, to provide screening modules for the assessment of patients' deficits.

All the CR tools support individual CR sessions, while MS-rehab is the only system that supports collective sessions. Another feature that MS-rehab provides is optional *Practice* for all the exercises using simplified versions. Also Rehacom and CogniPlus include practice, but with a different behavior: it terminates only when all the patient's reactions are considered to be correct by the system, while in MS-rehab the patient

	MS-rehab	Brainer	Reha com	Erica	Cogni plus	Happy NeuronPro	Cogni Fit
Number of exercises	52	78	25+	35	15	38	33
Individual sessions	✔	✔	✔	✔	✔	✔	✔
Collective sessions	✔	✗	✗	✗	✗	✗	✗
Practice	✔	✗	✔	✗	✔	✗	✗
MS-Cognitive profile	✔	✗	●	✗	●	✗	●
MS-Cognitive history	✔	✗	●	✗	●	✗	●
Semi-automatic conf.	✔	✔	✔	✗	✗	✔	✗
Remote control	✔	✗	✗	✗	✗	✔	✗
Monitoring	✔	✔	✔	✗	✔	✔	✔
Realistic content	✔	✗	✔	✗	✔	✗	✔
Autom. diff. variation	✔	✗	✔	✗	✔	✔	✔
Home work	✔	✔	✔	✗	✔	✔	✔
3D graphics	✗	✗	✔	✗	✔	✗	✔
Special hardware	✗	✗	✔	✗	✔	✗	✗
Multi-language	✗	✗	✔	✗	✔	✔	✔
Test-batteries	✗	✗	●	✗	●	✗	●

Table 4. Comparison of MS-rehab with state-of-the-art professional cognitive rehabilitation tools (✔ supported; ✗ not supported; ● not MS-specific).

decides to stop practicing when she thinks she has sufficiently understood the exercise.

Considering *cognitive profiles and history*, almost all the systems provide functionalities to store patient data, most of them store personal data, some of them (Brainer, MS-rehab, and Erica) include also clinical information. Concerning neuropsychological data: CogniFit includes screening modules for several diseases (not including MS), and stores their results; MS-rehab allows the operator to store results of specific MS batteries; Rehacom, Cogniplus, and CogniFit store the results of their own screening modules. All the systems that store neuropsychological data also support the *MS-Cognitive history* feature, although most of them are not MS-specific.

MS-rehab provides a *Semi-automatic configuration* interface to set up in a simple way appropriate exercises for a single patient or a group, also including home work. Erica, CogniPlus, and CogniFit do not provide this feature, but more complex configuration tools that require the definition of many parameters for configuring exercises, and are sometimes considered difficult to use by clinical operators.

Another distinguishing and novel feature of MS-rehab is a *Remote control* that the operator can use to conduct collective or individual rehabilitation sessions. By means of a monitoring interface, the operator can follow the cognitive training from her desk, without necessarily being in the same room where the patients are training, and can modify the difficulty of the exercises depending on how they are performing. Hardly provide other systems similar features, only Happy Neuron Pro allows the clinical operator to remotely monitor rehabilitation sessions, but collective session monitoring is not enabled.

MS-rehab like most of the other systems embeds mechanism to automatically increase the difficulty of an exercise if the patient performs well. The exceptions are Brainer, where the difficulty of an exercise is always the same, unless the operator changes it (selecting one of the three predefined levels), and Erica, where the next difficulty level must be set by the operator tuning targets, stimuli, distractors, and other relevant parameters of the exercise. Another limitation of Erica is that it does not support home training, while all the other systems provide this important feature:

MS-rehab, Brainer, Happy Neuron Pro, and Cognifit exploit a web based architecture for this, while Rehacom and Cogniplus use a specific USB key.

MS-rehab does not support advanced human-computer interaction features (i.e., *3D Graphics* and *Special hardware* like special keyboards and joysticks). However, it supports exercises with 2D realistic scenarios to train executive functions that require planning capabilities to solve everyday life tasks. The advantage of our solution for planning exercises with respect to the state of the art is that our plans are not hardcoded: we can automatically generate many different instances of an exercise and suggest the user the right strategies using automated planning techniques [51]. Brainer (like Erica, and Happy Neuron Pro) does not use realistic contents for brain games.

Considering multi-language support, Happy Neuron Pro, Cogniplus, CogniFit, and Rehacom have interfaces in several languages, while Erica, MS-rehab, and Brainer are in Italian only.

Computer administered *Test-batteries* are supported in some systems: Cogniplus and CogniFit provide their own screening modules, respectively the Vienna Test System [52][6], and the Cognitive Assessment Batteries (CAB) [53]. Similarly, Rehacom provides a set of screening modules for evaluating alertness, divided attention, response control, spatial search, neglect memory, logical reasoning, visual field, and visual scanning. The approach of MS-rehab is different: given that test-batteries are often disease-specific, and that computer administered tools for the assessment of cognitive deficits in MS already exist [54,55], we provide functionalities to store results of well known batteries, and to access them during the rehabilitation process. Indeed, cognitive rehabilitation and assessing cognitive dysfunctions are two complementary tasks and they call for different solutions.

In summary, although MS-rehab has some typical limitations of an experimental system (for instance the lack of multi-language support), it provides several advanced features compared to other state-of-the-art commercial systems. Moreover, given that it has been specifically designed for MS, it is more integrated with the care process of MS patients with respect to others.

5. Conclusions

In this paper, we have presented MS-rehab, a novel tool expressly dedicated to the individual and collective computerized cognitive rehabilitation of multiple sclerosis patients. Differently from other (general purpose) CR systems, the realization of MS-rehab originated from the idea that CR for a specific disease must be considered as a part of a comprehensive and complex care process that involves many aspects to be deeply analyzed to build an effective therapy. For this reason, the design and development of MS-rehab was based on a reference CR process defined in tight cooperation with clinical experts, and on the identification of how a computerized rehabilitation system can support the process phases. As a result of this development approach, MS-rehab incorporates a set of essential features for managing the CR care process for MS patients.

A preliminary assessment of MS-rehab in a pilot study involving a few MS patients gave indications that our system is potentially effective for CR and does not have negative side effects. In addition, the patients who used the systems gave a positive feedback on it, both on system usability, and as an instrument that motivates the

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[6]See also the SCHUHFRIED Web page: `https://www.schuhfried.com/vts/`.

patients in their CR process.

A comparison of MS-rehab to state-of-the-art professional tools for CR shows that several of the essential features are still not supported in most of them, highlighting a trade-off between commercial interests and health. In fact, the development of commercial systems for CR has the obvious goal of reaching more potential customers providing general purpose tools addressing different diseases. In our opinion, this marketing policy may be an obstacle to the full integration of these professional systems in the care process of MS patients, and this is possibly true also for other diseases.

As a future work, an extensive clinical study to validate the CR effectiveness of MS-rehab is planned. In addition, we want to fully incorporate in the system a promising reinforcement learning based mechanism to automatically adapt exercise difficulty to the actual performance of patients in the rehabilitation [29].

Conflict of Interest

The authors do not have any conflict of interest to declare.

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