

# Treatment of Cognitive Impairment Using a Computer Program in Patients with Depression in Remission

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**Abstract:** The patient with depressive disorder presents a cognitive impairment which does not disappear despite the fact that the depression is considered to be in remission. This study aims to assess the impact of training in the improvement of cognitive functions of patients with remitted depression (RD). Captain's Log Computerized Cognitive-Training Program (CLCT) was used as a cognitive trainer in a group of patients with RD and with Selective serotonin reuptake inhibitors (SSRI) as treatment; another group with RD was treated uniquely with SSRI. The treatment intervention's impact was evaluated using the Hamilton Rating Scales for Anxiety and Depression, the Wechsler Adult Intelligence Scale (WAIS-III), and the Integrated Program of Neuropsychological Examination-Revised Barcelona Test. CLCT was used in college students with RD, twice a week, for six months. Patients from both groups decreased depressive and anxious symptoms, however, patients who received CLCT substantially increased their intellectual performance; changes in the psychometric analysis of the Barcelona Test were consistent with the ones presented in WAIS-III. CLCT application is associated with an improvement of cognitive functions in patients with RD.

**Keywords:** Depression, Remission, Cognitive Functions, Cognitive Stimulation, College Students

## 1. Introduction

The objective of this trial is to improve cognitive functions in individuals with RD, using Captain's Log Computerized Cognitive-Training Program (CLCT) [1]. The World Health Organization (WHO) points that 15% of the population of developed countries suffer from severe depression, and identified that 30% of women are depressed [2].

In Mexico, 9 to 13% of the adult population suffers from depression, with a prevalence of 2 to 1 regarding women and men [3]. This disorder is more frequent among 15-19-year-old individuals and above 65 years, where the recurrence rate is 59% [4].

In the age group corresponding to university students, a

prevalence of 6.2% was determined in students of the first two years of Medicine. In 2005, Manelic and Ortega-Soto [5], assessed the prevalence of depression in the Faculty of Superior Studies of Aragon of the National Autonomous University of Mexico (UNAM) in 11.8%. Among the University of Colima, the prevalence of depression was about 21.8% in students of nursing school [6].

Reference [7] found that 92% of university students who suffered from depression showed academic impairment, in such a way that a student's negative perception of their academic competence represents a risk factor for depression. [8]. Depression in university students affects their academic productivity, school satisfaction, and social relationships, generating stress and enhancing the depressive state [9].

Trials like the one performed by Furr, Westefeld, McConnel & Jenkins in the year of 2001 [10], have reported that depression affects near of 50% of the university population, stating that multiple factors can contribute to the presentation of depressive symptoms. The most common elements are decreased academic productivity, social stressors, economic problems, and the inherent adjustment of family context to the university environment.

Patients with major depression disorder (MDD) show cognitive deficits [11]. For instance, failures in executive functions such as cognitive flexibility, problem-solving [12], processing speed [13], deficits in domains in memory [14, 15] and deficits in the domain of attention, concentration [14]. As a consequence of these failures, depression also may cause disabilities in cognitive functioning which may drive patients to show social, working performance, academic and intellectual impairment.

Among depressed patients, psychomotor retardation was the most critical factor in work reduction. Authors like Mintz J., Mintz L., Arruda, and Hwang [16] evaluated the effects of anti-depressants and psychotherapy on work impairment in depressed patients. Original databases from 10 published treatment studies were compiled and analyzed ( $N = 827$ ). Functional work impairment was common at baseline, manifested by unemployment (11%) or on-the-job performance problems (absenteeism, decreased productivity, interpersonal problems, 44%), only 55% fulfilled the criteria required to go back to work after treatment.

Academic deterioration is evidenced mainly in absenteeism, low academic performance, poor interpersonal relationships and wrong perception of academic competence. Reference [17] presented a linear structural model which co-relates children's school performance with anxiety and depression. Using intellectual quotient as the control variable of the model the academic performance showed an association between the severity of depression and the child's isolation due to his/her classroom execution and cognitive functioning. Children who were most depressed presented deficiencies in cognitive functioning, and those more introverted had the worst performance in the classroom. On the other hand, depression in university students affects academic performance, satisfaction with studies and social relationships which, in turn, generate stress and thus reinforce the depressive state [18]; reference [7] found out that 92% of the students diagnosed with depression presented academic impairment.

Cognitive damage persists despite the remission of depressive symptoms [14, 17]; thus, remitted depression (RD) is defined as the absence of depressive symptoms and the return to the patient's basal functioning [19].

Since there is no specific parameter to define depression in remission, previous studies have used Hamilton scale of 17 items, with a score of 7 points or less, as a criterion [20].

Some studies report the efficiency of cognitive rehabilitation using computer programs, for those patients with attention and concentration deficits. Trials like the one performed by Slate, Meyer, Burns, and Montgomery [21] used Captain's Log Computerized Cognitive Training

Program (CLCT), and combined electroencephalogram (EEG)/ neurofeedback, to treat children with Attention Deficit Hyperactivity Disorder (ADHD).

There were four cases involved in this study of children with severe emotional damage, diagnosed with psychosis and ADHD. A pre-test and a post-test design were used. All of the patients' symptoms decreased and demonstrated high levels of generalization of those skills that were the focus of treatment.

Some authors like Kotwal, Burns, and Montgomery [22] demonstrated that CLCT was able to operate changes in the brain-waves patterns measured by EEG/neurofeedback equipment. These changes were evaluated in 13 years old patients with a diagnosis of ADHD. A pre-test and post-test design were used. The patients received 35 treatment sessions where significant improvements in the symptoms were shown, and changes remained seven months after the experimental process concluded.

Reference [23] used the "Cogpack" program three times a week to schizophrenic patients who, after three months of therapy, improved cognitive functions such as verbal memory and speed processing.

Two studies carried out in 2007, and 2015 [24, 25] concluded that computerized programs enhanced cognitive functions, especially work memory in patients with schizophrenia. On the other hand, computerized programs were successfully used to reduce depressive symptomatology in patients with unipolar and bipolar depression [26]. Also, computer-assisted cognitive training was successfully employed to decrease negative symptoms in schizophrenic patients and with a schizoaffective disorder [27].

Another trial [28] showed in an experimental way that Alcor Program was efficient as a treatment for depression and in the reduction of the cognitive deterioration in patients with Major Depressive Disorder; also, it was demonstrated that the program significantly increased the patients' intellectual quotient, compared to control patients.

In a more recent study, Alvarez, Yépez, Jurado, Guerrero & Petra [29] demonstrated that Captain's Log Cognitive Training program helped to improve the intellectual performance of patients who suffered from Obsessive Compulsive Disorder (OCD), reflected in higher cognitive flexibility, processing speed, reasoning, and intellectual quotient.

Patients with dementia can benefit from computerized cognitive training programs if the impairment is mild [24, 30]. Other authors like Edwards et al. [31], discovered after 10-year-follow-up research, that training to increase processing speed delays dementia in elderly patients. Reference [32] in 2007 found that Cogni-Fit program significantly decreased the risk of dementia in older diabetic patients.

Some authors have worked with computerized programs to rehabilitate the impairment produced by some physical illnesses. For instance, Cerasa et al. in 2013 [33] used a computer-assisted cognitive rehabilitation (RehaCom) in patients with multiple sclerosis, showing with functional magnetic resonance imaging (fMRI) an increase in activity in the posterior lobe of the cerebellum (IV) and the superior parietal lobule after cognitive training with RehaCom. This

indicates an essential relation in the lobule IV of the cerebellum that is active in the articulatory control system.

Reference [34] observed an important increase in brain activity in fMRI in patients with multiple sclerosis who had received short-term computer-based cognitive training (8 sessions). These patients enhanced their cognitive functions compared to those patients who only received placebo. Authors observed significant changes in the activation of the posterior cingulate cortex and bilateral inferior parietal cortex; therefore, they suggest that rehabilitation produces adaptive cortical reorganization favoring better cognitive performance. After the cognitive intervention, only the group that was treated preserved the improvement in processing speed. Authors did not observe changes in brain volumes.

Since some authors have tried to explain the reason why computer-assisted rehabilitation programs may produce positive changes, several trials have been carried out. Reference [35] used fMRI on adolescents who played *Tetris* for three months and observed thicker cortex of some of the brain's regions which are related to visual-spatial functions. These findings may suggest that computer games can produce changes in the structure of the brain.

Other studies have shown in brain images that people who suffer from depression have hippocampal volume loss and this is associated with cognitive impairment [36].

Reference [37] pointed that MRI techniques provide information to understand behavioral improvements assessed with neuropsychological tests; for instance, reorganization in structural and functional connections, and neuroplasticity produced by cognitive rehabilitation. In the same way, it helps to comprehend changes in the brain structure that considerably benefit patients with multiple sclerosis, since rehabilitation with computer programs is a non-invasive, not pharmacologic and behavioral technique that may induce

neuroplasticity to try to normalize brain functions which are reflected in cognitive and behavioral improvements.

## 2. Method

### 2.1. Design

Single-blind randomized controlled trial.

### 2.2. Participants

In this study participated university students of the National Autonomous University of Mexico (UNAM) in remitted state of depression according to the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) criteria [38]. The diagnosis was confirmed with the Spanish digital version of the M. I. N. I (Mini- International Neuropsychiatric Interview) [39], based on the DSM-IV and International Statistical Classification of Diseases and Related Health Problems (ICD-10). To evaluate the criteria of remitted depression, the Hamilton Depression and Anxiety Rating Scales were used. Patients with psychotic disorders, Bipolar disorder or suicidal risk were excluded. Twenty-five students were selected, however, two of them were excluded because they got hired for a job and another one did not attend the final evaluation.

All of the patients were treated with Selective serotonin reuptake inhibitors (SSRI) and were randomly assigned to two groups. The Experimental group ( $n=12$ ), where 9 of them were women (mean age  $23.2 \pm 2.5$  years) and three men (mean age  $20.0 \pm 2.0$  years), and besides the pharmacologic treatment they received cognitive training. The Control group ( $n=13$ ) was formed of 10 women (mean age  $27.7 \pm 9.5$  years) and three men (mean age  $25.0 \pm 6.1$  years), and they only received SSRI. All of them signed an informed consent form.

**Table 1.** Distribution of participants by group and age.

Group	Men			Women			Total		
	Mean	SD	n	Mean	SD	n	Mean	SD	n
Experimental	20.0	2.0	3	23.2	2.5	9	22.4	2.7	12
Control	25.0	6.1	3	27.7	9.5	10	27.1	8.6	13

### 2.3. Instruments

- 1) Remitted Depression: Hamilton Depression Rating Scales (HAM-D). The Spanish version was made in 1986 by Ramos-Brieva and has 17 items. Remission has been considered with a score of 7 or less [40]. According to Zimmerman [41], the cut-off point for remitted depression is a score of 3 to 7 points. Scores from 0-2 are considered as a better remission.
- 2) Anxiety: Hamilton Anxiety Rating Scale (HAM-A) was designed in 1959. Initially, it was composed of 15 items, but in 1969 some of them fused; thus, it was formed of 14 elements. Each one is valued by a score of 0 to 4 points [42].
- 3) Wechsler Adult Intelligence Scale (WAIS-III) [43].

- 4) Integrated Program of Neuropsychological Examination-Revised Barcelona Test [44]. It is an abbreviated version, adapted for its application in Mexico [45].

### 2.4. Procedure

A psychiatrist was in charge of antidepressants. Captain's Log Computerized Cognitive-Training Program (CLCT) was used to exercise cognitive abilities [1]. CLCT was created to enhance cognitive functions like attention, concentration, memory, visuomotor coordination, abstract reasoning, logical reasoning and problem-solving skills [1]. The software has nine sections with 3 to 7 routines. It was designed as a game that motivates and entertains the patient at the same time it improves cognitive functions. Participants attended two sessions a week, of 45 minutes each, starting with memory

units and afterward, with logical reasoning.

The treatment intervention was assessed with WAIS-III, the Integrated Program of Neuropsychological Examination-Revised Barcelona Test, as well as the Hamilton Depression and Anxiety Rating Scales.

After six months, a second evaluation was performed using the same scales, to avoid the effects of previous learning.

### 3. Statistical Analysis

Categorical variables were presented as frequency and percentage, and dimensional variables, as the mean and standard deviation. Variables were assayed using the Analysis of variance (ANOVA) for repeated measures 2x2, with two intragroup evaluating levels (initial and final) and two intergroup levels of condition (experimental and control). The effect size was calculated using Cohen's *d* for the changes in the experimental group [46].

### 4. Results

#### Anxiety-Depression

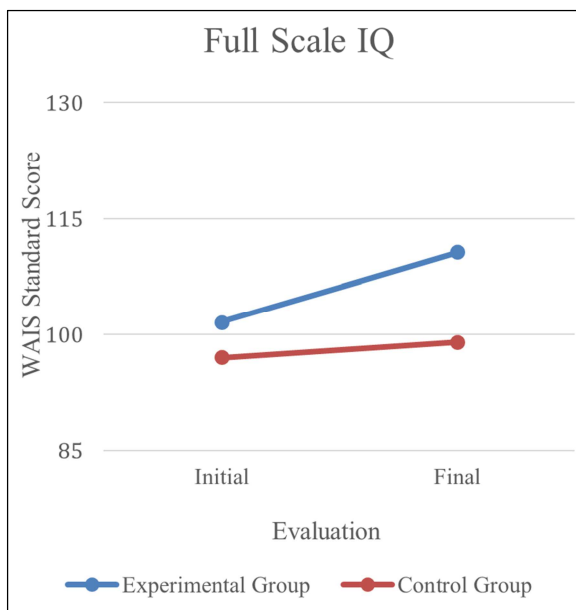


Figure 1. Full-scale IQ means by condition and evaluation.

Participants of both groups met the criterion of being depressed patients in remission and showed low anxiety scores. During the six months of evaluation, both groups decreased even more their levels of depression and anxiety, without differences between them (Table 2). As shown in Figure 1, the experimental group obtained a slightly higher IQ ( $IQ = 101.7$ ) than the participants of the control group ( $IQ = 97$ ), even though they were randomly assigned. In the post-test, the IQ of the experimental was 110.7 and in the control group was 99.0

#### WAIS-III Intellectual Quotient (IQ)

Significant differences were found in the WAIS-III quotients. The group who received cognitive training increased Verbal IQ in 11.2 points, which represents a large size effect:  $d=1.60$  [ $F$  condition  $\times$  evaluation (1.23) = 36.03,  $p<0.001$ ]. Total IQ increased 9 points, considering a large size effect  $d=1.3$  [ $F$  condition  $\times$  evaluation (1.23) = 28.59,  $p<0.001$ ] (Table 3).

#### WAIS-III Indexes

Significant differences were found in the WAIS Indexes; the group who received cognitive training increased the Verbal Comprehension Index by 7 points, which represents a medium size effect  $d=0.7$  [ $F$  condition  $\times$  evaluation (1.23)=5.53,  $p=0.028$ ]. The Working Memory Index increased 6.5 points, which is considered as a large size effect  $d=1.5$  [ $F$  condition  $\times$  evaluation (1.23) = 30.32,  $p<0.001$ ]. Processing Speed Index increased 10.1 points, which is a medium size effect  $d=0.6$  [ $F$  condition  $\times$  evaluation (1.23) = 6.95,  $p=0.015$ ]. Finally, Perceptual Organization Index showed no differences [ $F$  condition  $\times$  evaluation (1.23)=0.02,  $p=0.890$ ]. (Table 4).

#### Integrated Program of Neuropsychological Examination-Revised Barcelona Test: Subtests with significant changes

Significant differences were found in eight subtests, which are: Digit Span Forward ( $p=.005$ ), Digit Span Backward ( $p=0.01$ ), Pseudoword reading Time ( $p=0.001$ ), Bimanual pseudogesture imitation ( $p=0.001$ ), Alternating sequences: right limb/hand ( $p=0.012$ ), Alternating sequences: left limb/hand ( $p=0.034$ ), Story cued recall ( $p=0.011$ ), Digit-symbol (coding) (0.027). These results were consistent with the findings of the WAIS-III Indexes (Table 5).

(Tables are shown below).

Table 2. Distribution of participants by group and age: Depression and Anxiety means.

Variable	Condition	Initial		Interval		Final		Significance of Interaction Condition Evaluation	
		Mean	SD	Mean	SD	Mean	SD	F	p
HAM-D	Experimental	2.33	0.73	1.25	0.41	0.17	0.17	0.052	0.949
	Control	2.15	0.70	1.23	0.39	0.23	0.16		
HAM-A	Experimental	2.75	0.57	1.75	0.34	0.67	0.24	1.206	0.318
	Control	1.61	0.53	0.85	0.32	0.23	0.23		

**Table 3.** Distribution of participants by groups and age for the WAIS-III IQ Mean.

Variable	Condition	Evaluation				Significance of Interaction Condition Evaluation	
		Initial		Final			
		Mean	SD	Mean	SD	F	p
Verbal Iq	Experimental	99.3	7.0	110.5	6.9	36.03	< 0.001
	Control	96.3	5.8	97.5	6.0		
Performance Iq	Experimental	106.5	6.3	112.4	5.6	6.93	0.015
	Control	101.8	4.3	104.1	5.5		
Full Scale Iq	Experimental	101.7	7.0	110.7	6.5	28.59	<0.001
	Control	97	4.8	99	6.2		

**Table 4.** Distribution of participants by group and age: WAIS-III Indexes Mean.

Variable	Condition	Evaluation				Significance of Interaction	
		Initial		Final		Condition Evaluation	
		Mean	SD	Mean	SD	F	p
Verbal Comprehension Index	Experimental	112.8	9.9	119.8	6.6	5.53	0.028
	Control	110.2	8.9	112	8.1		
Perceptual Organization Index	Experimental	112.8	11	117.9	7.4	0.02	0.89
	Control	102.5	10.4	107.2	10.2		
Working Memory Index	Experimental	98.3	4.3	104.8	4.8	30.32	<0.001
	Control	96.1	2.9	96.6	3.1		
Processing Speed Index	Experimental	124.3	17.7	134.3	11	6.95	0.015
	Control	119.5	11.8	116.8	12.4		

**Table 5.** Distribution of participants by group and age: Integrated Program of Neuropsychological Examination-Revised Barcelona Test Subtests Means.

Variable	Condition	Evaluation				Significance of Interaction	
		Initial		Final		Condition Evaluation	
		Mean	SD	Mean	SD	F	p
Digit Span Forward	Experimental	5.2	0.7	6.3	0.9	9.59	0.005
	Control	4.9	0.5	5.1	0.5		
Digit Span Backward	Experimental	3.9	0.9	5.5	1.2	7.78	0.01
	Control	3.2	0.7	3.7	0.6		
Pseudoword reading time	Experimental	13.4	2.2	16.7	1.6	16.16	0.001
	Control	13.7	1.8	13.2	1.6		
Bimanual pseudogesture imitation	Experimental	7.1	0.8	8.0	0.0	14.29	0.001
	Control	7.7	0.5	7.5	0.7		
Alternating sequences: right limb/hand	Experimental	6.9	0.8	7.7	0.5	7.45	0.012
	Control	7.2	0.8	7.2	0.4		
Alternating sequences: left limb/hand	Experimental	7.0	1.0	7.7	0.5	5.09	0.034
	Control	7.1	1	7	0.4		
Story cued recall	Experimental	19.3	2.6	21.4	1.1	7.55	0.011
	Control	18.9	1.6	18.6	2.2		
Digit-symbol (coding)	Experimental	47.3	4.7	53.5	6	5.61	0.027
	Control	39.2	6.5	40.3	5.6		

## 5. Discussion

Depressed patients remained with remitted symptomatology, showing no significant differences among them. Both groups decreased anxiety levels.

Pharmacologic treatment, as well as cognitive training using CLCT, were able to maintain or modulate the remission in patients with depression; however, those who only received pharmacologic treatment did not show changes in their cognitive functions, even though they remained in remission.

Regarding intellectual performance, participants of the experimental group showed significant differences after the treatment, since their IQ increased 9 points, meanwhile

control group only increased 2. This pattern seems to be repeated in Verbal IQ as well as in Performance IQ, which may be because participants who received cognitive training had better performance and obtained a bonus time in some of the WAIS-III subtests; this was probably produced by the decreased in the delay of processing that depressed patients may show. On the other hand, patients of control group seemed to have the same cognitive impairments they presented in the first evaluation.

Patients who received cognitive training reflected an increase in Verbal IQ, which indicates that they enhanced their skills to use the knowledge previously stored to judge and solve problems that require abstraction of the relations between two different elements, as well as comprehension and concept formation. In the same way, they enhanced their

deductive reasoning skills, which is essential in their academic productivity.

The changes found in the Performance IQ of the experimental group demonstrates that the intervention is effective in training skills that are related to visual analysis (detection of missing small details from a whole); this requires sustained attention, associative thinking skills, and eye-hand coordination velocity. Significant improvements were found in visuospatial ability, integration of tridimensional designs, sequencing skills as well as in planning skills, selection, and self-regulation of answers and receive feedback on the learning to solve practical problems. This aspect is relevant since college students who continued attending classes formed the sample, and compared to the control group, there were no changes in their executive functions.

The increase of the Full-Scale IQ indicates that the students who received cognitive training showed a better development of strategies to solve problems that require verbal communication abilities as well as practical problem-solving skills that they may use in their academic life.

Regarding WAIS-III Indexes, significant differences were found in the Verbal Comprehension Index, which reiterates a better aptitude of the patients of the experimental group to understand, handle and solve problems related to the management of the language and long-term memory skills, compared to the results of the control group.

In the Working Memory Index, the experimental group demonstrated significant changes in the ability to store and retrieve new information. It should be mentioned that although the stimuli became more complicated, the subjects of the experimental group managed to evoke a higher number of stimuli, compared to the performance of the control group. These are very important since short-term memory skills are one of the functions that are most affected by depression.

The other Index that presented relevant changes was the Processing Speed Index. It is worth mentioning that these skills were favored since all the exercises that are carried out in CLCT require time control, which caused a more agile response. Thus, the participants who received the program showed an increase in the Verbal IQ, in the Performance IQ and the Full-Scale IQ; this may be due to patients receiving time bonuses on some of the WAIS-III subtests, probably produced by the reduction in the psychomotor retardation observed in depressed patients.

In the Integrated Program of Neuropsychological Examination-Revised Barcelona Test, consistent results with those demonstrated by the experimental group in the WAIS-III. For instance, better ability to retain and evoke information, understanding of verbal concepts, as well as showing greater cognitive flexibility, and attentional supervision, enhancing their decision making when solving problems that the computer program presented to them, an essential aspect since they are skills that these subjects could replicate in their school environment.

This may be associated to the results obtained by Jaeggi, Buschkuhl, Jonides, and Perrig in 2008 [47], which proved

that skills trained with cognitive software that increases intellectual performance could be transferred and improve academic productivity and daily life problem-solving skills.

All of these results may be associated with the hippocampal volume loss that non-treated depressed patients present and that is demonstrated with MRI, according to authors like Sheline, Gado y Kraemer, in 2003 [36]. The hippocampus is an essential structure regarding memory process. On the other hand, according to the results obtained by Eriksson *et al.* [48], it is known that the dentate gyrus of the hippocampus produces new neurons in the adult. These cells migrate to the cortex, based on the criterion of being “used or discarded” in the prefrontal, posterior, parietal and inferior temporal cortex. It is also known that many of the cellular mechanisms that occur during learning process and consolidation, some of the structures of the central nervous system have in common significant changes in synaptic transmission, as well as morphological changes in nerve cells, according to the results obtained by Prado and Bermúdez in 2001 [49], as well as the changes in the cerebral architecture obtained by Chiaravalloti, Genova and DeLuca in 2015 [37].

It is fundamental to highlight that depressed patients who are in remission remain with cognitive impairment; from this perspective, it is possible to realize and understand the importance of rehabilitation of cognitive functions of patients who have suffered from depression to obtain an accurate remission that will definitively improve their quality of life.

#### Limitations

These results are only valid for university students with remitted depression; therefore, it lacks external validity. It is necessary to replicate this research with adults or seniors with depression in remission.

## 6. Conclusion

Several trials have found that college education stressors may boost depressive symptomatology and intensify as the academic demands increase, affecting basic cognitive skills, such as attention, concentration, cognitive flexibility when solving problems, motivation, and functions related to short-term memory.

This study was able to show that cognitive training detected significant differences in students who participated in the intervention, in relation to the control group, since the experimental group not only enhanced the executive functions that are already reported in the literature but also functions related to verbal concepts management.

Since sustained attention was improved with cognitive training, participants could also improve comprehension skills for solving practical problems, optimizing processing speed. This aspect seems to be encouraging since one of the main complaints of depressive patients is slowing down during task execution.

The significant change in the results of the tasks related to the short-term memory of the experimental group also seems to be encouraging for future interventions with college

students with academic issues, since skill retention is essential in the daily chores of any university student.

The obtained results showed quantitative significant differences as well as relevant qualitative changes, which were reported by the experimental group at the end of the treatment, where patients answered a brief survey to know about the changes they could experience throughout treatment. Patients reported a substantial enhancement in the necessary skills for learning, such as sustained attention, memory, and concentration, which were reflected in a better academic productivity and motivation. They also reported improving the agility in the daily life problem-solving.

Another highlighted aspect is that there was not found any significant decline in any of the groups since all the participants were students who attended to classes and with remitted depression; however, results showed that participants who received cognitive training improved their intellectual performance and their quality of life too.

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## Conflict of Interest

All the authors do not have any possible conflicts of interest.

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