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ORIGINAL ARTICLE

Motor reaction time and accuracy in patients with multiple sclerosis: effects of an active computerized training program

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Abstract

In this study, we aimed to determine the difference of motor reaction time and accuracy between the patients with moderate multiple sclerosis (MS) and healthy subjects and to determine whether a specified cognitive-motor training can improve the speed and accuracy of information processing in patients with MS. A total of 205 patients (30% males) and 276 age-/gender-matched healthy subjects (31% males) were included in the study. Furthermore, using a stratified randomization method, patients with MS were randomly assigned to one of two groups: active information processing training (AIPT) ($n = 49$) or post-control ($n = 55$). The AIPT group was asked to complete a computerized visual-manual training program and the post-control group asked to complete the same task without an increase in difficulty. Before and after the intervention phase, the simple, choice, and semantic reaction times and accuracies of all participants were evaluated using the VLS measurement battery. Our results demonstrated that the case and control group were significantly different in terms of the simple, choice, and semantic motor reaction times and accuracies. Compared with the pre-intervention phase, the AIPT and control group's performances in the post-intervention phase were considerably improved in simple, choice, and semantic motor reaction times and choice and semantic motor reaction accuracies. The results also showed that the AIPT group performed significantly better than the post-control group in terms of simple and choice motor reaction times. We showed the positive effects of training on the performance of patients with MS in motor reaction time and accuracy.

Keywords Multiple sclerosis · Motor reaction time · Motor reaction accuracy · Visual-manual training program

Introduction

Multiple sclerosis (MS) is a neurodegenerative disease in which the demyelination of insulating covers of neurons in the brain and spinal cord reduces the transmission speed of the neural signals and ultimately causes the death of the neurons [1]. It was estimated that as of 2010, 2–2.5 million (approximately 30 per 100,000) people were affected by MS globally, with rates varying widely in different regions, as the highest and the lowest incidence were reported in Europe and Africa, respectively [2].

At present, the most important theory of MS pathology is the theory that considers MS as an autoimmune disorder, in which the immune system attacks and destroys the myelin sheaths of the neurons [3]. Genetic factors have also been found to influence MS pathogenesis susceptibility [4]. Besides, increasing evidence suggests the role of environmental risk factors for MS. For example, latitude gradient, vitamin D deficiencies, viral infections, and cigarette smoking have been demonstrated to contribute to the causation of the disease [5].

People with MS tend to have their early signs and symptoms between the second and third decades of their life. Usually, the symptoms get better, but then they come back. Some come and go, while others remain. The most common early clinical symptoms are optic neuritis, numbness and tingling, bladder and bowel problems, clumsiness or lack of coordination, emotional changes and depression,

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fatigue, and heat-related problems [6]. As the disease progresses, the patients face more severe problems, such as the inability to empty the bladder and urinary tract infections, inability to walk and a reduction in muscular tone and mass, and severe depression and cognitive problems [6].

Among the motor-cognitive symptoms, slow information processing and motor response speed are prevalent impairments in MS, occurring in 22–25% of patients [7]. In earlier studies in this field, Demaree et al. demonstrated that patients with MS have a considerably slower speed of auditory and visual information processing relative to healthy controls [8]. They reported that with an adequate amount of time to process information, the patients perform similarly to controls. Libon et al. showed a slowed processing speed and deficient decision making in relapsing-remitting MS [7] and Binétruy et al. demonstrated slowing of information processing speed in MS [9].

On the other hand, studies have also indicated a decrease in motor speed and motor learning capacity in MS patients [10]. However, whether the low speed of motor responses is associated with the decreased speed of information processing is still not clear. While D'Orio et al. reported that slower processing speed predicts slower gait speed in MS-affected individuals [11] and Almuklass et al. argue that motor speed in persons with MS is considerably reduced [12], Binétruy et al. demonstrated that slowed information processing in patients with MS may be observed without motor slowing [9].

Meanwhile, the effectiveness of some cognitive training strategies on improving information processing speed has been suggested by some studies. For example, Juntorn et al. indicated that an intervention strategy, based in the perceive-recall-plan-perform (PRPP) system combined with the four-quadrant model (4QM), may improve the participants' information processing speed and ability [13]. Also, evidence has suggested that training strategies such as bilateral object manipulation may promote motor reacting speed [14].

In this study, we pursued two goals: first, to determine the difference between the motor speed and accuracy between patients with MS and healthy subjects; and second, to determine whether a specified cognitive-motor training can improve motor speed and accuracy of patients. Obviously, the results of this study can bring the importance of cognitive-motor training into attention to improve the speed and accuracy of information processing and motor responses in patients with MS and increase the hope for designing effective methods in the future. In addition, the results of this study will show to a certain extent whether cognitive information processing and motor responses are performed separately or through an integrated process.

Materials and methods

Pre-intervention phase

Participants

A total of 205 patients with MS (63 males and 112 females; mean age = 32.76 ± 4.11) who had been diagnosed with the disease for at least 2 years were evaluated by two neurologists using EDS scale (expanded disability status scale). Only the patients who scored 3 to 7 in the EDS scale, and the severity of their disease determined moderate by the two neurologists, were included in the study. According to their reports, patients did not have any other neurological or mental disorders. Using convenience sampling, 276 mentally and physically healthy subjects (87 males and 189 females; mean age = 32.04 ± 4.63) were selected as the control group. None of the participants were addicted to drugs or alcohol and they all participated in the study with informed consent.

Assessment

The motor reaction time and accuracy of all participants were evaluated using the VLS measurement battery, which was used by Hultsch et al. with a purpose nearly similar to the aim of this study [15].

In the simple motor reaction time (simple MRT) task, participants were instructed to press a key as quickly as possible when the signal stimulus appeared followed by a warning stimulus in the middle of the screen. For choice motor reaction time (choice MRT) task, a 3 × 3 grid arranged according to the keys on the response board was displayed on the screen. One cell contained an O and the other eight cells contained Xs. The participants were asked to press the key corresponding to the location of the O cell.

In the semantic motor reaction time (semantic MRT) task, participants were instructed to judge as quickly as possible the believability of the sentences presented on the screen (e.g., the crash of the two cars caused a loud noise vs our domestic cat flew this morning and left our house). It was necessary for the participant to press a certain button in the face of the plausible sentence and press a different button in the face of an implausible sentence.

In each measurement, the participants first were trained with 10 trials and then were evaluated with 30 trails. Responses were recorded at an accuracy of minus or plus 1 ms. In addition to the reaction time, the motor response scores (MRS) of the participants were also recorded in each test.

Post-intervention phase

Participants

This step of investigation involved a blinded, placebo-controlled design. Using a stratified randomization method, patients with MS were randomly assigned to one of two groups: active information processing training ($n = 49$) or post-control ($n = 55$). The active training (AIPT) group was asked to complete a computerized visual-manual training program that specifically aimed to improve information processing speed.

Intervention

The visual-manual task required a manual response to a visual stimulus. The visual stimuli were gray-scale two faces with similar hair color, skin tone, and facial expression, and presented on a gray background. Subjects responded to each face with a distinct button press using the right index or the middle finger. The visual stimuli were each presented for 200 ms. After every three 30-min sessions, a face was added to the number of faces, so that after 9 sessions, the number of faces reached 5, and it was necessary for the person to press a different button by seeing each face. The entire training intervention consisted of 12 sessions held 1 day in a row.

The post-control group was asked to complete a computerized training program that was almost identical to the active training group, but this program did not aim to improve information processing speed. This latter program employed the same tasks as the former, but it did not increase in difficulty in order to challenge participants to improve.

One week after the end of the intervention period, individuals of both groups were re-evaluated using the same tests applied in the pre-intervention phase.

Data analysis

The female/male ratio was compared between the case and control group using Fisher's exact test. The data distribution was evaluated by the Shapiro-Wilk test. According to the distribution of data, the parametric paired and independent *t* test or the non-parametric Wilcoxon or Mann-Whitney U test was used to compare the scores between the case and control group and also between the pre-intervention and post-intervention phases.

Results

Pre-intervention stage

The evaluation of the obtained data using the Shapiro-Wilk test showed that none of the data sets had a normal distribution. Comparison of the female/male ratio between the case (142/63) and control group (189/87) using Fisher's exact test did not show a significant difference (p value = 0.921) (Fig. 1a). Also, comparison of the mean age of the two groups using the Mann-Whitney U test did not show a significant difference (case, $32.76 \pm 4.11 \neq$ control, 32.04 ± 4.63; $Z = -1.920$, p value = 0.055) (Fig. 1b).

The Mann-Whitney U test results showed that the case and control group were significantly different in terms of simple MRT ($385.53 \pm 35.63 \neq 350.97 \pm 36.44$; $Z = -10.69$, p value < 0.001), choice MRT ($700.02 \pm 39.70 \neq 547.33 \pm 29.18$; $Z = -18.58$, p value < 0.001), semantic MRT ($874.53 \pm 35.63 \neq 795.73 \pm 29.18$; $Z = -17.38$, p value < 0.001) (Fig. 2a), simple MRS ($26.30 \pm 2.53 \neq 27.36 \pm 1.75$; $Z = -4.56$, p value < 0.001), choice MRS ($23.47 \pm 2.75 \neq 26.36 \pm 1.75$; $Z = -11.16$, p value < 0.001), and semantic MRS ($23.30 \pm 2.53 \neq 25.41 \pm 1.84$; $Z = -8.84$, p value < 0.001) (Fig. 2b).

Post-intervention evaluation

The evaluation of the post-intervention which obtained data using the Shapiro-Wilk test showed that none of the data sets had a normal distribution. Comparison of the female/male ratio between the AIPT (36/13) and post-control group (45/10) using the Fisher's exact test did not show a significant difference (p value > 0.05) (Fig. 3a). Comparison of the mean age of the two groups using the Mann-Whitney U test did not show a significant difference (intervention, $32.48 \pm 4.17 \neq$ control, 31.71 ± 3.76; $Z = -0.839$, p value = 0.402) (Fig. 3b).

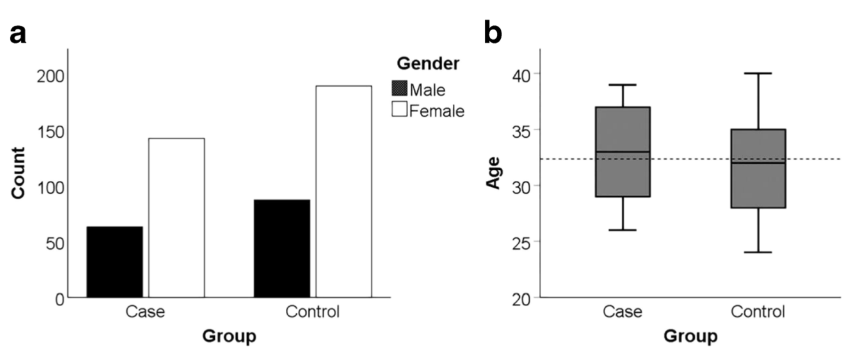


Fig. 1 **a** The number of females and males in each group. **b** Distribution of age data between two groups (the dashed line represents the total mean)

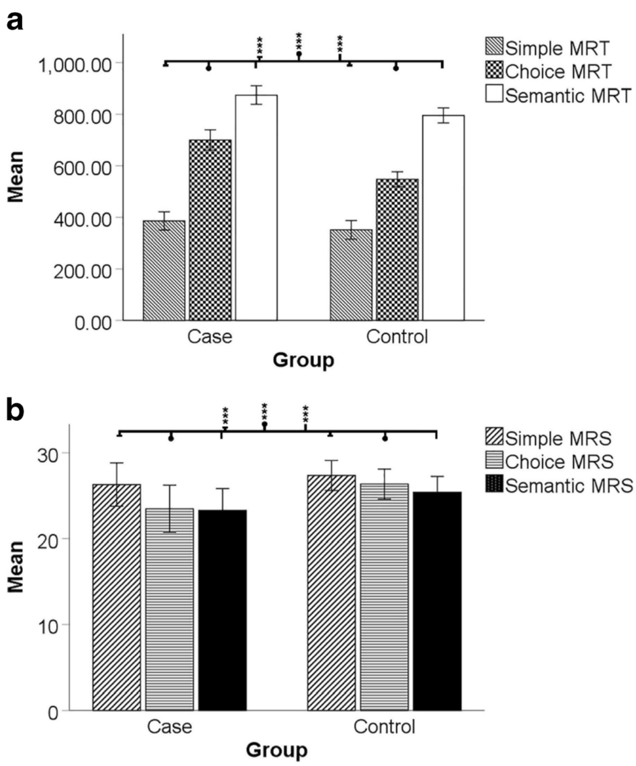


Fig. 2 **a** Comparison of the simple, choice, and semantic motor reaction times between the two groups. **b** Comparison of the simple, choice, and semantic motor response scores between the two groups. (* = p value < 0.05; ** = p value < 0.01; and *** = p value < 0.001)

The Wilcoxon test results showed that compared with the pre-intervention phase, the AIPT group's performance in the post-intervention phase was considerably improved in simple MRT (pre-intervention, 369.38 ± 15.42 ≠ post-intervention, 341.07 ± 16.75; $Z = -6.093$, p value < 0.001), choice MRT (pre-intervention, 654.61 ± 28.62 ≠ post-intervention, 542.59 ± 28.44; $Z = -6.083$, p value < 0.001), semantic MRT (pre-intervention, 830.07 ± 16.75 ≠ post-intervention, 795.71 ± 30.83; $Z = -5.098$, p value < 0.001) (Fig. 4a), choice MRS (pre-intervention, 23.76 ± 2.83 ≠ post-intervention, 28.51 ± 2.63; $Z = -5.210$, p value < 0.001), and semantic MRS (pre-intervention, 23.39 ± 2.44 ≠ post-intervention, 27.31 ± 1.58; $Z = -5.753$, p value < 0.001) (Fig. 4b).

Interestingly, the Wilcoxon test results showed that similar to the AIPT group, the post-control group's performance in the post-intervention phase was considerably improved in simple MRT (pre-intervention, 376.27 ± 5.85 ≠ post-intervention, 353.98 ± 37.04; $Z = -3.620$, p value < 0.001), choice MRT (pre-intervention, 689.95 ± 5.73 ≠ post-intervention, 559.70 ± 35.50; $Z = -6.452$, p value < 0.001), semantic MRT (pre-intervention, 865.27 ± 5.85 ≠ post-intervention, 804.46 ± 30.88; $Z = -6.426$, p value < 0.001) (Fig. 4a), choice MRS (pre-intervention, 22.93 ± 2.66 ≠ post-intervention, 27.73 ± 2.99; $Z = -5.779$, p value < 0.001), and semantic MRS (pre-intervention, 22.85 ± 2.57 ≠ post-intervention, 26.53 ± 2.56; $Z = -5.379$, p value < 0.001) (Fig. 4b) compared with the pre-intervention phase.

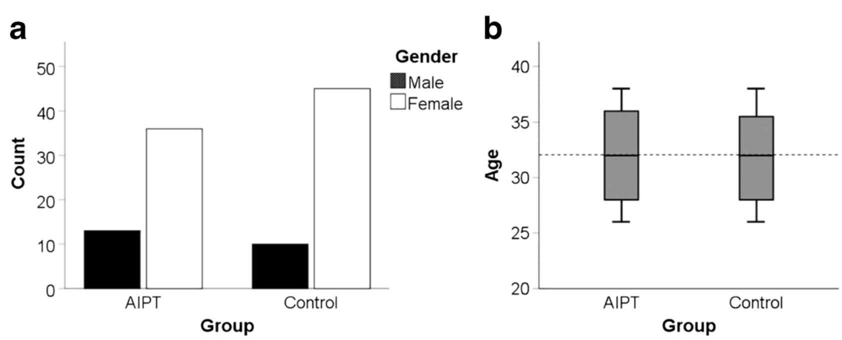
The results also showed that the performances of the AIPT and post-control group before the intervention were not significantly different, while their performances after the intervention were significantly different in terms of simple MRT (AIPT, 369.38 ± 15.42 ≠ control, 353.98 ± 37.04; $Z = -2.237$, p value = 0.025) and choice MRT (AIPT, 542.59 ± 28.44 ≠ control, 559.70 ± 35.50; $Z = -3.344$, p value = 0.001) (Fig. 4a).

Discussion

Evidence suggests that the speed of information processing and motor response is considerably reduced in patients with MS. In this study, we showed that in simple, choice, and semantic motor reaction time (MRT) and motor reaction accuracy (MRS) tests, healthy subjects have faster reaction time and greater response accuracy than those with MS, respectively. The reduction in reaction time in MS patients has been shown in numerous studies.

In one of the early studies, Jennekens-Schinkel et al. reported that simple and disjunctive reaction time, before and after the prolonged effort, was considerably longer in MS than in control subjects [16]. They argued that the longer reaction times in MS patients were related to disease severity and to the simultaneous presence of cerebellar, brainstem, and/or pyramidal signs. Reicker et al. showed that patients with MS

Fig. 3 **a** The number of females and males in each group. **b** Distribution of age data between the two groups (the dashed line represents the total mean)



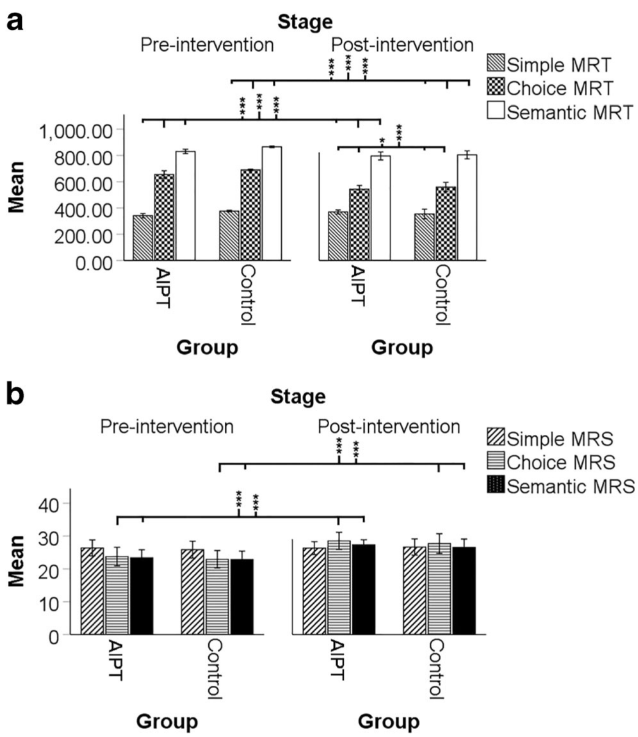


Fig. 4 **a** Comparison of the simple, choice, and semantic motor reaction times between the AIPT and post-control group, in the pre-intervention and post-intervention phases. **b** Comparison of the simple, choice, and semantic motor response scores between the AIPT and post-control group, in the pre-intervention and post-intervention phases. (* = *p* value < 0.05; ** = *p* value < 0.01; and *** = *p* value < 0.001)

respond significantly slower than healthy controls in a computerized test of information processing and by increasing the difficulty of the test, the difference in reaction time increases between the two groups [17]. They concluded that longer response time in MS patients was relevant to the lower information processing speed, which is in line with our results. More recently, Barr et al. have reported increased hand and foot simple reaction time in MS patients, due to their pathologic elevated levels of fatigue [18].

In the second phase, patients with MS were divided into the two groups: the active training (AIPT) group which was trained using a computerized visual-manual training program aimed to improve information processing speed, and the post-control group which was asked to complete the same training program that was almost identical to the active training group, but with no gradual increase in difficulty. The results showed that compared with the pre-intervention phase, the AIPT group's performance in the post-intervention phase was considerably improved in simple, choice, and semantic MRT, and also in choice and semantic MRS.

In this line, studies have shown that cognitive- and motor-specific training can improve reaction time. In 1992, Madanmohan et al. demonstrated that yoga training can significantly reduce visual and auditory reaction times in healthy young adults [19]. In 2000, Dean et al. suggested that task-related circuit training may improve locomotor performance in chronic stroke [20]. In 2001, Osborne et al. indicated that muscle onset latency decreases in specific injured muscles after an 8-week training program [21] and more recently, in 2017, Flachenecker et al. showed that reaction times of alertness were significantly decreased in MS patients followed by a 2-week neuropsychological training program [22].

Interestingly, we also found that similar to the AIPT group, the post-control group's performance in the post-intervention phase was considerably improved in simple, choice, and semantic MRT, and choice and semantic MRS, compared with the pre-intervention phase. In fact, in our study, it became clear that even a simple and regular training program could reduce motor reaction time and increase motor accuracy of the patients with MS. This could be due to increased use of neural circuits involved in motor responses and repairing damaged circuits following neuropsychological training. Studies have confirmed that particular exercises can enhance neuroplasticity in motor and cognitive circuits in patients with Parkinson's disease [23], and those injured by stroke [24]. Neuropsychological rehabilitation programs have also been suggested to induce neuroplasticity in motor circuits [25].

Finally, we investigated that the post-intervention performances of the AIPT and post-control group were significantly different in terms of simple and choice MRT. This suggests that exercises that gradually increased difficulty only lead to improved motor reaction time and has no effect on the speed and accuracy of semantic information processing. It might be said that the design of the training program was in such a way targeted only simple processes, and when the processing became complex and needed to use various mental and motor processes, the training program had no significant effect on improving the performance of individuals. As studies have shown that cognitive and motor information processing can be done separately at low levels, but at a complex level, they are processed in an integrated manner [26].

In conclusion, in this study, we demonstrated that patients with MS react more slowly and with less accuracy than healthy subjects. Furthermore, we investigated that our active and routine motor reaction time/accuracy training programs significantly improved simple, choice, and semantic MRT, and choice and semantic MRS in the both AIPT and post-control groups. Moreover, we investigated that the AIPT group did significantly better in terms of simple and choice MRT than the post-control group. Therefore, it seems that training programs can improve reaction time/accuracy in simple performances, but it does not affect complex functions and this can be due to the separation of cognitive and motor functions at lower levels and their integration at the higher complicated levels.

However, this study, similar to all experimental studies, had some limitations, and perhaps the most important limitation of this study was a low population in the intervention phase. It is advisable to use a variety of tests to measure the speed and accuracy of the patients in future studies and to evaluate the impact of different training programs on improving patients' performance. In addition, considering the subtype of the disease can lead to even better results. On the other hand, functional imaging studies can reveal the fact that training affects the function of which parts of the brains.

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