Virtual Reality-Based Cognitive–Motor Rehabilitation in Older Adults with Mild Cognitive Impairment: A Randomized Controlled Study on Motivation and Cognitive Function

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Abstract: The purpose of this study was to investigate the effects of virtual reality-based cognitive–motor rehabilitation (VRCMR) on the rehabilitation motivation and cognitive function in older adults. This study enrolled 40 older adults with mild cognitive impairment (MCI), living in the community. The subjects were randomly assigned to a VRCMR group (n = 20) or a conventional cognitive rehabilitation (CCR) group (n = 20). The VRCMR group underwent VRCMR using MOTOcog, a computer recognition program, whereas the CCR group underwent conventional cognitive rehabilitation, which included puzzles, wood blocks, card play, stick construction activity, and maze activity. Both interventions were performed 30 min per day, 5 days/week, for 6 weeks. This study performed a cognitive assessment using the Montreal Cognitive Assessment (MoCA) scale, Trail Making Test A and B (TMT-A/B), and Digit Span Test forward and backward (DST-forward/backward). In addition, a 0-to-10 numeric rating self-report scale was used to assess interest and motivation during the rehabilitation training. After the intervention, the VRCMR group showed a significantly greater improvement in the MoCA (p = 0.045), TMT-A (p = 0.039), TMT-B (p = 0.040), and DST-forward (p = 0.011) scores compared to the CCR group, but not in the DST-backward score (p = 0.424). In addition, subjects in the experimental group had significantly higher interest (p = 0.03) and motivation (p = 0.03) than those in the control group. Cohen’s d effect size was 0.4, 0.3, 0.35, 0.4, and 0.5 for the MoCA, TMT-A, TMT-B, DST-forward, and DST-backward tests, respectively. This study demonstrates that VRCMR enhances motivation for rehabilitation and cognitive function in older adults with MCI better than CCR.

Keywords: virtual reality; motivation; cognitive function; mild cognitive impairment

1. Introduction

Mild cognitive impairment (MCI) has been identified as a preclinical stage of dementia and is an important predictive risk factor for dementia [1]. Although the conversion rate to dementia in patients with MCI varies depending on diagnostic criteria and evaluation tools, it is estimated at 10–15% per year [2]. This is significantly higher than the conversion rate of 1–2% in normal adults over 65 years of age [3,4]. MCI is not an obvious pathological condition but is important in terms of early intervention, in that it can be objectively or clinically determined and indicates a pathological change [5].
Attention and memory are important cognitive functions in elderly adults, which significantly decline with the development of dementia [6]. A decrease in cognitive function is related to decreased self-esteem, depression, and impaired ability to perform daily activities in elderly adults with MCI. The better the cognitive function, the higher the self-esteem, and the worse the cognitive function and self-esteem, the more severe the depression [7]. Therefore, cognitive rehabilitation therapy is important to maintain and improve cognitive function in elderly adults with MCI.

Conventional cognitive rehabilitation (CCR) is a somewhat ambiguous term that encompasses mostly tabletop activities (e.g., puzzles, wood blocks, card play, stick construction activity, and maze activity) that have long been used in rehabilitation departments to improve memory, attention, performance, and problem-solving ability of patients with cognitive impairment [8–10]. However, when using CCR, it is difficult not only to systematically evaluate patients’ cognitive level but also to induce interest and motivation for rehabilitation. In order to overcome these limitations, computer-based cognitive rehabilitation has been developed, and several studies have found it to be effective in improving the cognitive function of patients with neurological disorders and dementia and of older adults [11–13]. This therapeutic modality not only can systematically adjust the difficulties of the activities according to the cognitive level of the patient, but also has the advantage of using a variety of cognitive rehabilitation programs. Computer-based cognitive rehabilitation is fundamentally different from CCR because it is static and simple in terms of training, including simply remembering, recalling, and calculating words, numbers, and pictures.

Recently, with the advancement of IT technology, virtual reality-based cognitive rehabilitation (VRCR) has been proposed [14,15]. VR facilitates the creation of a multisensory, dynamic, interactive virtual environment with a great similarity to real life [16]. In addition, VRCR is intuitive, interesting, and fun, promoting active participation by enhancing motivation for rehabilitation [17,18]. Several studies have reported that the application of exergame increases the motivation of the elderlies [19] and helps improve the cognitive function in MCI patients [20]. Nevertheless, research on VRCR therapy is lacking, and its effects are not clear. Furthermore, it is important to introduce new methods of VRCR therapy and prove their effectiveness due to the continuous development of IT technology. Therefore, in this study, we introduce VR-based cognitive–motor rehabilitation (VRCMR) and describe its effects on the cognitive function and motivation of older adults with MCI.

2. Materials and Methods

2.1. Participants

This study enrolled 40 older adults with MCI living in the community. The inclusion criteria were as follows: diagnosed with MCI through clinical examination by a neurologist, age > 65 years, Mini-Mental State Examination score > 16 (mean score; VRCMR group = 15.1 ± 2.1, CCR group = 15.5 ± 1.9), no limitation in the upper extremity ranges of motion, fair grade on manual muscle testing of upper extremity, ability to grip objects with various forms (cylindrical, spherical, and power grip), ability to follow the study instructions, independence in daily activities, ability for adequate communication, no history of neurological disorders, including stroke, no history of visual perception deficits, and consent to participate actively. The exclusion criteria were as follows: unstable medical problems, history of psychiatric disorders, severe communication difficulties, problem with visual and auditory functions (e.g., color blindness, hearing impairment).

2.2. Ethics

The objectives and requirements of the study were explained to all participants, who voluntarily signed an informed consent form. Ethical approval was obtained from the Seoul medical center Institutional Review Board prior to study commencement (SEOUL2019-09-002-001).
2.3. Sample Size Estimation

The sample size was calculated using G-power 3.1.9.3 software (University of Dusseldorf, Dusseldorf, Germany). The power and alpha levels were set at 0.80 and 0.05, respectively, and the effective size was set at 0.9. According to a prior analysis, each group required at least 16 subjects. Therefore, 20 participants in each group were enrolled, considering possible dropouts.

2.4. Study Design and Procedures

The study was conducted in two groups of subjects on a 6-week schedule. Subjects were randomly assigned to either the VRCMR group ($n = 20$) or the CCR group ($n = 20$) using blocked randomization after taking baseline measures. Allocation was concealed using sealed opaque envelopes. All experimental procedures were performed by occupational therapists with more than 8 years of clinical experience. Figure 1 shows the flow diagram for this study.

![Flow diagram for this study.](image)

VRCMR was performed using the MOTOCOG® system (Cybermedic Inc., Gwangju, Gwangju, Korea). This equipment was developed specifically for the purpose of VRCMR therapy. It includes a software that uses VR for performing activities such as driving, bathing, cooking, and shopping, enabling attention, memory, problem-solving, and executive training. The hardware consists of a touchscreen monitor, grip air bulb, and various joysticks or attachments (e.g., thumb pinch, doorknob, button, gas valve, tool turn, steering wheel). Thus, preserved ranges of motion and strength of the upper limbs are required for continuous manipulation of the grip air bulb and various joysticks or attachments.
in relation to the realistic environment (Figure 2). VRCMR sessions were conducted 30 min per day, 5 days/week, for 6 weeks by two experienced occupational therapists.

![Figure 2](image)

**Figure 2.** Virtual reality-based cognitive–motor rehabilitation. (A) After entering the bathroom, personal hygiene; (B) driving; (C) door opening; (D), shampoo; (E) attachable handles in various forms; (F) virtual reality-based cognitive–motor rehabilitation using Motocog.

CCR was performed with tabletop activities, including puzzles, wood blocks, card play, stick construction activity, maze and pencil–paper with table activities. The selection and level of tasks and training programs were chosen by experienced occupational therapists to match the patient’s cognitive function. CCR sessions were performed 30 min per day, 5 days/week, for 6 weeks.

### 2.5. Outcome Measurement

The following tests with proven sensitivity, validity, and reliability were used for cognitive function evaluation: Montreal Cognitive Assessment (MoCA) [21], Trail Making Test A and B (TMT-A/B) [22], and Digit Span Test forward and backward (DST-forward/backward) [23].

Evaluations were performed immediately before the start of the intervention (pre-training) and after 6 weeks of intervention (post-training). A 0 to 10 numeric rating self-report scale (NRSS) was used to assess the interest and motivation of the subjects during training [24]. The subjects completed the questionnaire after each training, and the average of all scores was calculated. Higher scores indicated higher interest and motivation for rehabilitation.

### 2.6. Statistical Analysis

All statistical analyses were performed using SPSS 15.0 software (SPSS Inc., Chicago, IL, USA). Descriptive statistics are presented as means with standard deviations. The Shapiro–Wilk test was used to check the normality of the outcome variables. To evaluate the training effects, the paired t-test was used to compare measures before and after the intervention in each group. The independent t-test was used to compare post-intervention values and changes in outcome measures between the two groups. The significance level was set at $p < 0.05$. In addition, the effect sizes (Cohen d) of the changed
scores between the two groups were calculated. An effect size of 0.2, 0.5, and 0.8 represented a small, moderate, and large effect, respectively.

3. Results

3.1. Subjects’ Characteristics

A total of 40 older adults with MCI were enrolled. There were no significant differences between the groups based on general characteristics, MoCA ($p = 0.460$), TMT-A ($p = 0.83$), TMT-B ($p = 0.35$), DST-forward ($p = 0.50$), and DST-backward ($p = 0.75$) scores. Thirty-five of the 40 subjects completed the study; 5 subjects (VRCMR group [$n = 2$] and CCR group [$n = 3$]) dropped out due to refuse or poor participation rate. Therefore, 35 subjects were included in the analysis (Table 1).

Table 1. Demographic characteristics of the patients.

|                     | VRCMR Group ($n = 18$) | CCR Group ($n = 17$) |
|---------------------|------------------------|----------------------|
| Number of subject   | 18                     | 17                   |
| Gender (man/woman)  | 10:8                   | 7:10                 |
| Age (year)          | 75.8 ± 8.5             | 77.2 ± 7.2           |
| Educational level   | Uneducated             | 2                    |
|                     | Elementary school      | 13                   |
|                     | Middle School          | 2                    |
|                     | High school            | 1                    |
|                     | University             | 0                    |

3.2. Cognitive Function Evaluation

Based on within-group comparisons (pre-training vs. post-training), the VRCMR group showed a statistically significant improvement in the MoCA, TMT-A, TMT-B, DST-forward, and DST-backward scores ($p < 0.001$, all). In contrast, the CCR group showed statistically significant improvement in the MoCA ($p = 0.047$), DST-forward ($p = 0.029$), and DST-backward ($p = 0.008$) scores but not in the TMT-A ($p = 0.079$) and TMT-B ($p = 0.060$) scores (Table 2).

Table 2. Changes in cognitive function after intervention.

|                  | VRCMR Group ($n = 18$) | CCR Group ($n = 17$) | Between Groups p-Values |
|------------------|------------------------|----------------------|------------------------|
| MoCA             | Before Intervention    | 17.7 ± 3.4           | 20.9 ± 3.4            | 0.001* | 17.8 ± 2.4 | 18.3 ± 3.0 | 0.047* | 0.045 † |
|                  | After Intervention     |                      |                       |       | 18.3 ± 3.0| 0.047*     |         |         |
| TMT—A            | Before Intervention    | 72.2 ± 4.4           | 65.1 ± 4.4            | 0.001* | 69.6 ± 4.3| 68.6 ± 4.6 | 0.079 | 0.039 † |
|                  | After Intervention     |                      |                       |       | 68.6 ± 4.6| 0.079     |         |         |
| TMT—B            | Before Intervention    | 152.3 ± 9.1          | 144.4 ± 7.7           | 0.001* | 154. ± 10.9| 152.3 ± 11.2 | 0.060 | 0.040 † |
|                  | After Intervention     |                      |                       |       | 152.3 ± 11.2| 0.060   |         |         |
| Digit Span Test  | Before Intervention    | 3.1 ± 0.8            | 4.7 ± 0.8             | 0.001* | 3.2 ± 0.8 | 3.7 ± 0.9 | 0.029* | 0.011 † |
|                  | After Intervention     |                      |                       |       | 3.7 ± 0.9 | 0.029*    |         |         |
| DST—forward      | Before Intervention    | 2.0 ± 0.7            | 2.6 ± 0.7             | 0.001* | 2.0 ± 0.5 | 2.4 ± 0.6 | 0.008* | 0.424   |
|                  | After Intervention     |                      |                       |       | 2.4 ± 0.6 | 0.424     |         |         |

Values are expressed as mean ± standard deviation; VRCMR: Virtual reality-based cognitive–motor rehabilitation. CCR: conventional cognitive rehabilitation. * $p < 0.05$ by paired t test, † $p < 0.05$ by independent t test.

Based on the between-group post-training comparison, the VRCMR group showed greater improvement than the CCR group in the MoCA ($p = 0.045$), TMT-A ($p = 0.039$), TMT-B ($p = 0.040$), and DST-forward ($p = 0.011$) scores, but not in the DST-backward ($p = 0.424$) (Table 2).

Regarding the amount of change in both groups, significant differences were observed in the MoCA ($p < 0.001$), TMT-A ($p < 0.01$), TMT-B ($p = 0.009$), DST-forward ($p < 0.001$) scores, but not in the DST-backward ($p = 0.468$) score (Table 3). Cohen’s d effect size was 0.4, 0.3, 0.35, 0.4, and 0.5 for the MoCA, TMT-A, TMT-B, DST-forward, and DST-backward tests, respectively (Table 3).
Table 3. Comparison of improvement after the intervention in the two groups.

|                           | VRCMR Group | CCR Group | p-Value | Cohen's d |
|---------------------------|-------------|-----------|---------|-----------|
| Δ Montreal Cognitive Assessment | 3.21 ± 0.89 | 0.50 ± 0.85 | <0.001 † | 0.8       |
| Δ Trail Making Test       | -7.14 ± 1.70 | -1.00 ± 1.96 | <0.001 † | 0.135     |
| Δ Trail Making Test-B     | -7.93 ± 6.67 | -2.14 ± 3.90 | 0.009 †  | 0.6       |
| Δ Digit Span Test-forward | 1.57 ± 0.75  | 0.50 ± 0.76  | <0.001 † | 1.19      |
| Δ Digit Span Test-backward | 0.57 ± 0.51 | 0.43 ± 0.51  | 0.468  | 0.2       |

Values are expressed as mean ± standard deviation; † p < 0.05 by independent t test.

3.3. Interest and Motivation Evaluation Using NRSS

The average scores for interest and rehabilitation motivation were 6.07 and 7.14 points in NRSS, respectively, for the VRCMR group, and 3.64 and 3.50 points in NRSS, respectively, for the CCR group. Based on the between-group comparison, the subjects in the VRCMR group had significantly higher interest and rehabilitation motivation than those in the CCR group (p < 0.001, both) (Figure 3).

4. Discussion

VR has been applied in various ways in the rehabilitation area, including for cognitive rehabilitation, because it has the advantage of providing fun, interest, and real-time feedback [25]. This study examined the effects of a new VRCR method, VRCMR, on the cognitive function of older adults with MCI. Our results indicate that VRCMR was more effective in improving the cognitive function of these subjects than CCR. There are several possible explanations for these findings. In this study, an NRSS
was used to evaluate the subjects’ interest and motivation for training. The VRCMR group yielded significantly higher scores than the CCR group, indicating that the program offered was more fun and interesting, resulting in increased motivation for rehabilitation. In order to encourage active participation in rehabilitation, providing motivation is an important factor. This motivation theory supports the findings of our study. In particular, older adults with cognitive impairment often exhibit lethargy and depression [26]; thus, participation in rehabilitation is generally low. Because VR can increase the motivation for rehabilitation through immediate feedback, fun, and interest, it can increase training participation [18]. Increased involvement through motivation is known to trigger the thinking process by activation of brain neurotransmitter pathways, such as the cholinergic and dopaminergic systems, which helps improve concentration and memory in older people [18,27,28]. In addition, compliance is better because the surroundings are more familiar, as cognitive training is performed in virtual environments of everyday life, such as shopping, driving, cooking, and those involving calculating and opening doors [29]. Previous studies have reported that increased motivation through VR improves visual and auditory focus, which has a positive effect on the short-term visuospatial memory and attention of older adults and patients with stroke and dementia [18,27]. Therefore, in this study, higher motivation induced by through VRCMR in comparison to CCR may have helped improve the subjects’ cognitive function.

Another possible explanation for the findings of this study is brain plasticity and reorganization [30,31]. Multisensory approaches, such as VRCMR, continuously stimulate relevant brain regions. VRCMR, unlike CCR, provides continuous visual, auditory, and spatial stimuli through monitors and speakers. In VR environments, subjects are given multiple sensory modalities to interact with images and virtual objects in real time. Doniger et al. (2018) [16] reported that VRCR increased the cerebral blood flow in the prefrontal and the middle and posterior cingulate cortices, presumably due to increased brain activity during cognitive training.

Moreover, the equipment used in this study requires simultaneous continuous upper extremity movement during cognitive training. Physical exercise is known to affect cognitive functions, such as executive function, by increasing the level of brain-derived neurotrophic factor and the blood flow in the hippocampus, resulting in beneficial metabolic effects [14,16]. These outcomes might enhance the brain neuroplastic potential and enhance learning during cognitive rehabilitation [32]. In addition, physical exercise stimulates the hypothalamic–pituitary–adrenal axis, resulting in increased cortisol levels, which promote learning and memory improvement [33]. Ten Brinke et al. (2019) [13] also reported that CCR is effective in improving the cognitive function in elderly adults, but combining cognitive rehabilitation with physical exercise fosters broader benefits, similar to and supportive of the findings in this study. Therefore, both cognitive and physical exercise contribute to the process of brain repair and neuroplasticity. The findings of our study are likely due to a synergistic effect induced by performing both activities simultaneously.

This study has some limitations. First, it is difficult to generalize the results due to the small number of subjects; second, changes in brain function were not confirmed using brain imaging equipment, such as fMRI and PET; third, we did not perform follow-up evaluations after the intervention; thus, we could not determine the durability of the effects. Therefore, further large-scale studies that would include imaging evaluations and follow-up are needed to overcome the limitations of this study.

5. Conclusions

In conclusion, VRCMR may help improve rehabilitation motivation and cognitive function, including memory and attention, in older adults with MCI more than CCR. Therefore, VRCMR can be used as a cognitive rehabilitation intervention in older adults with MCI. However, further large-scale studies that would include imaging evaluations and follow-up are needed.

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References

1. Livingston, G.; Sommerlad, A.; Orgeta, V.; Costafreda, S.G.; Huntley, J.; Ames, D.; Ballard, C.; Banerjee, S.; Burns, A.; Cohen-Mansfield, J.; et al. Dementia prevention, intervention, and care. Lancet 2017, 389, 2673–2734. [CrossRef]
2. Luck, T.; Luppa, M.; Briel, S.; Riedel-Heller, S.G. Incidence of mild cognitive impairment: A systematic review. Dement. Geriatr. Cogn. Disord. 2010, 29, 164–175. [CrossRef]
3. Bruscoli, M.; Lovestone, S.I. Is MCI really just early dementia? A systematic review of conversion studies. Int. Psychogeriatr. 2004, 16, 129–140. [CrossRef] [PubMed]
4. Petersen, R.C.; Doody, R.; Kurz, A.; Mohs, R.C.; Morris, J.C.; Rabins, P.V.; Ritchie, K.; Rossor, M.; Thal, L.; Winblad, B. Current concepts in mild cognitive impairment. Arch. Neurol. 2001, 58, 1985–1992. [CrossRef]
5. Johnson, D.K.; Storandt, M.; Morris, J.C.; Galvin, J.E. Longitudinal study of the transition from healthy aging to Alzheimer disease. Arch. Neurol. 2009, 66, 1254–1259. [CrossRef]
6. Murman, D.L. The Impact of Age on Cognition. Senin. Hear. 2015, 36, 111–121. [CrossRef] [PubMed]
7. Artero, S.; Ancelin, M.L.; Portet, F.; Dupuy, A.; Berr, C.; Dartigues, J.F.; Tzourio, C.; Rouaud, O.; Poncent, M.; Pasquier, F.; et al. Risk profiles for mild cognitive impairment and progression to dementia are gender specific. J. Neurol. Neurosurg. Psychiatry 2008, 79, 979–984. [CrossRef]
8. Bahar-Fuchs, A.; Clare, L.; Woods, B. Cognitive training and cognitive rehabilitation for persons with mild to moderate dementia of the Alzheimer’s or vascular type: A review. Alzheimers Res. Ther. 2013, 5, 35. [CrossRef]
9. Kueider, A.M.; Parisi, J.M.; Gross, A.L.; Rebok, G.W. Computerized cognitive training with older adults: A systematic review. PLoS ONE 2012, 7, 40588. [CrossRef]
10. Fan, F.; Zou, Y.; Tan, Y.; Hong, L.E.; Tan, S. Computerized cognitive remediation therapy effects on resting state brain activity and cognition in schizophrenia. Sci. Rep. 2017, 6, 4758. [CrossRef]
11. Bernini, S.; Alloni, A.; Panzarasa, S.; Picascia, M.; Quaglini, S.; Tassorelli, C.; Sinforiani, E. A computer-based cognitive training in Mild Cognitive Impairment in Parkinson’s Disease. NeuroRehabilitation 2019, 44, 555–567. [CrossRef] [PubMed]
12. Lee, G.J.; Bang, H.J.; Lee, K.M.; Kong, H.H.; Seo, H.S.; Oh, M.; Bang, M. A comparison of the effects between 2 computerized cognitive training programs, Bettercog and COMCOG, on elderly patients with MCI and mild dementia: A single-blind randomized controlled study. Medicine 2018, 97, 13007. [CrossRef] [PubMed]
13. Ten Brinke, L.F.; Best, J.R.; Chan, J.L.; Ghag, C.; Erickson, K.I.; Handy, T.C.; Liu-Ambrose, T. The Effects of Computerized Cognitive Training with and without Physical Exercise on Cognitive Function in Older Adults: An 8-week Randomized Controlled Trial. J. Gerontol. 2019, 75, 755–763. [CrossRef] [PubMed]
14. Liao, Y.Y.; Tseng, H.Y.; Lin, Y.J.; Wang, C.J.; Hsu, W.C. Using virtual reality-based training to improve cognitive function, instrumental activities of daily living and neural efficiency in older adults with mild cognitive impairment: A randomized controlled trial. Eur. J. Phys. Rehabil. Med. 2019, 56, 47. [CrossRef]
15. Zajac-Lamparska, L.; Wilkoś-Dębczyńska, M.; Wojciechowski, A.; Podhorecka, M.; Polak-Szabela, A.; Warchol, L.; Kedziora-Kornatowska, K.; Izedebski, P. Effects of virtual reality-based cognitive training in older adults living without and with mild dementia: A pretest-posttest design pilot study. BMC Res. Notes 2019, 12, 776. [CrossRef]
16. Doniger, G.M.; Beeri, M.S.; Bahar-Fuchs, A.; Gottlieb, A.; Tkachov, A.; Kenan, H.; Livny, A.; Bahat, Y.; Sharon, H.; Ben-Gal, O.; et al. Virtual reality-based cognitive-motor training for middle-aged adults at high Alzheimer’s disease risk: A randomized controlled trial. Alzheimers Dement. 2018, 4, 118–129. [CrossRef]
17. Park, J.H.; Liao, Y.; Kim, D.R.; Song, S.; Lim, J.H.; Park, H.; Lee, Y.; Park, K.W. Feasibility and Tolerability of a Culture-Based Virtual Reality (VR) Training Program in Patients with Mild Cognitive Impairment: A Randomized Controlled Pilot Study. Int. J. Environ. Res. Public Health 2020, 17, 3030. [CrossRef]
18. Yang, S.; Chun, M.H.; Son, Y.R. Effect of virtual reality on cognitive dysfunction in patients with brain tumor. Ann. Rehabil. Med. 2014, 38, 726–733. [CrossRef]
19. Subramanian, S.; Dahl, Y.; Skjærret Maroni, N.; Vereijken, B.; Svanaes, D. Assessing Motivational Differences Between Young and Older Adults When Playing an Exergame. *Games Health J.* 2020, 9, 24–30. [CrossRef]

20. Amjad, I.; Toor, H.; Niazi, I.K.; Pervaiz, S.; Jochumsen, M.; Shafique, M.; Haavik, H.; Ahmed, T. Xbox 360 Kinect Cognitive Games Improve Slowness, Complexity of EEG, and Cognitive Functions in Subjects with Mild Cognitive Impairment: A Randomized Control Trial. *Games Health J.* 2019, 8, 144–152. [CrossRef]

21. Lee, J.Y.; Lee, D.W.; Cho, S.J.; Na, D.L.; Jeon, H.J.; Kim, S.K.; Lee, Y.R.; Yoon, J.H.; Kwon, M.; Lee, J.H.; et al. Brief screening for mild cognitive impairment in elderly outpatient clinic: Validation of the Korean version of the Montreal Cognitive Assessment. *J. Geriatr. Psychiatry Neurol.* 2008, 21, 104–110. [CrossRef] [PubMed]

22. Llinas-Regla, J.; Vilalta-Franch, J.; Lopez-Pousa, S.; Calvo-Perxas, L.; Torrents Rodas, D.; Garre-Olmo, J. The Trail Making Test. *Assessment* 2017, 24, 183–196. [CrossRef] [PubMed]

23. Tamez, E.; Myerson, J.; Morris, L.; White, D.A.; Baum, C.; Connor, L.T. Assessing executive abilities following acute stroke with the trail making test and digit span. *Behav. Neurol.* 2011, 24, 177–185. [CrossRef]

24. Kothari, M.; Svensson, P.; Jensen, J.; Holm, T.D.; Nielsen, M.S.; Mosengaard, T.; Nielsen, J.F.; Ghovanloo, M.; Baad-Hansen, L. Tongue-controlled computer game: A new approach for rehabilitation of tongue motor function. *Arch. Phys. Med. Rehabil.* 2014, 95, 524–530. [CrossRef]

25. Fransson, P.A.; Patel, M.; Jensen, H.; Lundberg, M.; Tjernström, F.; Magnusson, M.; Ekvvall Hansson, E. Postural instability in an immersive Virtual Reality adapts with repetition and includes directional and gender specific effects. *Sci. Rep.* 2019, 28, 3168. [CrossRef]

26. Culpepper, L.; Lam, R.W.; McIntyre, R.S. Cognitive Impairment in Patients with Depression: Awareness, Assessment, and Management. *J. Clin. Psychiatry* 2017, 78, 1383–1394. [CrossRef]

27. Kim, B.R.; Chun, M.H.; Kim, L.S.; Park, J.Y. Effect of virtual reality on cognition in stroke patients. *Ann. Rehabil. Med.* 2011, 35, 450–459. [CrossRef]

28. Kim, M.Y.; Lee, K.S.; Choi, J.S.; Kim, H.B.; Park, C.I. Effectiveness of cognitive training based on virtual reality for the elderly. *Ann. Rehabil. Med.* 2005, 29, 424–433.

29. Calabrò, R.S.; Russo, M.; Naro, A.; De Luca, R.; Leo, A.; Tomasello, P.; Molonia, F.; Dattola, V.; Bramanti, A.; Bramanti, P. Robotic gait training in multiple sclerosis rehabilitation: Can virtual reality make the difference? Findings from a randomized controlled trial. *J. Neurol. Sci.* 2017, 377, 25–30. [CrossRef] [PubMed]

30. You, S.H.; Jang, S.H.; Kim, Y.H.; Hallett, M.; Ahn, S.H.; Kwon, Y.H.; Kim, J.H.; Lee, M.Y. Virtual reality-induced cortical reorganization and associated locomotor recovery in chronic stroke: An experimenter-blind randomized study. *Stroke* 2005, 36, 1166–1171. [CrossRef] [PubMed]

31. Oh, Y.B.; Kim, G.W.; Han, K.S.; Won, Y.H.; Park, S.H.; Seo, J.H.; Ko, M.H. Efficacy of Virtual Reality Combined With Real Instrument Training for Patients With Stroke: A Randomized Controlled Trial. *Arch. Phys. Med. Rehabil.* 2019, 100, 1400–1408. [CrossRef] [PubMed]

32. Mandolesi, L.; Polverino, A.; Montuori, S.; Foti, F.; Ferraioli, G.; Sorrentino, P.; Sorrentino, G. Effects of Physical Exercise on Cognitive Functioning and Wellbeing: Biological and Psychological Benefits. *Front. Psychol.* 2018, 9, 509. [CrossRef] [PubMed]

33. Luger, A.; Deuster, P.A.; Kyle, S.B.; Gallucci, W.T.; Montgomery, L.C.; Gold, P.W.; Loriaux, D.L.; Chrousos, G.P. Acute hypothalamic-pituitary-adrenal responses to the stress of treadmill exercise. Physiologic adaptations to physical training. *N. Engl. J. Med.* 1987, 316, 1309–1315. [CrossRef] [PubMed]

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