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Article

# Enhancing Cognitive Rehabilitation in Multiple Sclerosis via P300 Brain-Computer Interfaces: A Proof of Concept

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## Abstract

**Background:** Multiple sclerosis (MS) affects mainly young and middle aged adults and cognitive impairment significantly impacts their quality of life. This study explores the effects of a cognitive rehabilitation therapy using a P300-based brain-computer interface (BCI) in people with MS (pwMS). **Methods:** The therapy consisted of 16 cognitive rehabilitation sessions using a P300-based BCI. In each session, three different tasks were rehearsed, designed to stimulate different cognitive functions. As outcomes of the study, the cognitive functions were evaluated via the brief international cognitive assessment for MS (BICAMS) component scales before and after the intervention. The quality of life was evaluated using the MS international quality of life (MUSIQoL) questionnaire. The amplitude and latency of the P300 were obtained from the EEG signal recorded during the first and last sessions. **Results:** Three pwMS completed the cognitive rehabilitation therapy. A general improvement was seen in the BICAMS and MUSIQoL. In particular, all the subjects achieved an increase higher than 10% in the component scale symbol digit modalities test (SDMT) and this difference is clinically meaningful. Concerning the characteristics of the P300, the mean latency of the group decreased 50.89 ms and the mean amplitude showed no change between the two moments. These results may reflect changes at cortical level after the intervention. **Conclusions:** These findings suggest that the therapy described could positively affect cognitive function and that the P300 may be considered as an objective indicator of cognitive performance which complements the evaluation of the effects of P300-based BCI therapies.

**Keywords:** P300; BCI; cognitive rehabilitation; multiple sclerosis; BICAMS

## 1. Introduction

Multiple Sclerosis (MS) is an inflammatory, chronic, demyelinating, autoimmune neurodegenerative disease that affects the central nervous system. MS can alter different functions and is characterized by relapses, remissions and progression of the disability with time [1–3].

MS is one of the main causes of disability in young and middle aged adults. Cognitive impairment can affect up to 70% of people with MS (pwMS) [4] in every stage and subtypes of the disease [3–6]. The severity and type of cognitive impairment vary within the individuals and can be observed both in the first and last stage of the disease. The cognitive functions that have shown to be more affected are: information processing speed, working memory, complex attention and executive function [3–6]. Cognitive impairment has major effects in the quality of life of pwMS, affecting their work productivity [7,8] and their ability to engage in activities of daily living [9–11].

There is consistent evidence about the benefits of cognitive rehabilitation in pwMS to restore specific cognitive functions, such as information processing speed, working memory and attention [12,13]. With this purpose, cognitive rehabilitation is based on repetitive training, frequently through technology-based tasks, in both clinical environments and at home with remote guidance. A meta-analysis that included 20 randomized controlled trials and 982 pwMS found small to moderate effects for information processing speed, executive function and memory after cognitive rehabilitation [13].

Considering the impact of cognitive impairment on the life quality of pwMS and the benefits of cognitive training, research has been focused on finding rehabilitative approaches that enhance cognitive rehabilitation for pwMS as possible add-on treatments [14].

Brain-computer interfaces (BCIs) are an emerging technology that may be used for cognitive rehabilitation therapies [15–17]. A BCI system uses electroencephalography (EEG) to record electrical activity in the brain, extracting specific features and transforming them into a control signal that triggers an actuator to replace, restore, enhance or complement functions [18]. Event-related potentials (ERPs) recorded via EEG have been suggested as reliable features in BCIs. The most widely used and studied ERP is the P300 [18]. This ERP component is a positive deflection that is elicited 300 ms after a stimulus delivered under specific conditions, known as the oddball paradigm. In this paradigm, a series of visual or auditive stimuli is presented to a participant to categorize. There are two possible categories, one of which is less frequent than the other. When a less frequent or oddball stimulus is recognised by the participant, a P300 is elicited [18,19]. In 1988, Farwell and Donchin [19] proposed for the first time a P300-based BCI as a communication tool. In this system, a series of repetitive stimuli is randomly presented to the user in such a way that, when they attend to a selected element while ignoring the rest, a P300 is generated, which allows the BCI system to detect it [19,20]. P300-based BCIs have numerous advantages, such as non-invasiveness, quick configuration for new users, no need for intensive training and reliability, to name a few [18].

On the other hand, the amplitude and latency of P300 have been reported as characteristics for the assessment of cognitive functions [21,22]. These characteristics may also depend on other factors such as motivation, mental fatigue, frustration, anxiety [22]. In addition, these characteristics have shown alterations due to aging and diseases such as stroke, ADHD and MS [21,23–27].

Several studies intended to improve attention by using P300-based BCIs, and reported that amplitude and latency of P300 exhibited variations after the intervention [22,28–32]. One study has been found that proposed a P300-based BCI for rehabilitation of attention, working memory, executive functions and visuospatial skills simultaneously [33]. However, the effects of using it for cognitive rehabilitation in pwMS are unknown.

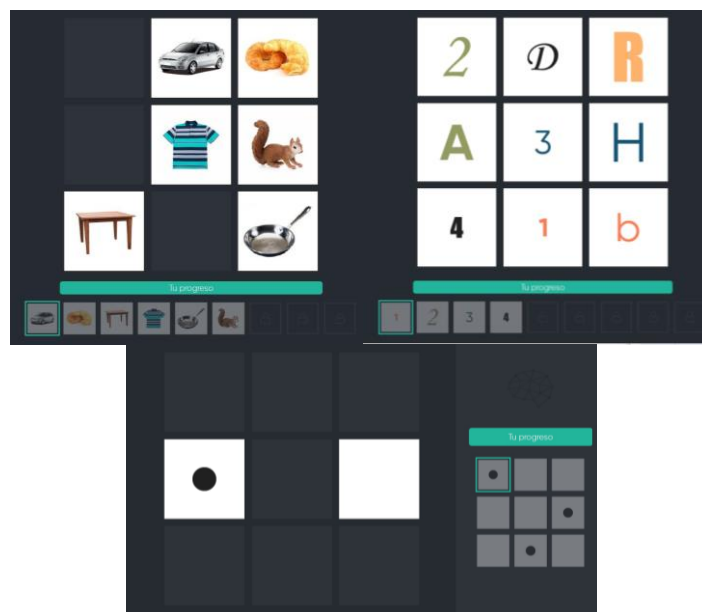
This article describes an exploratory study that aimed to evaluate the effects of a cognitive rehabilitation therapy using a P300-based BCI in pwMS and cognitive impairment.

## 2. Materials and Methods

In this section, the materials and methodology applied for the study are described.

### 2.1. BCI Based Technology: Cognitask

The P300-based BCI used was Cognitask [33] and is aimed at cognitive training. Cognitask enables the user to perform a cognitive task by using the oddball paradigm to elicit a visual P300. The cognitive tasks available are spelling, puzzles and sequences. All of them have selectable difficulty levels. Cognitask has a user interface to display stimuli by means of a matrix. This matrix, as it can be seen in Figure 1, is formed by 9 cells, each of which may be empty or contain letters, numbers, objects or even parts of a picture, depending on the cognitive task [33].



**Figure 1.** Examples of cognitive tasks available in Cognitask.

In this study, Cognitask was used with the EEG amplifier g.Nautilus with the g.Scarabeo active gel based electrodes of g.tec<sup>1</sup>. The data were digitized with a resolution of 24 bits and sampling frequency of 250 Hz. The EEG signal was recorded by means of 5 channels using the positions Cz, Pz, Oz, PO7 and PO8 according to the 10-20 International System. The ground and reference electrodes were placed in the right earlobe and AFz position, respectively. The EEG signal was filtered with a bandpass filter with cutoff frequencies of 0.1 Hz and 30 Hz (Butterworth, order 8) and a notch filter with cutoff frequencies of 48 Hz and 52 Hz (Butterworth, order 4).

Cognitask needs two stages for operation: calibration and closed-loop. The main objective of the calibration is to train the classifier that detects the P300. This stage consists of three tasks without feedback to the user. Each task involves spelling a four-letter word by selecting the corresponding letter from the matrix. In the closed-loop stage, the therapist sets the cognitive task and Cognitask provides feedback to the user. Each cognitive task involves a different matrix. In order to complete the cognitive task, the user has to choose the cell of the matrix that corresponds to the correct answer and repeat the process until the task is finished. If the user cannot select the correct cell after three consecutive attempts, the answer is selected by the BCI to avoid frustration. Furthermore, Cognitask shows different messages according to the performance of the user, to increase motivation [33].

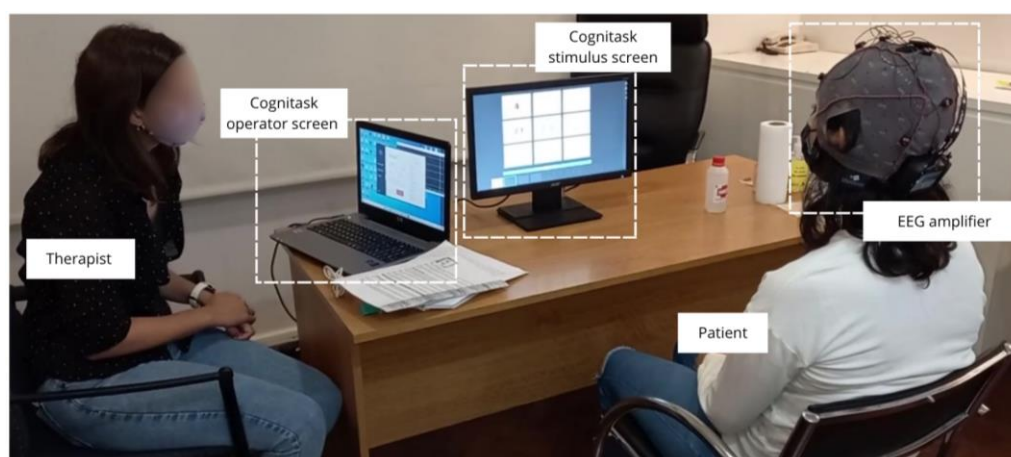
## 2.2. Study Protocol

The study was exploratory and single-arm interventional in design, and was single-blinded. Using convenience sampling, participants were recruited over a restricted 6-month period. The study protocol was approved by the ethics committee of the Fundación Rosarina de NeuroRehabilitación (RENIS IS005256). The inclusion criteria for the participants were: diagnosis of MS according to the McDonald criteria for any of its clinical forms (Relapsing-Remitting, Secondary Progressive or Primary Progressive); age range of 18–60 years; no relapses in the last three months; no corticosteroid treatment in the last month; no changes to treatment during the intervention period; a Snellen visual test score of at least 20/60 with corrected vision; mild to moderate cognitive impairment with an SDMT score less than 44 points, corresponding to a cut-off score of 1.5 standard deviations below the mean [13,34], prior to entering the study and a minimum of twelve years of education. The exclusion criteria were: major psychiatric condition or neurological condition different from MS, seizures; high doses of medication, capable of inhibiting the neuroplasticity or altering the attention of the patient;

<sup>1</sup> <https://www.gtec.at/product/g-nautilus-research/>

uncontrolled high blood pressure, severe heart failure; uncontrolled dyslipidemia or diabetes, obesity; alcohol or drug abuse, excessive smoking; a score on Beck's depression scale equal or higher than 21 points; missing three or more treatment sessions, or two consecutive sessions; difficulty to understand the task; incapability of signing the informed consent.

The study consisted of 16 cognitive rehabilitation sessions, with two sessions carried out per week for eight weeks. In Figure 2 the set up for a session is shown. The duration of each session was between 35 and 45 minutes, depending on the performance and needs of the participant. In each session Cognitask was used. First, the calibration took place as it was previously described. Then, Cognitask was used in the closed-loop stage and three different cognitive tasks were presented to be solved by the participant. These tasks were designed to stimulate different cognitive functions: attention, working memory, executive functions and visuospatial skills.



**Figure 2.** Set-up for a cognitive rehabilitation session with Cognitask.

The tasks had three difficulty levels according to the cognitive demand associated with them. In the first session, all the cognitive tasks were set in the first level. For each participant, the true positive mean rate (TPMR) was calculated weekly by averaging the ratio of correct selections to total selections across the corresponding sessions. Once a participant achieved a TPMR score of more than 50%, they could advance to the next level. Conversely, if they did not reach the required TPMR score, they could level up after four weeks.

### 2.3. Outcomes of the Study

The outcomes of the study were related to the cognitive functions and to the characteristics of the P300 obtained from the EEG signal recorded during the sessions of the intervention.

#### 2.3.1. Cognitive Measures

Cognitive performance was evaluated using the Brief International Cognitive Assessment for MS (BICAMS) battery [35], which consists of three validated measures: the Symbol Digit Modalities Test (SDMT), the California Verbal Learning Test II (CVLT-II), and the Brief Visuospatial Memory Test-Revised (BVRT-R). For these three measures, higher scores indicate superior cognitive performance [13,35]. These measures were acquired at two moments: the day before the therapy began and the day after the intervention.

The SDMT measures information processing speed and sustained attention [35,36]. The score of this test ranges from 0 to 120 [37]. For identifying impaired cognitive performance in pwMS, a cut-off score of 1.5 standard deviations below the mean corresponds to a score equal or less than 44 points [13,34]. A clinically significant change for the SDMT in pwMS is established at an increase of 4 points or a 10% change from baseline [38]. The cognitive measure CVLT-II assesses verbal memory. The outcome measure ranges from 0 to 80. Cognitive impairment is defined by a cut-off score equal or

less than 39 points, corresponding to 1.5 standard deviation below the mean [13,34,35,39]. The BVMT-R evaluates visuospatial memory. This outcome measure ranges from 0 to 36 points. A score equal or less than 17 points is the established cut-off for identifying visuospatial impairment in MS [34,35,39].

### 2.3.2. Quality Of Life Measure

The Multiple Sclerosis International Quality of Life (MusiQoL) questionnaire was used to survey the health-related quality-of-life of the participants [40]. This is a multidimensional, self-administered questionnaire designed specifically for pwMS. This questionnaire has been validated in Spanish. Scores range from 0 to 100. Higher scores suggest that pwMS perceive a better quality of life [40].

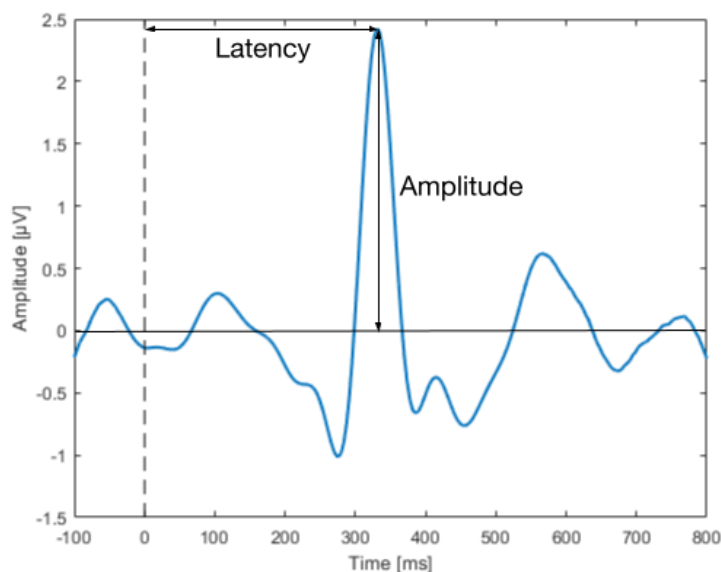
### 2.3.3. P300 Characteristics

For computing the P300 latency and amplitude, the P300 waveforms from the raw EEG signal were obtained. To this end, the calibration data from the first and last session of each subject were processed using the Tuned Residue Iteration Decomposition (t-RIDE) algorithm proposed by De Venuto et al. [41]. The algorithm involves two steps: the first one aims to condition the signal, and the second one obtains the P300 waveforms for each EEG channel [41].

In the first step, the signal is filtered using a lowpass butterworth 6th order filter with a cutoff frequency of 15 Hz. Then, the EEG is segmented into epochs, each ranging from 100 ms before to 800 ms after stimulus onset. Subsequently, an artifact rejection is implemented by setting minimum and maximum thresholds for each EEG channel, computed as four standard deviations below and above the mean, respectively. After this, the epochs are visually inspected to identify possible artifacts that have not been eliminated by the automatic threshold. The first step of the algorithm then involves detrending each epoch, by subtracting its 6th order polynomial fitting from the original epoch. Finally, the mean value of the segment ranging from 100 ms before to the onset of the stimulus is subtracted from the epochs and they were normalized [41].

In the second step, the t-RIDE algorithm is applied. It comprises two sub-steps: Window optimization and Results extraction. The first sub-step consists of applying the Residue Iteration Decomposition (RIDE) algorithm [42] to a virtual channel calculated as the mean between Cz and Pz, iterating over 7 different windows [41]. The first window starts at 250 ms, while the last ends at 600 ms. The P300 peak can occur up to 600 ms after stimulus onset [43], meaning the entire temporal range in which the P300 peak can appear is covered. As a result, the optimal window is identified as the one that allows the highest P300 amplitude. The Results extraction sub-step is carried out by applying the RIDE algorithm to each EEG channel, within the previously determined optimal window [41,42].

Once the P300 waveform was obtained for all channels, the P300 latency and amplitude were calculated based on Cz and Pz. The P300 amplitude was computed as the mean of the maximum positive peaks within a time window between 250 and 600 ms after stimulus onset (Figure 3). The P300 latency was determined as the average time from stimulus onset to these peak amplitudes (Figure 3). In pwMS, it has been observed that P300 latency is increased and amplitude is reduced compared to healthy people [21,44].



**Figure 3.** Depiction of the P300 amplitude and latency determination for the P300 waveform of channel Cz.

### 3. Results

This section presents the results of this exploratory study. In the period of the sampling, 13 pwMS were evaluated and 5 of them met the inclusion criteria. Three of them completed the intervention protocol (age  $51.33 \pm 7.37$  years; 2 female); two dropped out due to issues unrelated to the intervention.

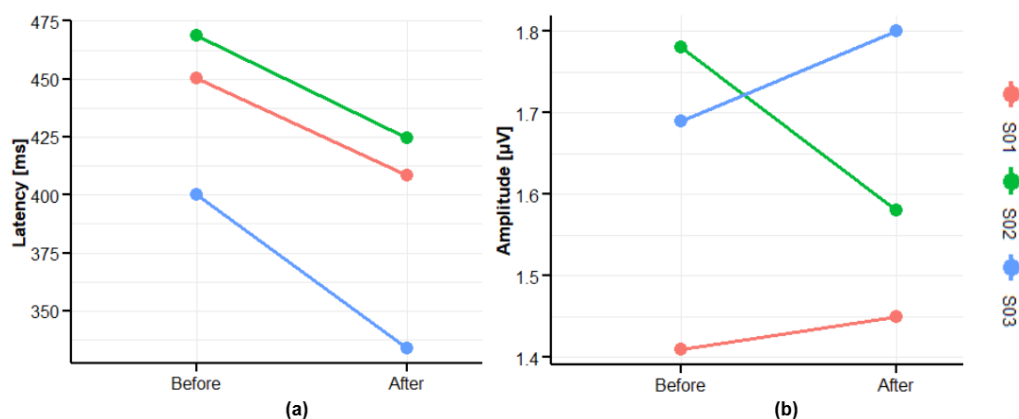
The outcomes of the cognitive measures for the three subjects are shown in Table 1. Most of them exhibited an increase in the scores of the three cognitive tests. Regarding the SDMT, all the participants obtained a higher score after the intervention. The greatest improvement was seen in S01, who showed an increase higher than 10 points. The mean scores of the SDMT across the three subjects were 26 and 35 before and after the intervention, respectively. For the CVLT-II, S01 and S03 improved their score after the intervention, while S02 had the same result. In this test, as in the SDMT, the highest increase was achieved by the first participant. The mean scores of the CVLT-II were 43 before and 52 after the intervention. Finally, for the BVMT-R, S02 and S03 showed a higher score after the intervention. S01 presented a 2 point decrease in this cognitive test. The mean score of the BVMT-R was 21 before the intervention, and remained unchanged after it. With regards to the quality of life, the scores of MUSIQoL after the therapy were higher in two subjects (S01 and S03).

**Table 1.** Cognitive measures before and after the intervention.

Subject	SDMT		CVLT-II		BVMT-R		MUSIQOL	
	Before	After	Before	After	Before	After	Before	After
S01	28	46	45	64	29	27	57.52	66.43
S02	28	34	53	53	21	22	68.51	66.54
S03	23	26	32	39	13	15	71.41	82.72

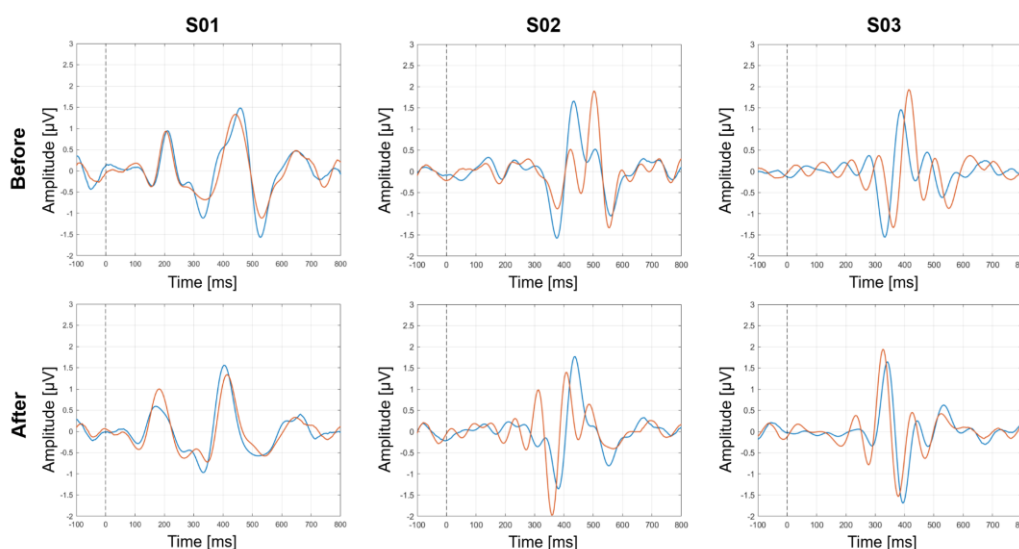
In Figure 4, P300 latency and amplitude for each participant are presented. A decrease in P300 latency was observed. This change was seen in the three subjects in Figure 4a (S01: Before = 450.45 ms, After = 408.26 ms; S02: Before = 468.53 ms, After = 424.33 ms; and S03: Before = 400.22 ms, After = 333.93 ms). The amplitude showed an increase for two subjects as it can be seen in Figure 4b (S01: Before = 1.41  $\mu$ V, After = 1.45  $\mu$ V; and S03: Before = 1.69  $\mu$ V, After = 1.80  $\mu$ V).

In addition, the mean latency of the group decreased 50.89 ms after the intervention (Before = 439.73 ms, After = 388.84 ms). While the mean amplitude values exhibited minimal variation (Before = 1.63  $\mu$ V, After = 1.61  $\mu$ V).



**Figure 4.** (a) Latency and (b) amplitude of the P300 before and after the intervention for each subject. S01, S02 and S03 correspond to colors red, green and blue, respectively.

The P300 waveforms obtained for Cz and Pz electrodes for the first and last session are presented in Figure 5. It was observed that the P300 of Pz was earlier for all the participants after the intervention. An earlier appearance of the P300 peak was observed in Cz after the intervention in S03 and S01. Regarding the P300 amplitude, the three subjects showed an increase in the P300 amplitude in Cz after the intervention. In this electrode, the difference was higher than 10% for S03 (Before = 1.46  $\mu\text{V}$ , After = 1.65  $\mu\text{V}$ ).



**Figure 5.** P300 waveforms for Cz (blue) and Pz (red) electrodes before and after the intervention.

#### 4. Discussion

To our knowledge, this is the first study that explored the effects of a cognitive rehabilitation therapy for pwMS using a P300-based BCI.

In this study, all the participants achieved an improvement higher than 10% in the SDMT. According to Benedict et al. [38], this increase in the SDMT score is considered as a clinically meaningful change in pwMS. In addition, one of them reached a score higher than 44 points, which is the cut-off score established by Beier et al. [34] identifying cognitive impairment in pwMS. These changes suggest that the intervention could have a positive effect on the cognitive performance of the participants. This hypothesis is supported by the fact that most participants achieved higher scores in the CVLT-II and BVMT-R after the intervention. However, no reports were found regarding clinically significant changes of these cognitive measures for pwMS.

The results of MUSIQoL indicate that two subjects perceived a better quality of life. It is interesting to note that the patient S03 who had the lowest scores in the BICAMS battery perceived the higher improvement in their quality of life after the intervention. This could be related to different factors such as level of education, physical or cognitive impairment due to MS or emotional state [45], all of which could have influenced the scores of the measure.

Concerning the P300 characteristics, the mean latency of the group after the intervention evidenced a decrease of 50.89 ms, suggesting a change at a cortical level. It has been reported that pwMS show longer P300 latency compared to healthy controls [21,44,46], although no statistically significant differences were found [46]. This fact has been linked to the slowing of information processing caused by the demyelination process in pwMS, which could be indicated by a delayed P300 [46].

With regards to the P300 amplitude, two participants (S01 and S03) showed an increase of this characteristic after the intervention. For pwMS, a reduced P300 amplitude was found [21,44]. A study using magnetic resonance imaging demonstrated that abnormally low P300 amplitude is associated with cortical volume loss in pwMS. On the other hand, P300 amplitude has been related to the amount of attentional resources involved in the resolution of a task [27]. Thus, the reason for the improvement seen in this study is unclear, and further research is needed to address this.

In line with existing literature, the correlation between improved cognitive measures and P300 characteristics suggests that the P300 may be an indicator of cognitive function in pwMS [44]. However, the present study has limitations that prevent us from generalising our findings. Firstly, this was a single-arm study without a control group and with recruitment restricted to a short period of time. This resulted in a small sample size, which was further reduced when two participants withdrew from the study. Although they dropped out for personal reasons, adverse events were not monitored in this study. In addition, the results presented in this study could be reinforced by employing imaging techniques or EEG analysis with topographical maps.

The approach presented here serves as a foundation for future innovations, contributing to the creation of systems that enhance the quality of life for pwMS.

**Author Contributions:** Conceptualization, C.T. and L.C.; methodology, C.T. and L.C.; software, C.T. and L.C.; formal analysis\_ A.B. and L.C, A.B. and L.C.; investigation, M.C.S. and F.C.; resources, C.B.; data curation, A.B.; writing—original draft preparation, A.B.; writing—review and editing, L.C. and C.T.; visualization, A.B.; supervision, L.C.; project administration, C.T.; funding acquisition, C.B. All authors have read and agreed to the published version of the manuscript.

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**Institutional Review Board Statement:** The study was conducted in accordance with the Declaration of Helsinki, approved by the Ethics Committee of the Fundación Rosarina de Neurorehabilitación (Rosario, Santa Fe, Argentina) and registered at the Registro Nacional de Investigaciones en Salud (RENIS), code: IS005256.

**Informed Consent Statement:** Informed consent was obtained from all subjects involved in the study.

**Data Availability Statement:** The data presented in this study are available on request from the corresponding author.

**Conflicts of Interest:** The authors declare no conflicts of interest.

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