

Task-Oriented Virtual Reality Enhances Motor Network Connectivity in Progressive Multiple Sclerosis: A Randomized Trial

Mehrnaz Hamedani^{1*}, Giada Lombardi¹, Giacomo Boffa^{1,2}, Caterina Pistarini³, Federico Maria Cossa⁴, Elisabetta Capello^{1,2}, Simona Malucchi⁵, Arianna Anselmino⁴, Elena Maria Fiabane⁶, Alessia Di Sapio⁵, Ilaria Poirè², Chiara Sciolla⁵, Cinzia Calautti⁷, Fabio Incollu⁷, Francesca Spada⁷, Antonio Bertolotto⁸, Isabella Springhetti⁹, Antonio Nardone^{9,10}, Riccardo Sollazzo⁹, Giulia Fazio⁷, Ginevra Galetti⁷, Maria Pia Sormani¹¹, Andrea Boghi¹², Marta Ponzano¹¹, Matilde Inglese^{1,2}, Maria Cellerino¹, Gianluigi Mancardi^{1,3}

1. University of Genoa, DINOGMI, Genova, Italy; 2. IRCCS Policlinico Hospital San Martino, Genova, Italy; 3. Istituti Clinici Scientifici Maugeri, IRCCS, Department of Neurorehabilitation, Pavia, Italy; 4. Istituti Clinici Scientifici Maugeri, IRCCS, Gattico-Veruno, Piedmont, Italy; 5. University Hospital San Luigi Gonzaga, Orbassano, Torino, Italy; 6. Istituti Clinici Scientifici Maugeri, IRCCS, Psychology Unit, Pavia, Italy; 7. Istituti Clinici Scientifici Maugeri, Department of Physical and Rehabilitation Medicine, Genova Nervi, Italy; 8. Koelliker Hospital, Turin & Neuroscience Institute Cavalieri Ottolenghi (NICO), University of Turin, Orbassano; 9. Istituti Clinici Scientifici Maugeri, IRCCS, Neurorehabilitation and Spinal Units of Pavia, Pavia, Italy; 10. Department of Clinical-Surgical, Diagnostic and Pediatric Sciences, University of Pavia, Pavia, Italy; 11. University of Genova, DISSAL, Genova, Italy.

Introduction

Patients with progressive multiple sclerosis (MS) generally demonstrate a decline in clinical condition over time, raising questions about the effectiveness of rehabilitation therapy in slowing disease progression. Recent studies suggest that anti B monoclonal antibodies therapy may have a partial beneficial effect on disease progression.

Objectives

- This study aims to evaluate whether a high-tech rehabilitation protocol combined with an intensive rehabilitation programme is more effective for motor recovery, particularly in the upper limbs, compared to traditional intensive motor rehabilitation and standard care, which include passive mobilization, active mobilization exercises, and antigravity muscle strengthening.
- In addition, the study will assess the effects of these rehabilitation programmes on central nervous system reorganization using functional magnetic resonance imaging (fMRI) and examine the duration of their effects on clinical and instrumental parameters.

Methods

Demographics
Clinical data
Biological samples collection
Neuroimaging data

81 progressive MS treated with anti-B monoclonal antibodies for at least six months
 $3 \leq \text{EDSS} \leq 7$

90 min, 3 times a week, 8 weeks

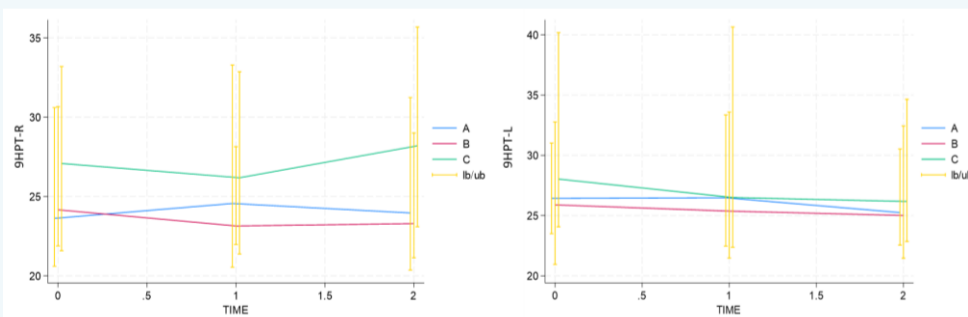
- A) Experimental group: Task-oriented + general rehabilitation + 30 minutes virtual reality (Nirvana device)
- B) Comparison group: Similar to the experimental group, but without virtual reality
- C) Control group: passive mobilization upper and lower limbs + active mobilization and exercises for the lower limbs

Outcomes

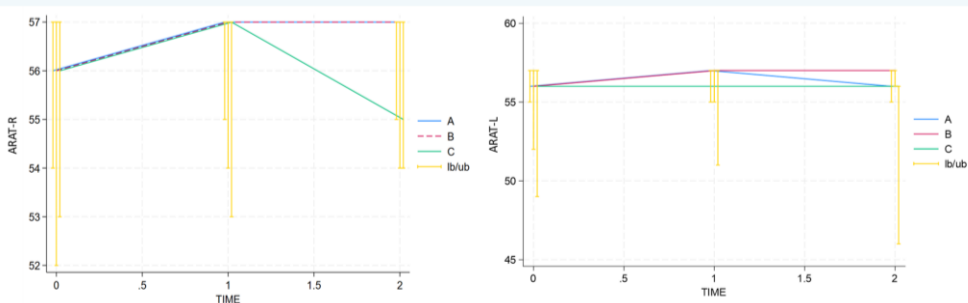
- ✓ Nine-Hole Peg Test
- ✓ Action Research Arm Test
- ✓ Hand Test System (computerized glove)
- ✓ Manual Ability Measurement, MAM-36
- ✓ ABILHAND
- ✓ Multiple Sclerosis Functional Composite
- ✓ Functional Independence Measure
- ✓ 25-Foot Walk Test
- ✓ Multiple Sclerosis Walk Scale
- ✓ Trunk Control Test
- ✓ Modified Fatigue Impact Scale
- ✓ Brief International Cognitive Assessment for Multiple Sclerosis
- ✓ Hospital Anxiety and Depression Scale
- ✓ Short Form 36 Health Survey

Results

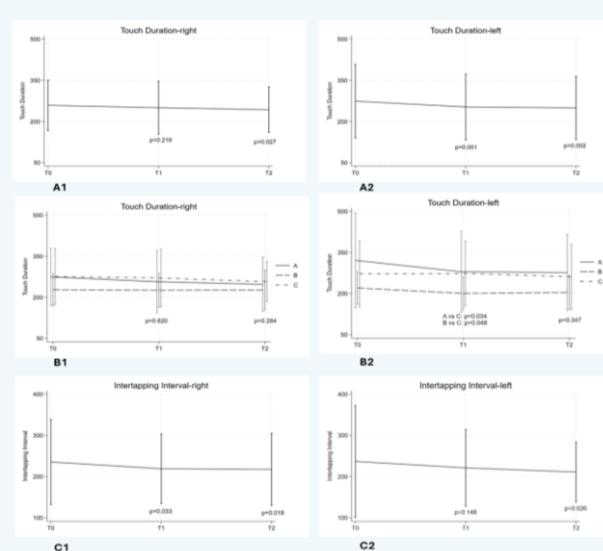
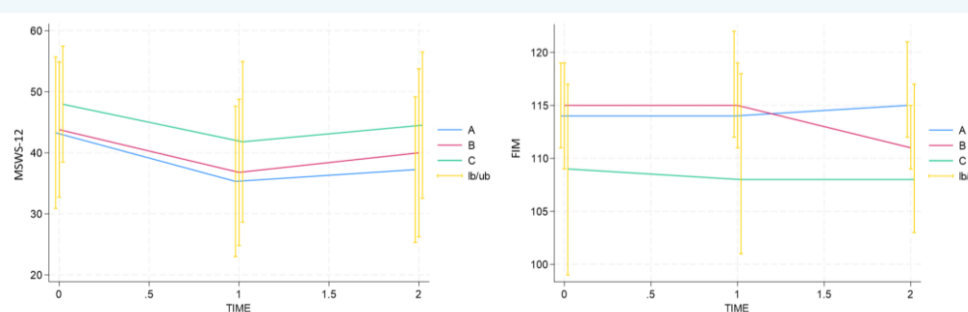
The primary endpoint was the Nine-Hole Peg Test (9HPT), but no significant differences were found between assessments at baseline (T0), end of treatment (T1), and 3-month follow-up (T2) for either arm.



The Action Research Arm Test (ARAT) showed a significant difference between groups at T2 vs T0 ($p < 0.0029$; A vs C: $p = 0.059$ B vs C: $p = 0.010$).



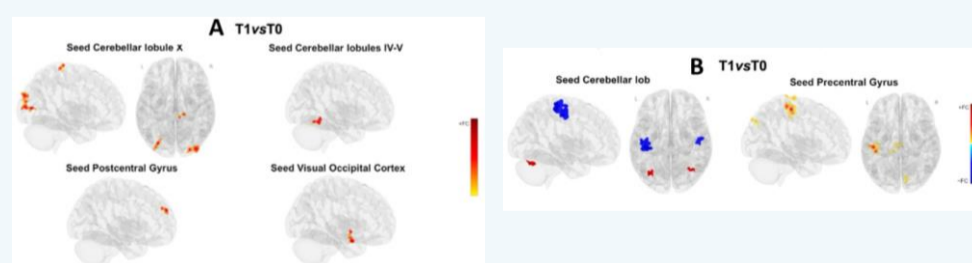
Neurological assessments showed a significant decrease in Timed 25-Foot Walk ($p = 0.011$) at T1 vs T0, with improved MS Walking Scale (MSWS-12) ($p < 0.001$) and Functional Independence Measure (FIM) ($p = 0.001$).



The Hand Test System showed a significant reduction in Touch Duration at T2 vs T0 with the right hand (Fig. A1) and at T1/T0 and T2/T0 with the left hand (Fig. A2). A significant difference was

also found in the left interaction test (Figs. B1–B2). Overall, the inter-tapping interval was reduced at T1/T0 and T2/T0 with both hands (Figs. C1–C2).

Several changes in seed base connectivity were noted between T1 and T0 in both A and B groups, while no changes were observed in the C.



Conclusions

Although the 9HPT endpoint was not achieved, we observed upper limb improvements with alternative assessments in advanced progressive MS. Task-oriented rehabilitation proved feasible, induced clinical improvement, and was associated with meaningful brain connectivity changes.