HTTPS://DOI.ORG/10.1016/J.MSARD.2022.104455

EFFECT OF IMMERSIVE VIRTUAL REALITY TRAINING ON HAND-TO-MOUTH TASK PERFORMANCE IN PEOPLE WITH MULTIPLE SCLEROSIS: A QUANTITATIVE KINEMATIC STUDY

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Revised version of the manuscript MSARD-D-22-01071 on November 8th, 2022

This manuscript is composed of 4290 words. The abstract is 281 words long

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Abstract

Background: Although the use of Virtual Reality (VR) has received increasing interest as an add-on treatment in neurorehabilitation programs in the last fifteen years, there is scarce information about the effectiveness of fully immersive VR-based treatments on upper limb (UL) motor function in people with Multiple Sclerosis (PwMS).

Methods: In this bicentric 2-period interventional crossover study, 19 PwMS with moderate to severe disability (mean EDSS score 5.5) and relevant UL impairment underwent 12 immersive-VR sessions over a period of 4 weeks, using commercially available VR platform (Oculus Quest) and games (Fruit Ninja, Beat Saber and Creed - Rise to Glory). Possible changes associated with the treatment were objectively assessed through instrumental kinematic analysis of the "hand-to-mouth" (HTM) movement by means of optical motion capture system. Clinical tests to assess gross and fine manual dexterity (i.e., the Box and Blocks and Nine Hole Peg Test) were also administered.

Results: The results of the kinematic analysis suggest that the VR training positively impacted the ability of the tested PwMS to perform the HTM task. In particular, a significant reduction of the overall time required to complete the task of approximately 20% for both most and least affected limb, and an improved degree of precision and stability of the movement, as indicated by the reduced value of adjusting sway, especially for the most affected limb (-60%).

Conclusion: Based on the results of the quantitative analysis, a 4-week treatment with immersive VR is able to improve speed and stability of the HTM movement in PwMS. This suggests that such an approach might be considered suitable to facilitate an immediate transfer of the possible positive effects associated with the training to common activities of daily living.

Keywords: multiple sclerosis (MS); upper limb; virtual reality (VR); kinematics; hand to mouth

Introduction

Multiple Sclerosis (MS) is a chronic inflammatory disease of the central nervous system (CNS) which affects almost 3 million individuals worldwide (Walton et al., 2020). During its course, MS leads to the accumulation of deficits and disability, as a consequence of demyelination and axonal loss within the CNS. In particular, a progressive deterioration of basic motor functions like postural control and ambulation is commonly observed (Cameron and Lord, 2010; Lamers and Feys, 2014; Reich et al., 2018). However, a significant percentage of PwMS (estimated between 50% and 80% Holper et al., 2010; Kraft et al, 2014) also report upper limb (UL) dysfunctions under the form of weakness, spasticity, ataxia, tremor, sensory loss, and pain, which eventually lead to gross and fine manual dexterity loss, slowness of movements, dysmetria and clumsiness (McDonald and Compston, 2006; Bertoni et al., 2015).

Virtual reality (VR) has recently received increasing interest as an add-on treatment in neurorehabilitation, allowing high-intensity task-oriented training with multisensory feedback in a motivating and attractive environment (Nascimiento et al., 2021). Besides the potential benefits in terms of mobility, balance and UL function (Voinescu et al., 2021), VR systems are characterized by affordable cost and high availability as "off-the-shelf" solutions immediately usable even by users with no specific technical background. Early attempts to integrate VR in rehabilitation have been mostly carried out with non-immersive systems (in particular those using consoles, like

Nintendo Wii, Microsoft Kinect, etc.), in which the virtual scenarios are displayed on computer monitors or TV screens, and the interaction between user and VR is mediated by input devices like keyboards, mice, or controllers. However, at present, low-cost fully immersive systems are available, which give users the most realistic simulation experience by integrating a 360° field view with stereoscopic vision, sound and real-time feedback. Such equipment prevents users from receiving the sensory flow of information from the real world and replaces it with the computer-generated one, thus strengthening the idea that what is presented in the virtual scenario is the actual real world (Georgiev et al., 2021). Although relatively new, immersive VR is considered a very promising enhancement which is hypothesized to bring even greater benefits to the rehabilitation plans.

A series of recent reviews which summarized the results of the studies carried out in the last 15 years, pointed out that VR-based training has a positive effect in PwMS as regards fatigue, quality of life and postural control, at least equal to, or greater than, conventional exercise (Cortés-Pérez et al., 2021; Nascimiento et al., 2021). However, it is noteworthy that most of the screened interventions targeted balance, gait or other lower limb function outcomes, while the use of this approach to improve UL function appears to have been explored less. In this regard, recently Webster et al. (2021), who summarized the results of 11 studies specifically focused on UL rehabilitation, concluded that although there is some evidence on the effectiveness of VR-based treatments in terms of improvements in UL motor function, there is no consensus about which approach is most effective, and about duration and intensity of the treatment. In particular, since most studies were based on non-immersive VR, they were unable to establish whether immersive VR can actually provide further benefits and thus additional data are needed. At the same time, Webster et al. (2021) also noted a certain heterogeneity in terms of outcome measurements and the scarcity of outcomes assessing the effects on ADL.

On the basis of the aforementioned considerations, in this study we aimed to quantitatively and objectively assess the effects of an immersive VR-based treatment on UL functioning of PwMS by analysing several kinematic features of the "hand-to-mouth" (HTM) functional task. Such movement, which is representative of important activities of daily living (ADL) like eating and drinking (Menegoni et al., 2008), was investigated in previous studies on UL functions in individuals affected by neurological diseases (Mackey et al., 2005; Caimmi et al., 2008, 2015; Cimolin et al., 2020; Corona et al., 2018b) including MS (Corona et al., 2018a), and thus can be considered suitable to verify the actual impact of the improvements possibly achievable with the VR training to real-life scenarios.

Materials and Methods

Study design and assessment procedures

This was originally designed as a bicentric randomized single blind (assessor) 2-period (no treatment controlled) crossover study in which participants were recruited at the outpatient services of both Multiple Sclerosis Center of Sardinia, Cagliari, Italy and the IRCCS Santa Maria Nascente of Don Gnocchi Foundation, Milan, Italy, that are two centres dedicated to diagnosis and treatment of PwMS. They were allocated to 2 counterbalanced arms sequence, by randomization in a 1:1 ratio, as follows: 1) Treatment-Waiting List (T-WL); 2) Waiting List-Treatment (WL-T). However, due to the COVID-19 outbreak and the subsequent limitations in terms of accessibility to the hospitals which oversaw the recruitment of participants, it was not possible to fully comply with the randomization sequence. Moreover, we included 3 extra subjects to the original sample to compensate for the lack of instrumental assessment.

The first group (sequence T-WL) carried out 12 sessions (45 minutes each) of VR immersive training over a 4-week period (treatment period, T), followed by a 4-week wash-out period and a 4-week waiting list period (WL). For the second group, the protocol was administered in the reverse order (sequence WL-T). All participants were tested at three time points, namely: immediately before the beginning of the study (T0), after the end of the first 4-week period (T1), at the end of the wash-out period and finally at the end of the third 4-week period (T2). During the washout period, participants were asked not to be engaged in any specific physical therapy/training program focused on upper limb function and to regularly perform their usual activities of daily living

Participants

Among those followed at the two centres involved in the study, 37 PwMS were enrolled on the basis of the following inclusion criteria: diagnosed with MS according to the 2017 McDonald criteria (Thompson et al., 2017), age ≥18 years, free from relapses for at least three months before the beginning of the study and characterized by a relevant UL impairment, established on the basis of the time necessary to complete the Nine Hole Peg Test (NHPT), which was required higher than 30 seconds for at least one limb (Lamers et al., 2015). However, even those unable to complete NHPT were still considered eligible for inclusion in the study if their score in the Box and Block Test (BBT) was 1 or higher. PwMS either not suitable, upon clinical judgement, to undergo a treatment based on immersive VR due to cognitive impairment or affected by other concomitant conditions that could potentially interfere with treatment administration were not considered. The study, which was approved by the Ethics Committees of the two centres, was conducted in compliance with the ethical principles for research involving human subjects expressed in the Declaration of Helsinki and its later amendments and registered on ClinicalTrials.gov (NCT04027491). All participants agreed to participate by signing an informed consent form.

Intervention

PwMS underwent 12 immersive VR sessions (supervised by a certified Physical Therapist) over a period of 4 weeks, which were articulated into 3 blocks of 10-minutes exercises interspersed with 5-minute rest. A commercially available VR platform (Oculus

Rift, Meta Platforms, USA) was employed for the treatment. This system includes head-mounted goggles (equipped with positional tracking, stereoscopic 3D-imaging and integrated audio), two tabletop infrared LED sensors and two hand controllers. The software that was used in each session to perform exercises was chosen by the physical therapists of the research group from those available for the Oculus Rift platform, provided that they were considered able to induce participants to perform bilateral UL movements (involving proximal and distal joints) consistent with their residual function, playable in both seated and upright positions and characterized by adjustable level of difficulty to follow possible changes in upper limb function occurring during the treatment. In particular, the games which satisfied such requirements and thus selected for the treatment, were:

- Fruit Ninja™ (Halfbrick Studios Pty Ltd., Red Hill, Australia, https://www.halfbrick.com/games/fruit-ninja): The purpose of this game is to chop different flying fruits, as soon as they appear in front of the player, using virtual swords controlled by hands, at the same time avoiding flying bombs that are randomly presented.
- Beat Saber (Beat Games, Prague, Czech Republic, https://beatsaber.com): The player controls a pair of glowing sabres with which he/she must cut a stream of approaching blocks, which appear in sync with a background song. The cut must be performed according to the direction of an arrow displayed in the block (i.e., vertical, horizontal, diagonal).

- Creed - Rise to Glory (Survios, Los Angeles, USA, https://survios.com/studio/): This is a boxing game that can be played either in a "free" mode, during which the player is allowed to perform several types of exercises in a virtual gym (i.e., punching bag, punching ball, etc.) or in a "match" mode, which proposes a competitive fight against a computer opponent.

The overall effort exerted during each 10-min block was properly modulated by the physical therapist according to the current status of the PwMS. The therapist also managed the difficulty levels and the selection of the options available for each game, provided advice regarding posture and safety and solved technical issues if necessary. The perceived effort was continuously monitored by means of Borg's RPE scale to keep the exertion level between 13 (somewhat hard) and 15 (hard).

The "Hand to Mouth" task

The "Hand to Mouth" (HTM) task was carried out by PwMS seated on a chair positioned in front of a table adjustable in height. The initial position was set so that the shoulders and wrists were in a neutral position, with the elbows flexed at approximately 90° and the forearm prone, according to what described in previous similar studies (Mackey et al., 2005; Caimmi et al., 2008; Menegoni et al., 2008; Cimolin et al., 2012; Corona et al., 2018a). The hands were placed with palms down on the table (see Figure 1). Subsequently, following a verbal signal, the participants moved their hand towards the face until the fingertip touched their mouth, then returned it to the initial position.

This movement was repeated three consecutive times by each limb, at a self-selected speed.

Please insert Figure 1 approximately here

Kinematic data acquisition and processing

Retro-reflective markers were positioned on the participant' skin (see Figure 1) according to standardized protocols previously designed for similar purposes (Rab et al., 2002; Petuskey et al., 2007). Using an 8-camera optical motion capture system (SMART-D, BTS Bioengineering, Milan, Italy), the 3D marker's trajectories during the HTM task execution were acquired. They were then processed using a dedicated custom routine developed under the Smart Analyzer environment (BTS Bioengineering, Milan, Italy) which provided to segment the movement into the following three phases according to a predefined threshold for the linear velocity of the fingertip equal to 20% of the peak velocity (Menegoni et al., 2008; Cimolin et al., 2012; Carpinella et al., 2014; Corona et al., 2018a):

- Going Phase, during which the hand is moved from the table to the mouth;
- Adjusting Phase, dedicated to precisely locating the mouth;
- Returning Phase, which corresponds to the period during which the hand is moved back to the starting position.

The task performance was quantitatively characterized by computing the following spatio-temporal parameters:

- Total HTM movement duration (s).
- Duration of the Going, Adjusting and Return Phases (s).
- Adjusting Sway (mm), which represents the length of the 3D path followed by the fingertip marker during the Adjusting Phase. This is a measure of the magnitude of the adjustments made to reach the final target and is representative of the movement stability (Cimolin et al., 2012).
- Frequency of changes in direction (Hz). This is another measure of smoothness which characterizes the finger displacements associated to the possible presence of tremor (Quintern et al., 1999; Menegoni et al., 2009). Previous studies indicated that PwMS exhibit significantly higher values of this parameter with respect to unaffected individuals (Corona et al., 2018a).

Clinical outcomes

Two clinical tests (BBT and NHPT) were administered to all participants to assess, respectively, unilateral gross and fine manual dexterity. For the BBT, a wooden box divided in two compartments by a partition and 150 blocks are used. The subject is required to move, one block at time, the maximum number of blocks possible from one compartment to the other in 60 seconds. Thus, a higher number of blocks indicates a better performance. Typical values for PwMS range between 40-50 blocks (Goodkin et al., 1988; Solaro et al., 2020). For the NHPT, a square board with 9 pegs is employed; the subjects are required to take the pegs from their initial position, one at time, and place them into the holes on the board, as quickly as possible. The mean rate of two trials, calculated as pegs per second (pegs/sec), for each hand was considered (Lamers et al., 2014; Feys et al., 2017).

Statistical analysis

Descriptive statistics are provided, together with the main demographic and clinical variables, both for the entire sample and for each sequence separately. The limbs were labelled as “most affected” or “least affected” according to the BBT or the NHPT score. In particular, a between-limb difference of 8 blocks at BBT or, alternatively, a difference of 10 seconds at NHPT was used as cut-off to categorize the most affected side.

The kinematic outcome measures were analysed using mixed linear effect models. Treatment efficacy was assessed based on the within-subject differences. Specifically, we calculated the intra-individual differences at the end of both periods (T1 and T2) for each subject. Nine subjects were allocated in sequence T-WL and 10 in the sequence WL-T. Differences in scores between sequences was calculated as: [(within difference, T-WL) – (within difference, WL-T)] / 2, and these represented the focus of the analysis. As random effect, we had intercepts in a nested design with side nested within subjects, without random slopes. Any presence of carry-over effect was also reported. Effectiveness analyses were conducted using an as-treated approach (α-level=5%). Analyses were performed with the software R (version 4.0.2).

Results

We recruited 23 participants and allocated them in one sequence (T-WL) or the other (WL-T); four participants dropped out during the study (Figure 2).

Please insert Figure 2 approximately here

The baseline characteristics of the participants depict a sample with moderate to severe UL impairments (Table 1). Most of them were diagnosed with the relapsing-remitting type of MS (n=11, 58%), while approximately a third of the sample was composed by PwMS with secondary progressive (n=6, 32%) and primary progressive type (n=2, 10%). No clinically significant between-sequence differences were found at baseline for age and disease duration, while participants of the WL-T sequence showed a higher disease severity (EDSS) with a lower level of gross functional dexterity for the less affected side (BBT).

Please insert Table 1 approximately here

Overall HTM movement time

We observed carryover effects both for the least (p=0.002) and most affected sides (p=0.02). Regarding the least affected side of the T-WL sequence, subjects were found faster in performing the HTM movement after the training period (1.2 s, T1, Figure 3) compared with the post waiting list period (1.34 s, T2, Figure 3) with a difference (T-WL) of -0.14 s (Table 2). As expected, results were similar in the WT-L sequence, in which subjects were faster after the training period (1.72 s, T2, Figure 3) compared with the post waiting list period (1.96 s, T1, Figure 3) with a difference of 0.24 s. These differences resulted in an overall statistically significant between-sequence difference [(T-WL vs WL-T)]/2 of -0.2 s (p<0.003) favouring treatment period. Compared to baseline assessment (T0) after treatment, we observed a reduction of 0.53 s (30%) in the T-WL sequence and of 0.35 s (17%) in the WL-T sequence.

The results were also consistent for the most affected side with a statistically significant between-sequence difference [(T-WL vs WL-T)]/2 of 0.14 s (p<0.02) favouring treatment period. Compared to baseline assessment (T0) after treatment, we observed a reduction of 0.61s (32%) in the T-WL sequence and of 0.28 s (12%) in the WL-T sequence.

Please insert Table 2 approximately here

Please insert Figure 3 approximately here

HTM sub-phases

We observed carry over effects both for the going and return phases ($p<0.01$). The analysis revealed improvement favouring the treatment period for both sides and sequences as regards the Going Phase (Table 2, and Supplementary Figure S1), even though the between-sequence comparison was statistically significant only for the least affected side. For the Adjusting Phase, we observed within- and between-sequence changes favouring the treatment period for both sides. This was not the case for the Returning Phase, for which the between-sequence difference was statistically significant only for the least affected side.

Adjusting Sway

We did not observe carryover effects for both the least ($p=0.21$) and most affected side ($p=0.13$). The least affected side (Figure 4) did not show a statistically significant between-sequence difference (-3.2 mm, $p=0.27$), while we observed a statistically significant between-sequence difference of -7.3 mm ($p=0.02$) favouring treatment period in the most affected side, with a reduction of 6.5 mm (78%) in the T-WL sequence after treatment compared to baseline. The value was reduced up to 4.5 mm (48%) in the WL-T sequence. The results did not change after the removal of one outlier in the WL-T sequence.

Please insert Figure 4 approximately here

Frequency of changes in direction

In this case as well, no carryover effects were observed for both the least (p=0.36) and most affected side (p=0.12). For both limbs (Figure 5), the between-sequence difference was not statistically significant (least affected: 0.4 Hz, p=0.81; most affected: 1.13 Hz, p=0.51). The results did not change even after the removal of one outlier.

Please insert Figure 5 approximately here

Discussion

The present study was aimed at verifying the effects of the 4-week immersive VR-based treatment on UL functioning of PwMS with moderate-severe disability by analysing the kinematics of a functional task. The choice of HTM was made not only for its excellent capability to reproduce important daily tasks (i.e., eating and drinking), but also to obtain accurate information about the actual impact of the possible improvements consequent to the VR treatment on ADL performance, as well as to effectively integrate clinical assessment and patient reported outcomes.

The results suggest that the VR training positively impacted the ability of the tested PwMS to perform the HTM task. In particular, while at baseline, the average time required to complete it was 1.9 and 2.0 s for the least and most affected side respectively (values higher than those typical of unaffected individuals; Corona et al., 2018a), after the treatment, reductions of approximately 30% and 15% were observed. Interestingly, the VR training not only improved the HTM performance in terms of time, but also as regards the movement accuracy, as indicated by the significant reduction observed in the Adjusting Sway, a parameter which provides information about the degree of precision and stability of the movement. In particular, after the training this parameter reached mean values (of 4.8 mm and 3.5 mm for the least and most affected side respectively) closer to those typical of unaffected individuals (2.1 to 2.6 mm, depending on the age) (Corona et al., 2018b, 2018b; Fadda et al., 2019). The Adjusting Sway can be considered a proxy of intentional tremor in PwMS, which is related to alterations of cerebellar-thalamo-cortical pathways and associated with alterations of manual dexterity (Alusi et al., 2001) and motor control during the execution of the final part of target movements (Carpinella et al., 2012). As robust and effective therapeutic approaches for the management of tremor in MS are not available yet, even though promising results have been obtained using botulinum toxin and robot-assisted training (Carpinella et al., 2012; Makhoul et al., 2020). In this context, the findings of the present study suggest that immersive VR might represent a suitable approach to support the treatment of tremor during UL movements, by promoting high number of repetitions of UL reaching goal-directed movements with the active use of the whole arm.

Unfortunately, as mentioned previously, there is a scarcity of data about the use of immersive VR as a tool for UL rehabilitation in MS. Moreover, the few existing studies are quite heterogeneous in terms of equipment, training duration and intensity, and outcome measurements, leading to mixed results (Webster et al., 2021). Generally speaking, a trend towards a positive effect is noticeable, both in terms of gross and fine dexterity assessed using clinical tests (i.e., NHPT, Jebsen-Taylor Hand Function Test and Wolf Motor Function Test) and patient-reported outcomes (Webster et al., 2021). However, the impact on movement quality was never investigated (Fadda et al., 2019), unlike in the case of other neurologic diseases like stroke. For instance, Erhardsson et al. (2020) investigated the effects of a 10-week training in 7 individuals suffering from chronic stroke, using a hardware/software combination similar to those used in the present study, and performed a kinematic analysis of a drinking task. They report that after the VR training, half of the participants completed the drinking task in a shorter time and the movement was found to be smoother.

The introduction of quantitative techniques to analyse the effect of immersive VR on a functional movement like HTM represents an added value for the assessment of UL performance, and has the potential to effectively integrate clinical findings, by detecting important changes not feasible to be investigated with the conventional dexterity tests. In this regard, it is noteworthy that when the UL motor function of a similar sample of PwMS was assessed using clinical tests only (for details see Bertoni et al., 2022), the obtained data suggested a slightly different effect of the VR treatment from the one here described. In fact, in such case the results highlighted improvements mostly in the gross manual dexterity for the least affected limb, while no significant modifications or advancements were observed in terms of self-reported ability to carry out ADL or in fine hand dexterity, strength or fatigue. Therefore, it is likely that only by combining data coming from different sources (i.e., conventional clinical tests, questionnaires, patient-reported outcomes and instrumental measurements), it is possible to define a detailed and more exhaustive picture of the actual effects of the VR-based approach. Finally, it appears important to recall that since the HTM task reproduces the execution of a functional movement frequently performed during common ADLs, improvements of motor performance due to serial execution of the task (i.e., practice effect like those observed in clinical tests; Solari et al., 2005) are unlikely to occur.

This study has its strengths and limitations. Its major novelty lies on the fact that is one of the first attempts to employ immersive VR for UL rehabilitation in PwMS. Since it has been hypothesized that the fully immersive experience might improve factors like understanding and delivery of the task to be performed, as well as the perception of the movement performance, our findings may be of some interest to clarify whether immersive VR actually has a superior potential in comparison to the previously employed approaches (Webster et al., 2021). The study also makes use of quantitative state-of-the art techniques for human movement analysis, to investigate a functional task widely performed daily. This should help to better understand the actual transferability of the potential improvements associated with the training in real-life contexts.

However, the limitations of the study must be noted as well. Firstly, since the sample size here was relatively small, and the COVID-19 pandemic situation affected some phases of this study, particularly as regards the randomization, which was not possible to perform as originally planned, the reliability of the results is limited, a block randomization would have also reduced the between sequence differences observed at baseline. Secondly, although the commercial games adopted for the training were considered suitable to properly stimulate uni- and bilateral UL movements during the sessions, it should be considered that they were designed for the entertainment purposes of unaffected individuals. It is likely that specific task-oriented routines, which are designed based on the particular impairments associated with MS, and whose features are easily adjustable according to each PwMS needs, might be able to produce even better results. In this context, it appears useful to recall that the Oculus system is fully programmable with open-source software (for instance, Unity 3D) and thus there are no barriers in terms of design and creation of specific serious games, as also recently demonstrated in a "proof of concept" study by Hollywood et al. (2022) who tested different types of hand exercises (piano playing for isolated finger flexion and maze tracking for coordination and arm flexion) with encouraging results in terms of usability feedback received from therapists and PwMS. Finally, even though the HTM task is well representative of important ADL, further studies should be carried out considering an extended set of gross and fine UL movements.

Conclusion

Based on the results of the quantitative analysis performed using state-of-the-art techniques for human movement analysis, it may be concluded that a 4-week treatment with immersive VR is able to improve speed and stability of the HTM movement. This suggests that such an approach might be suitable for facilitating an immediate transfer of the possible positive effects associated with the training to common ADLs. Of course, there are several important issues that should be addressed in future studies, including a detailed analysis of intensity and dosage of the training, together with the assessment of the actual feasibility of this technique as a genuine home-based training system in the absence of supervision by a physical therapist. Nonetheless, immersive VR has a great potential to represent a motivating, cost-effective and engaging tool to expand the possibilities of interventions targeted to restore the UL function in PwMS.

Acknowledgements

The authors are grateful to Federico Arippa, Michela Deidda, Veronica Garcia and Giuseppina Pilloni for their valuable support during the data acquisition process.

Disclosure Statement

The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

This work was supported by the Italian Multiple Sclerosis Foundation (FISM) Grant 2017/R/19.

Author Contributions

MPa and DC: Conceptualization, Methodology, Funding acquisition, Project administration, Writing – original draft, Writing – review & editing. DC: statistical analysis. RB and FGMM: Data curation, Writing – original draft, Writing – review & editing. MPo: Investigation, Data curation. EC: Clinical assessments, Writing – review & editing.

References

Alusi SH, Worthington J, Glickman S et al. A study of tremor in multiple sclerosis. Brain. 2001;124:720–730.

Bertoni R, Lamers I, Chen CC et al., Unilateral and bilateral upper limb dysfunction at body functions, activity and participation levels in people with multiple sclerosis. Mult Scler J. 2015; 21(12): 1566–1574.

Bertoni R, Mestanza Mattos FG, Porta M et al. Effects of immersive virtual reality on upper limb function in subjects with multiple sclerosis: A cross-over study. Mult Scler Relat Disord. 2022;65:104004.

Caimmi M, Carda S, Giovanzana C et al. Using kinematic analysis to evaluate constraint-induced movement therapy in chronic stroke patients. Neurorehabil. Neural Repair 2008; 22(1): 31–39.

Caimmi M, Guanziroli E, Malosio M et al. Normative data for an instrumental assessment of the upper-limb functionality. Biomed Res Int. 2015, 484131.

Cameron MH, Lord S. Postural control in multiple sclerosis: implications for fall prevention. Curr Neurol Neurosci Rep. 2010;10(5):407-12.

Carpinella I, Cattaneo D, Bertoni R et al. Robot training of upper limb in multiple sclerosis: comparing protocols with or without manipulative task components. IEEE Trans Neural Syst Rehabil Eng. 2012;20(3):351-60.

Carpinella I, Cattaneo D, Ferrarin M. Quantitative assessment of upper limb motor function in multiple sclerosis using an instrumented action research arm test. J. Neuroeng Rehabil. 2014; 11 (1): 67.

Cimolin V, Beretta E, Piccinini L et al. Constraint-induced movement therapy for children with hemiplegia after traumatic brain injury: a quantitative study. J Head Trauma Rehabil. 2012; 27 (3): 177–187.

Corona F, Gervasoni E, Coghe G et al. Validation of the Arm Profile Score in assessing upper limb functional impairments in people with multiple sclerosis. Clin Biomech. (Bristol, Avon). 2018a;51:45-50.

Corona F, Pilloni G, Arippa F et al. Quantitative assessment of upper limb functional impairments in people with Parkinson's disease. Clin Biomech. (Bristol, Avon). 2018b;57:137-143.

Cortés-Pérez I, Sánchez-Alcalá M, Nieto-Escámez FA et al. Virtual Reality-Based Therapy Improves Fatigue, Impact, and Quality of Life in Patients with Multiple Sclerosis. A Systematic Review with a Meta-Analysis. Sensors (Basel). 2021;21(21):7389.

Erhardsson M, Alt Murphy M, Sunnerhagen KS. Commercial head-mounted display virtual reality for upper extremity rehabilitation in chronic stroke: a single-case design study. J Neuroeng Rehabil. 2020;17(1):154.

Fadda L, Corona F, Floris G et al. Upper limb movements in dementia with Lewy body: a quantitative analysis. Exp Brain Res. 2019;237(8):2105-2110.

Feys P, Lamers I, Francis G et al. Multiple Sclerosis Outcome Assessments Consortium. The Nine-Hole Peg Test as a manual dexterity performance measure for multiple sclerosis. Mult Scler. 2017; 23(5):711-720.

Georgiev DD, Georgieva I, Gong Z et al. Virtual Reality for Neurorehabilitation and Cognitive Enhancement. Brain Sci. 2021;11(2):221.

Goodkin DE, Hertsgaard D, Seminary J Upper extremity function in multiple sclerosis: improving assessment sensitivity with box-and-block and nine-hole peg tests. Arch Phys Med Rehab. 1988;69 (10): 850–854.

Hollywood RA, Poyade M, Paul L, Webster A Proof of Concept for the Use of Immersive Virtual Reality in Upper Limb Rehabilitation of Multiple Sclerosis Patients. Adv Exp Med Biol. 2022; 1356:73-93.

Holper L, Coenen M, Weise A et al. Characterization of functioning in multiple sclerosis using the ICF. J Neurol. 2010; 257 (1): 103–113. doi:10.1007/s00415-009-5282-4.

Kraft GH, Amtmann D, Bennett SE et al. Assessment of upper extremity function in multiple sclerosis: review and opinion. Postgrad. Med. 2014; 126 (5): 102–108.

Lamers I, Cattaneo D, Chen CC et al. Associations of upper limb disability measures on different levels of the International Classification of Functioning, Disability and Health in people with multiple sclerosis. Phys Ther. 2015;95(1):65-75.

Lamers I, Feys P. Assessing upper limb function in multiple sclerosis. Mult Scler J. 2014 20(7):775-84.

Mackey AH, Walt SE, Lobb GA et al. Reliability of upper and lower limb three-dimensional kinematics in children with hemiplegia. Gait Posture 2005; 22 (1): 1–9.

Makhoul K, Ahdab R, Riachi N et al. Tremor in Multiple Sclerosis-An Overview and Future Perspectives. Brain Sci. 2020;10(10):722.

McDonald I and Compston A. “The symptoms and signs of multiple sclerosis. In McAlpine’s Multiple Sclerosis. 4th edition”. Edited by A Compston, G Ebers, H Lassmann. London: Churchill Livingstone. pp. 287-346, 2006.

Menegoni F, Milano E, Trotti C et al. Quantitative evaluation of functional limitation of upper limb movements in subjects affected by ataxia. Eur J Neurol. 2009;16(2):232-9.

Menegoni F, Trotti C, Milano E et al. Kinematic analysis of upper limb movements in multiple sclerosis patients. Gait Posture 2008; 28 (1): S25–S26.

Nascimento AS, Fagundes CV, Mendes FADS et al. Effectiveness of Virtual Reality Rehabilitation in Persons with Multiple Sclerosis: A Systematic Review and Meta-analysis of Randomized Controlled Trials. Mult Scler Relat Disord. 2021;54:103128.

Petuskey K, Bagley A, Abdala E et al. Upper extremity kinematics during functional activities: three-dimensional studies in a normal pediatric population. Gait Posture. 2007; 25(4):573-9.

Quintern J, Immisch I, Albrecht H et al. Influence of visual and proprioceptive afferences on upper limb ataxia in patients with multiple sclerosis. J Neurol Sci. 1999; 163: 61–69.

Rab G, Petuskey K, Bagley A. A method for determination of upper extremity kinematics. Gait Posture 2002; 15 (2): 113–119.

Reich DS, Lucchinetti CF, Calabresi PA. Multiple Sclerosis. N Engl J Med. 2018 378(2):169-180.

Solari A, Radice D, Manneschi L, et al. The multiple sclerosis functional composite: Different practice effects in the three test components. J Neurol Sci 2005; 228: 71–74.

Solaro C, Di Giovanni R, Grange E et al. Box and block test, hand grip strength and nine-hole peg test: correlations between three upper limb objective measures in multiple sclerosis. Eur J Neurol. 2020;27(12):2523-2530.

Thompson AJ, Banwell BL, Barkhof F et al. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. Lancet Neurol. 2018; 17(2):162-173.

Voinescu A, Sui J, Stanton Fraser D. Virtual Reality in Neurorehabilitation: An Umbrella Review of Meta-Analyses. J Clin Med. 2021;10(7):1478.

Walton C, King R, Rechtman L et al. Rising prevalence of multiple sclerosis worldwide: Insights from the Atlas of MS, third edition. Mult Scler. 2020;26(14):1816-1821.

Webster A, Poyade M, Rooney S et al. Upper limb rehabilitation interventions using virtual reality for people with multiple sclerosis: A systematic review. Mult Scler Relat Disord. 2021;47:102610.

Table 1 Demographic and clinical characteristics of the participants. Median (IQR) or number (%) are reported.

	PwMS (n = 19)	**T-WL (n = 9)**	**WL-T (n = 10)**	**P-value**
Age (years)	60.0 (11.5)	59 (13)	63.5 (11.5)	0.17†
Female, n (%)	14 (70%)	6 (66.6%)	8 (72.7%)	0.89††
EDSS score	6.5 (3)	3.5 (4.5)	6.75 (0.9)	**0.01†**
Disease duration (years)	20.0 (17)	15 (26.5)	22.5 (15.5)	0.20†
Right hand dominance, n (%)	17 (89%)	9 (100%)	7 (70%)	0.50††
Right most affected limb, n (%)	5 (26%)	1 (5%)	4 (40%)	0.36††
BBT most affected (blocks)	41 (37)	45 (43)	33.5 (36.5)	0.16†
BBT least affected (blocks)	45.7 (8.8)	55 (8)	34.5 (23.7)	**0.002†**
NHPT most affected (peg/s)	0.18 (0.2)	0.16 (0.16)	0.26 (0.24)	0.83†
NHPT least affected (peg/s)	0.25 (0.2)	0.25 (0.16)	0.21 (0.24)	0.15†

PwMS: People with Multiple Sclerosis; EDSS: Expanded Disability Status Scale; BBT: Box and Block test; NHPT: Nine-hole peg test; T-WL: Treatment-Waiting List; WL-T: Waiting List-Treatment
P-value: †Mann-Whitney U-test, ††Chi Square.

Table 2. Differences within and between sequences for the HTM movement. Values are expressed as mean±SD.

		Within sequence difference (s) *	**Within sequence difference (s)†**	**Between sequence difference (s) ***	
	Side	**T-WL**	**WL-T**	**[(T-WL)-(WL-T)]/2**	**P-value**
Overall HTM Movement	Least Affected	-0.14 ± 0.08	0.24 ± 0.08	-0.20 ± 0.06	0.003
	Most Affected	-0.20 ± 0.08	0.09 ± 0.08	-0.14 ± 0.06	0.020
Going Phase	Least Affected	-0.06 ± 0.03	0.09 ± 0.03	-0.07 ± 0.2	0.006
	Most Affected	-0.02 ± 0.03	0.04 ± 0.03	-0.03 ± 0.02	0.160
Adjusting Phase	Least Affected	-0.02 ± 0.02	0.08 ± 0.02	-0.05 ± 0.02	0.005
	Most Affected	-0.04 ± 0.02	0.05 ± 0.02	-0.04 ± 0.02	0.01
Returning Phase	Least Affected	-0.07 ± 0.05	0.08 ± 0.04	-0.08 ± 0.3	0.02
	Most Affected	-0.06 ± 0.05	-0.006 ± 0.04	-0.03 ± 0.03	0.39

* negative values represent better performance after the treatment period; † positive values represent better performance after the treatment period.
T-WL: Treatment-Waiting List; WL-T: Waiting List-Treatment

Figure 1 Position of the participants for the HTM task. Left: initial and final position; right: target reaching

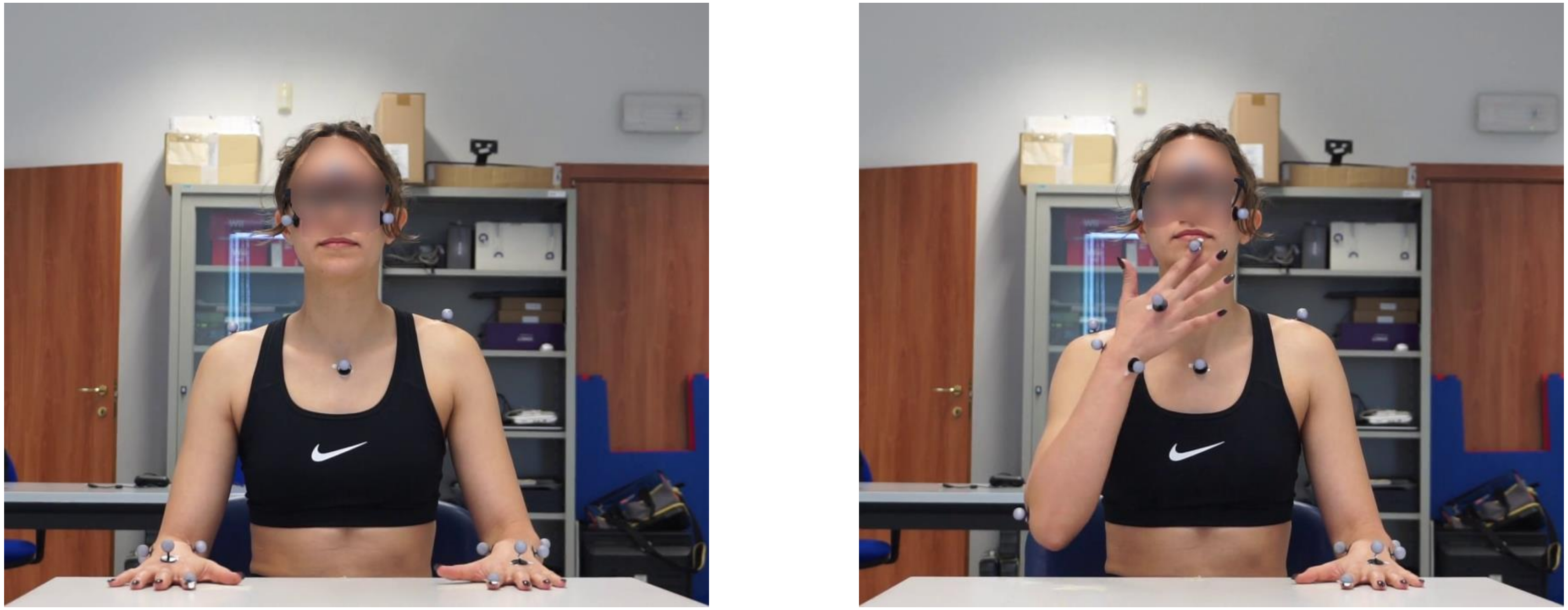
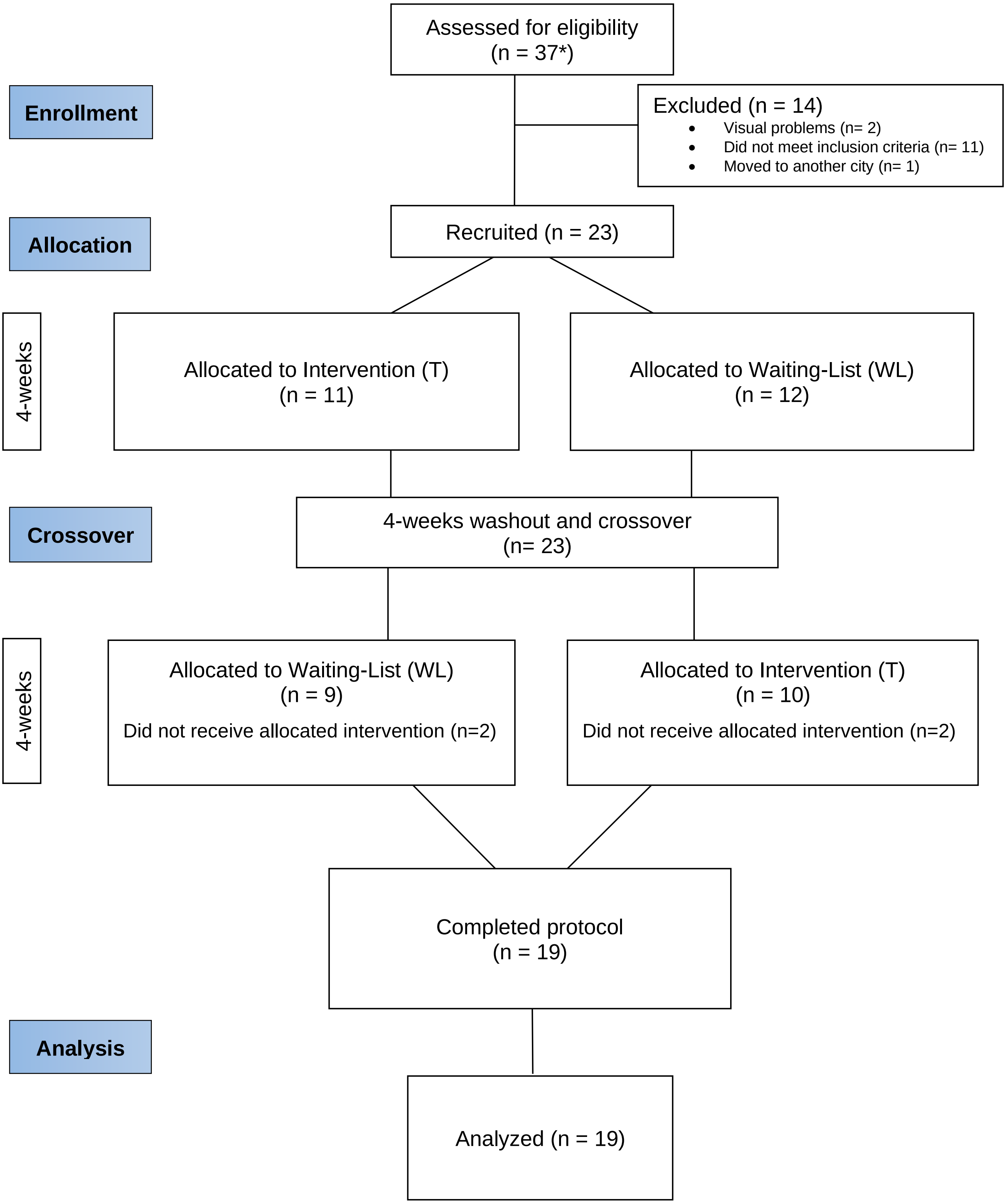


Figure 2 CONSORT Diagram



* 3 extra subjects were recruited to compensate for lack of instrumental assessment.

Figure 3 Overall HTM movement time in the Treatment-Waiting List (n= 9) and Waiting List –Treatment (n=10) sequences for the least affected (top) and most affected (below) limb.

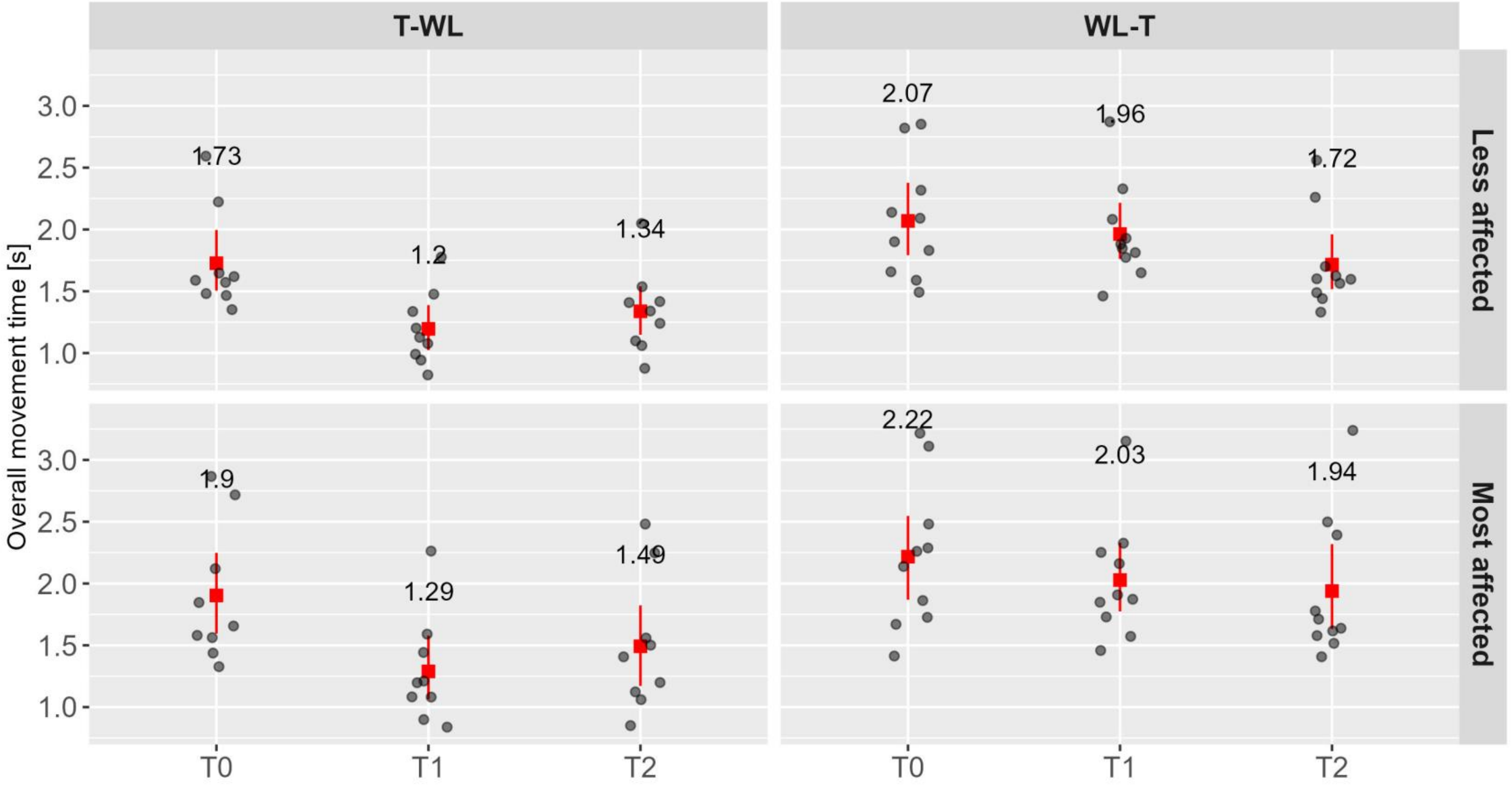


Figure 4 Adjusting Sway in the Treatment-Waiting List (n= 9) and Waiting List –Treatment (n=10) sequences for the least affected (top) and most affected (bottom) limb

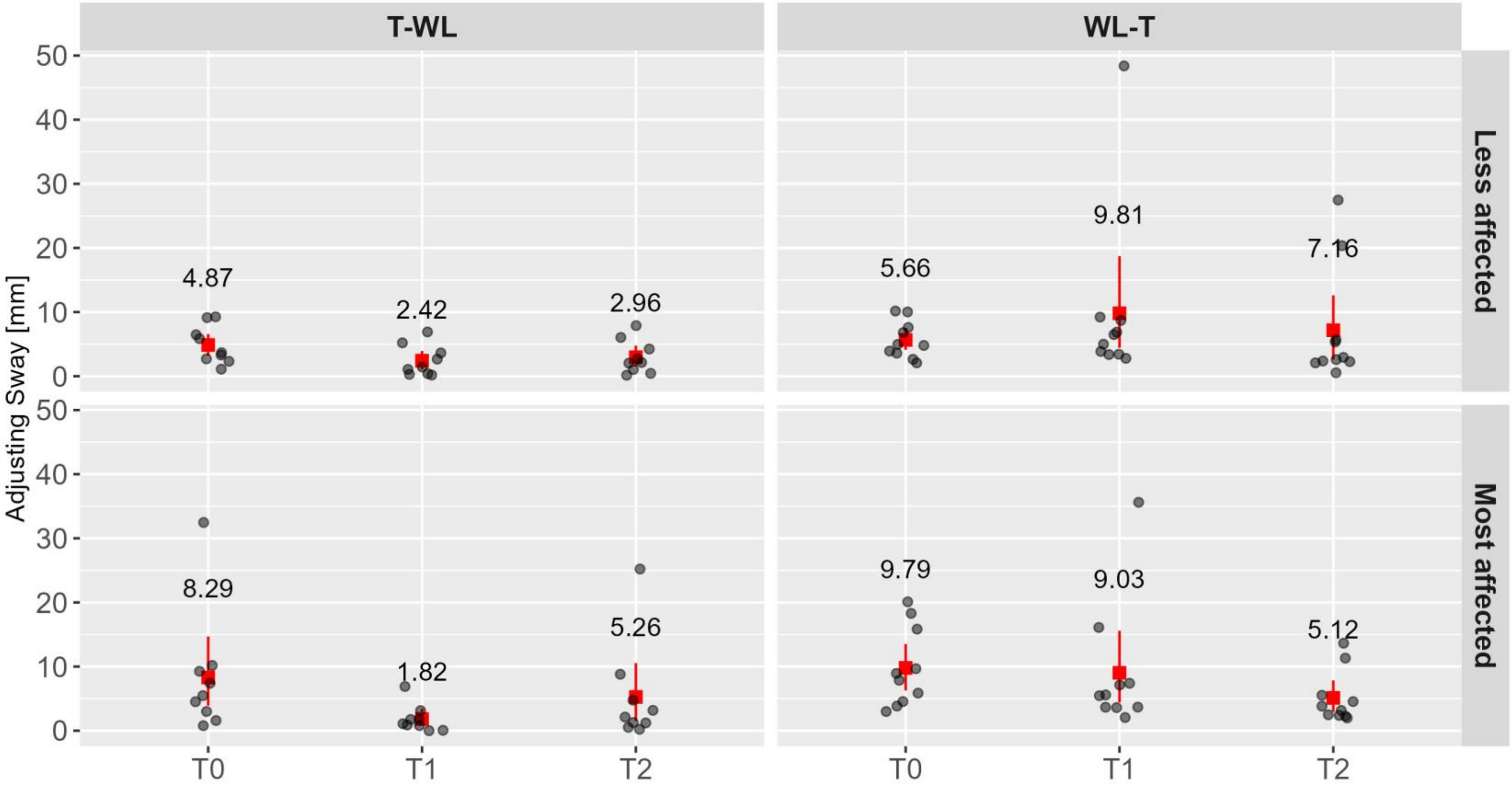


Figure 5 Frequency of changes in direction [Hz] in the Treatment-Waiting List (N= 9) and Waiting List –Treatment (N=10) sequences for the most affected (top) and less affected (bottom) limb.