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Cognitive rehabilitation in subjects suffering from environmental diseases

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ABSTRACT. Dopo una breve introduzione sui meccanismi eziologici coinvolti nello sviluppo di alcune malattie ambientali quali la sensibilità chimica multipla, la fibromialgia, la sindrome da fatica cronica e l'elettrosensibilità, in questo articolo vengono presentati i risultati di un training di riabilitazione cognitiva effettuato su un gruppo eterogeneo di 25 soggetti affetti da tali malattie. La perdita di capacità di memoria, attenzione e concentrazione sono le principali conseguenze sul piano cognitivo di queste sindromi, ancora poco conosciute nonostante siano studiate dagli anni Cinquanta. Dopo un periodo di circa tre settimane, consistente nella somministrazione di esercizi atti a stimolare le aree neurali interessate, si sono ottenuti complessivi miglioramenti in tutti i soggetti nelle capacità in questione. I miglioramenti realizzati vanno poi stabilizzati mediante programmi di mantenimento appositamente costruiti.

SUMMARY. There is a lack of studies about environmental diseases, such as multiple chemical sensitivity, fibromyalgia, chronic fatigue syndrome and electrosensitivity. The main cognitive consequences of these syndromes are the loss of memory, attention and concentration. The aim of the study is to experimentally verify the impact of cognitive rehabilitation on these aspects in people suffering from these diseases. Two phases of training for memory were administered to an experimental group of 25 subjects suffering from environmental diseases and to a control group made up of 12 healthy people. Subsequently they were administered again in order to evaluate a possible improvement of the neuropsychological functions. The training shows in both groups a general improvement in memory. The improvement is more considerable in people suffering from the diseases, probably because of the lower starting level of the patients. People suffering from environmental diseases can improve their cognitive functions through a rehabilitation training of memory, like the one presented in this study. These functions are essential to let people to have a regular everyday life. There is a need for more studies in order to find the best neuropsychological therapy, to help people suffering of environmental diseases to have a better life.

Keywords: *Cognitive rehabilitation, Environmental diseases, Multiple chemical sensitivity, Fibromyalgia, Chronic fatigue syndrome, Myalgic encephalomyelitis, Electromagnetic hypersensitivity, Idiopathic environmental intolerance*

INTRODUCTION

In 1952 Randolph defined the set of disorders complained after exposure to various chemicals as environmental disease. Since then, many similar reports began to be registered: literature contains more than 1500 works and over the years different definitions of this disease have been developed. In 1987 Cullen defined it as: "an acquired disorder characterized by recurrent symptoms, affecting multiple organs and systems, arising in response to demonstrable exposure to chemicals, even at concentrations much lower than those that are capable of causing disorders in the general population".

Today, multiple chemical sensitivity syndrome (MCS), fibromyalgia, chronic fatigue syndrome (CFS), and electrosensitivity are recognized as environmental diseases (Hvidberg, Schouborg Brinth & Olesen, 2015; Rubin, das Munshi & Wessely, 2006). These serious organic diseases, defined and included in the ICD-10 classification code of the World Health Organization, would be caused by environmental changes and variations in the lifestyles of developed societies (Bartha et al., 1999). In particular, pollution is the cause of syndromes and diseases that keep having an increasing impact, often found in the list of rare diseases (Bartha et al., 1999).

In 1996, the International Programme of Chemical Safety (IPCS) defined MCS as an "acquired disorder with multiple recurrent symptoms, associated with a variety of environmental factors, tolerated by most of the population, and unexplained by currently available internist and psychiatric knowledge". MCS is a complex pathology characterized by hypersensitivity to chemicals with the onset of a series of generic symptoms affecting various systems and of varying severity (e.g. nausea, headache, malaise, sense of fatigue, anxiety, musculoskeletal pain, sense of suffocation, panic attacks). These consequences tend to occur after an exposure to chemicals - often emanating strong odors - completely harmless for most of the population. The cause of this syndrome is still a matter of debate in the international scientific community. Among the causes hypothesized to date there is an impaired ability to metabolize certain xenobiotic substances due to a genetic deficiency or an alteration of the enzymatic mechanisms responsible for their metabolization (Pall, 2009). Another possible origin could be purely psychosomatic due to the absence of known pathogenic bases, the impossibility of independent testing, the frequent coexistence of psychopathologies and the positive results of inverted tests (absence of seizures upon unconscious exposure to the incriminated substances and onset of seizures upon exposure to inert substances presented as the incriminated substance). In some cases, the subjective perception of the exposure seems to be more important than the exposure itself.

MCS patients are present all over the country, but an important role is played by the type of work performed, as one of the risk factors would be contact with agents that could trigger the mechanism of sensitization and therefore cause the onset of the disease in subjects.

Cullen (1987) underlined the causal importance of exposure not only to chemical substances (such as toner, bleach, personal hygiene products, detergents, deodorants, petroleum-derived products, micro-dusts, chemicals, paints, glues, polishes) but also to physical risk factors (e.g. electromagnetic fields).

Epidemiological projections, which started in the 1990s (Binkley et al., 2001; Meggs, 1991) to 2009 (Pall, 2009), estimated the incidence of environmental diseases to range from 3 to 10% of the US and European populations (i.e., approximately 9 to 29 million individuals). At the end of a 2016 study regarding a sample of 1137 US adults, Steinemann (2018) states that the incidence of cases diagnosed as MCS has increased by 300% and self-reported hypersensitivity to chemical agents has increased by 200% over the past 10 years.

Useful indications are contained in the "Regional guidelines for the diagnosis and treatment of fibromyalgia" (Azzoni et al., 2018) both from the application point of view and to recognize the characteristics of the disease, still poorly known in the Italian medical field, despite the Consiglio Superiore di Sanità (Health Council) has estimated that about 900,000 people are affected by fibromyalgia (2015). In Italy, the latest estimates assume a 2-5% of the population susceptible to sensitization by chemical compounds, with a clear prevalence in the female sex such as to indicate a gender ratio of about 3:1 (Branco et al., 2010; Salaffi et al., 2005). Branco et al. (2010) estimate, by combining the London Fibromyalgia Epidemiology Study Screening Questionnaire (White, Harth, Speechley & Ostbye, 1999) and the American College of Rheumatology criteria (ACR; Wolfe, 2010), that 3.7% of the Italian population aged 15 years and older would be affected by environmental diseases. According to Salaffi et al. (2005), who instead identified cases through the ACR criteria, it is estimated that 2.2% of the Italian adult population would be affected.

Research purpose

A constant symptom frame of environmental diseases concerns deficits in memory, attention, and concentration, more generically defined within a set of neurocognitive disorders (Azzoni et al., 2018).

Subjects suffer a relevant worsening of working memory and simultaneous difficulties in attention and in the amount of information they can process. In the most severe situations, damage in executive functions is also present (Orriols et al., 2009). There are no medical or pharmacological therapies to date for this type of damage.

For environmental diseases there are no biomarkers and the etiopathogenesis of the syndromes is still uncertain. It should also be noted that multiple chemical sensitivity allows the assumption of a very small number of drugs, because these are made up of chemicals that could potentially harm the patient. The therapy of choice is the removal of the subject from the agents that are deleterious to him (Youdim, Rea & Liang, 1991).

Fibromyalgia is handled with drugs that can induce a myorelaxant effect, anxiolytics and antidepressants. Oxygen therapy is indicated, as well as the intake of therapeutic cannabis (Azzoni et al., 2018). But the results are not as appreciable as one would wish. The same conclusions are reached for electrosensitivity and chronic fatigue syndrome.

This work is the first to aim at verifying and measuring possible clinical improvements and in daily life of patients with environmental diseases, after a rehabilitation of memory function. To date, in fact, we are not aware of other studies aimed at demonstrating the effectiveness of cognitive training for these diseases.

METHOD

The rehabilitation therapy of neuropsychological functions used and described here has been implemented for some time, especially in Anglo-Saxon countries, which we know are very sensitive to such practices, but there are no traces in the literature of its use in subjects affected by environmental diseases.

Participants

The sample consists of an experimental group and a control group. The first group includes 25 subjects suffering from environmental diseases, diagnosed simultaneously by the National Health Service and private specialists. The experimental sample includes 25 patients (21 women, 4 men) from Northern Italy (15), Central Italy (5) and Southern Italy (5), with a mean age of 47.88 years (SD = 7.73), with various occupations (company manager, metalworker, socio-sanitary operator, technical operator with secretarial duties, employee in public institution); affected by fibromyalgia (12), MCS (3), fibromyalgia and MCS (3), fibromyalgia, MCS and electrosensitivity (2), fibromyalgia, MCS, CFS and electrosensitivity (5).

The control group consisted of 12 subjects (6 women, 6 men) similar in age and gender composition to the experimental group, with an average age of 50.58 years (SD = 8.55) without any environmental symptoms (2 Prato; 2 Florence; 4 Turin; 2 Bologna; 1 Caserta; 1 Arezzo). All subjects were volunteers informed about the aims of this research.

Materials

The rehabilitation tools used consist of programs on compact disc to be administered during the training phases. This has allowed the subjects, who often have great difficulty in moving, to be able to perform the entire rehabilitation phase at home with their PC, with the same benefits. The tools used for memory training are contained in the program developed by Trevor Powell and Kit Malia: "Training di Riabilitazione Cognitiva [Cognitive Rehabilitation Training]" (2009).

Administration methodology

Subjects were evaluated with an initial administration of exercises that allow the acquisition of the beginning level of their memory abilities, since the training programs express the percentage of success achieved after each exercise. Approximately two days after the end of treatment, the administration was repeated in order to estimate any changes. The rehabilitation consists of a series of tasks, which activate or reactivate the neural areas involved,

administered individually, each time highlighting the areas of greatest impairment and therefore customizing the mode of training.

Each subject underwent memory function training for 3 to 4 sessions of approximately 1 hour each, over the course of a week, between March 2019 and April 2021. All subjects were trained by the same operator (GC).

Memory rehabilitation

There were 17 planned memory exercises, subdivided also into multiple exercises of the same type, for a total of 34 exercises, many of them timed. These tasks are listed below in order of presentation.

1. *Ricorda le informazioni [Remember the information]* (3 exercises). The subject is asked to answer a series of questions that they must then rewrite exactly the same.
2. *Ricorda le sequenze [Remember the sequences]* (3 exercises). The subject is placed in front of a sequence of cards that light up containing a word, a musical note, and a sentence fragment and they will have to reconstruct the exact sequence in which these are presented.
3. *Ricorda un disegno [Remember a drawing]* (2 exercises). The subject must observe a drawing for a short period of time and then they must select from a list of words that correspond to the elements in the drawing.
4. *Ricorda i nomi delle persone [Remember people's names]* (3 exercises). The subject is shown the faces and names of 6-8 people and then asked to match them up again.
5. *Il gioco di Kim [Kim's game]* (2 exercises). The subject is shown 12 pictures for a short time, then asked to categorize them.
6. *L'elenco di parole [The word list]*. The subject is asked to remember and divide 15 words into three categories.
7. *Le notizie del giornale [Newspaper news]* (2 exercises). The subject is presented with two articles separately and will have to fill in a diagram by answering some questions.
8. *Chi partecipa al corso? [Who's attending class?]*. The subject is asked to remember a list of names associated with their respective jobs.
9. *Immagini appiglio in rima [Rhyming cue pictures]*. After observing 8 drawings, the subject is asked to write the words corresponding to the drawings without the visual aid, but with the handhold of rhyming words.
10. *La stanza [The room]*. After observing a picture of a kitchen with various elements, the subject is asked to relocate the missing objects.
11. *La piramide [The pyramid]*. The subject is shown a pyramid with objects from related categories, which he or she will be asked to relocate.
12. *Ricorda il tracciato [Remember the path]* (3 exercises). The subject is asked to reproduce traces of increasing difficulty consisting of dots.
13. *Osserva una persona [Observe a person]* (2 exercises). The subject is presented with pictures of two people which the subject will be asked to remember and describe.
14. *Memoria di immagini [Picture memory]*. The subject is shown 9 pictures that will have to be placed back in their original order.
15. *Il menù cinese* [The Chinese menu]. The subject is asked to select dishes from a Chinese menu, after which he or she will be asked to remember them and choose exactly the same dishes.
16. *Inventare una storia [Inventing a story]* (3 exercises). Three times the subject is presented with key words for a few seconds that he or she will have to include in a story he or she has developed.
17. *Ricorda i numeri [Remember the numbers]* (4 exercises). In this exercise the subject has to memorize and then reproduce three sets of number sequences.

Statistical analysis

Because of the non-normality of the data, verified graphically and with the Shapiro-Wilk test, we used nonparametric tests for analysis. We applied the Mann-Whitney *U* test to the total score and to individual trials of the memory training program in order to assess differences in initial performance between the two groups. We also tested for differences in subjects' performance using the nonparametric Wilcoxon signed-rank test. The choice of this test over the sign test is motivated by its greater statistical power, as it considers information derived from both the sign of the difference and the magnitude of differences of pairs of scores. Given the non-normality of the data, it was also chosen to summarize them in terms of medians, namely estimators that are unaffected by deviations from normality, as opposed to averages. The significance level of the test was set equal to $\alpha = .05$. Data analysis was conducted using the SPSS software (IBM SPSS Statistics v. 25).

RESULTS

The frequencies of exercises' success regarding the memory training are shown in Table 1 in the form of medians and averages before (pre-test) and after training (post-test) for the two groups, experimental and control. Figure 1, on the other hand, shows the improvement in the total performance of the two groups following the treatment.

The preliminary analysis, aimed at investigating the performance differences between the experimental group and the control group at the pre-test, showed overall differences between the two groups, with the subjects affected by environmental diseases showing significant lower performance than the control group (Total: $U = 66$, $p =. 01$); these significant differences are also confirmed for Le notizie del giornale [Newspaper news] ($U = 66$, $p = .01$), Osserva una persona [Observe a person] ($U = 73.5$, $p = .03$), and Ricorda i numeri [Remember the numbers] ($U = 73$, $p = .03$) tests.

Several improvements emerged from the Wilcoxon test that were statistically significant between pre-test and post-test detections in both the experimental and control groups, with the sum of positive ranks being significantly greater than the sum of negative ranks (see Table 2). Specifically, all significant trials in the control group are also significant in the experimental group, but not the other way around. This effect could be due to the lower numerosity of the control group, which resulted in lower power of the statistical test, but also better baseline performance levels in the control group than in the experimental group. The tests in which a significant improvement in the experimental group was observed were Ricorda le informazioni [Remember the information], Ricorda un disegno [Remember a drawing], Ricorda i nomi delle persone [Remember people's names], L'elenco di parole [The word list], Le notizie del giornale [Newspaper news], Chi partecipa al corso? [Who's attending class?], Immagini appiglio in rima [Rhyming cue pictures], La stanza [The room], Osserva una persona [Observe a person], Memoria di immagini [Picture memory], and Inventare una storia [Inventing a story].

The pyramid exercise turned out too easy for the subjects of both groups, in fact a ceiling effect is observed both at pre and post test.

In the remaining tests Ricorda le sequenze [Remember the sequences], Il gioco di Kim [Kim's game], The pyramid [La piramide], Ricorda il tracciato [Remember the path], Il menù cinese [The Chinese menu] and Ricorda i numeri [Remember the numbers] there is no significant improvement in either the experimental or the control group.

Overall, there is a significant improvement in performance in subjects in the control group and the experimental group, with a 10 percentage point improvement in performance in the latter (see Table 1 and Figure 1).

The increase in the success rate in the "Chi partecipa al corso [Who's attending class?]" exercise, considering its difficulty of execution, represents a highly positive sign of the progress of the subjects in both groups. In fact, from the median value of 57, it goes to a median value of 93 for the control group and 86 for the experimental group, which signals a significant improvement in that specific stimulated memory ability. Furthermore, we found overall that the rehabilitation training succeeded in producing progress that was then confirmed by the participants as improvements in their daily lives.

Similar results occurred in the control group. Here, the starting level of the abilities under examination was higher; therefore, the improvements obtained were of less conspicuous intensity than those achieved by the subjects affected by the syndromes, but hey proceeded in the same direction.

CONCLUSION

Environmental diseases are pathologies still a little unknown, although they are constantly increasing. Among these, multiple chemical intolerance, fibromyalgia, chronic fatigue syndrome and electrosensitivity are known. These diseases share the causes which are linked to environmental changes and share the symptoms that fall under the umbrella of neurocognitive deficits.

The purpose of this work was to test a possible mnemonic improvement in patients suffering from these diseases following training of specific and standardized exercises, administered about two/three days apart.

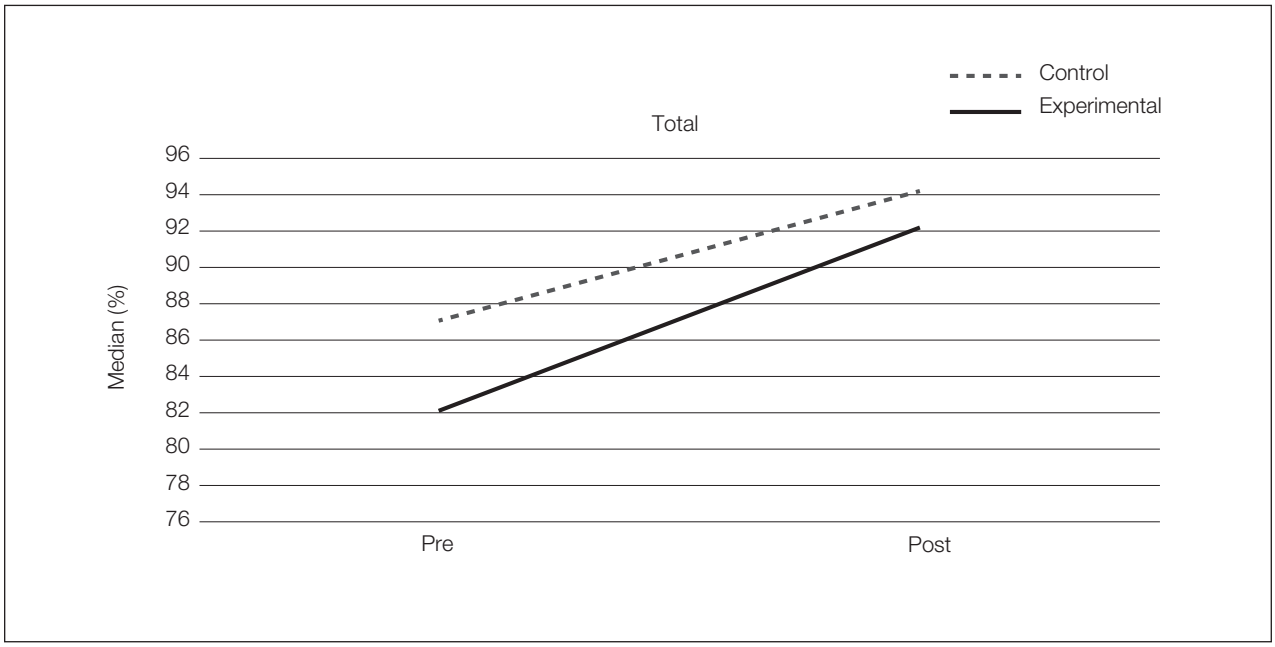
Following such training, an overall improvement in memory abilities was observed, which occurred in 11 of the 17 trials (65 %) in the experimental group.

The follow-up of the patients in the months following the end of the training showed that in some there were partial relapses of the improvements acquired, probably due to the interruption of cognitive training. This has led

Table 1 – Descriptive statistics of pre- and post- treatment success rates in the two groups

	Group							
	Control				**Experimental**			
	Media		**Median**		**Media**		**Median**	
	Pre	**Post**	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**
Ricorda le informazioni [Remember the information]	94	98	94	98	91	94	92	96
Ricorda le sequenze [Remember the sequences]	94	91	94	99	85	89	94	97
Ricorda un disegno [Remember a drawing]	87	90	86	91	87	90	86	91
Ricorda i nomi delle persone [Remember people's names]	89	97	91	100	86	93	91	100
Il gioco di Kim [Kim's game]	96	95	100	100	96	95	100	100
L'elenco di parole [The word list]	56	68	60	67	49	68	47	67
Le notizie del giornale [Newspaper news]	83	99	80	100	68	95	70	100
Chi partecipa al corso? [Who's attending class?]	53	86	57	93	47	77	57	86
Immagini appiglio in rima [Rhyming cue pictures]	93	100	100	100	87	95	88	100
La stanza [The room]	84	100	71	100	84	98	100	100
La piramide [The pyramid]	100	100	100	100	100	97	100	100
Ricorda il tracciato [Remember the path]	97	97	100	100	92	94	92	96
Osserva una persona [Observe a person]	80	94	80	100	71	92	70	95
Memoria di immagini [Picture memory]	94	100	100	100	85	96	100	100
Il menù cinese [The Chinese menu]	99	99	100	100	98	99	100	100
Inventare una storia [Inventing a story]	93	91	91	89	85	93	89	100
Ricorda i numeri [Remember the numbers]	84	94	100	100	65	74	75	75
Total	87	94	87	94	81	91	82	92

Figure 1 – Pre- and post- treatment success rates in the two groups



to the development of three maintenance programs already clinically tested with success, with a smaller structure compared to the training programs administered previously. These programs have the same efficacy as the full training programs in stimulating the neural areas, so that in the near future people affected by these diseases can at least recover, if not completely, a significant part of the decayed functions regressed over time.

The limitations of this research are mainly due to the difficulty of organizing a randomized controlled trial, since this is a group of rare diseases. In Italy, in particular, there seems to be a lack of contributions not only on these diseases, but publications specifically on neuropsychological damage are also lacking in the broad sense, that is, concerning diseases with larger sample sizes and a greater spread within the general population.

Table 2 – Results of the nonparametric Wilcoxon signed-rank test

	Group							
	Control				Experimental			
	Negative ranks	Positive ranks	*Z*	*p*	Negative ranks	Positive ranks	*Z*	*p*
Ricorda le informazioni [Remember the information]	2	43	2.442	**.015**	49	182	2.325[b]	.020
Ricorda le sequenze [Remember the sequences]	26	10	1.123	.261	77.5	112.5	.707[b]	.480
Ricorda un disegno [Remember a drawing]	6	39	1.992	**.046**	12	124	2.929[b]	.003
Ricorda i nomi delle persone [Remember people's names]	5.5	30.5	1.757	.079	20	116	2.486[b]	.013
Il gioco di Kim [Kim's game]	12	9	.333	.739	46	45	.038[c]	.969
L'elenco di parole [The word list]	5	23	1.527	.127	29.5	246.5	3.307[b]	**.001**
Le notizie del giornale [Newspaper news]	0	36	2.536	**.011**	0	325	4.405[b]	**<.001**
Chi partecipa al corso? [Who's attending class?]	0	55	2.816	**.005**	0	231	4.023[b]	**<.001**
Immagini appiglio in rima [Rhyming cue pictures]	0	15	2.121	**.034**	10	81	2.513[b]	**.012**
La stanza [The room]	0	21	2.449	**.014**	10	81	2.581[b]	**.010**
La piramide [The pyramid]	0	0	0	1.000	3	0	1.414[c]	.157
Ricorda il tracciato [Remember the path]	7	8	.138	.890	75	135	1.132[b]	.258
Osserva una persona [Observe a person]	0	36	2.585	**.010**	0	276	4.214[b]	**<.001**
Memoria di immagini [Picture memory]	0	6	1.732	.083	4	62	2.607[b]	**.009**
Il menù cinese [The Chinese menu]	1.5	1.5	0	1.000	2.5	7.5	1.000[b]	.317
Inventare una storia [Inventing a story]	16.5	4.5	1.294	.196	39.5	131.5	2.013[b]	**.044**
Ricorda i numeri [Remember the numbers]	5	16	1.190	.234	40	113	1.882[b]	.060
Total	0	66	2.936	**.003**	0	325	4.373 [b]	**<.001**

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