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Clinical trial

# Unilateral arm rehabilitation for persons with multiple sclerosis using serious games in a virtual reality approach: Bilateral treatment effect?

Johanna Jonsdottir[a,*], Gloria Perini[a], Antonio Ascolese[b], Thomas Bowman[a], Angelo Montesano[a], Michael Lawo[c], Rita Bertoni[a]

[a] IRCCS Fondazione Don Carlo Gnocchi, Milan, Italy
[b] Imaginary srl, Milan, Italy
[c] Universität Bremen-TZI – Center for Computing and Communication Technologies, Am Fallturm 1 – 28359 Bremen, Germany

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ABSTRACT

*Impaired:* arm function and loss of manual dexterity can lead to decreased independence in activities of daily living in persons with Multiple Sclerosis (MS). In this study we verified the feasibility and efficacy of a serious games approach to supervised upper limb rehabilitation of the more affected arm in persons with MS and the cross-over effect to the nontreated arm.

*Methods:* Eighteen persons with moderate to severe MS symptoms participated (mean age 56.1 (range 28–73) years; mean disease duration 17.6 (4–35) years). Each participant received 12 supervised sessions of serious games (45 min, 12 sessions) aimed at improving the most affected upper limb. Primary outcomes were the Nine Hole Peg Test (9HPT) and the Box and Blocks Test (BBT). Perceived health was evaluated pre and post intervention with SF-12 and the VAS of the EuroQual-5DL. Non parametric tests were used and P was set at 0.05.

*Results:* After the serious games training participants improved dexterity and arm function bilaterally (10–18%), however, there was a statistically significant improvement only in the treated arm ($P < 0.05$). Perceived menthal health improved follwing training ($P < 0.05$) but not perceived physical health.

*Conclusion:* An in clinic intervention with a serious-games virtual reality approach positively influenced arm recovery in persons moderately to severely affected by MS, improving mainly the treated arm but with positive effects on the nontreated arm. The persons were motivated during the intervention and expressed being willing to continue this kind of training at home as part of continuity of care.

Persons with Multiple Sclerosis (MS) have various disorders affecting coordination and movement of the upper and lower limbs that impact upon participation in daily life situations. After 15 years of disease about 80% of persons with MS report some kind of hand function problem and almost half of them has to make adjustments or reduce activities involving upper limb functions (Kister et al., 2013; Bertoni et al., 2015). Accordingly, different studies have showed that loss of manual dexterity in persons with MS is associated with a decreased independence in activities of daily living (Bertoni et al., 2015; Kierkegaard et al., 2012; Lamers et al., 2015; Cattaneo et al., 2017).

Despite the fundamental role of upper limbs in daily life relatively little attention has been paid to addressing deficits in arm function of persons with MS and frequently upper limb rehabilitation is only a part of a training program directed also at improving lower limbs and balance (Lamers et al., 2016; Spooren et al., 2012). At present these multidisciplinary approaches have shown insufficient evidence of upper limb improvements. Interventions specifically aimed at the upper limb in persons with MS, such as robot training or functional electrical stimulation, have also shown limited benefits (Lamers et al., 2016; Spooren et al., 2012; Sampson et al., 2016; Carpinella et al., 2010). More importantly, given the importance of bilateral arm use in daily life activities, most publications have reported only on results in the treated

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* Corresponding author at: Servizio riabilitazione neurologica adulti (Int. 282), IRCCS Fondazione Don Carlo Gnocchi Onlus. Via Capecelatro 66 – 20148, Milan, Italy.
*E-mail address:* jjonsdottir@dongnocchi.it (J. Jonsdottir).

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arm while it is known that most persons with MS have involvement of both arms (Bertoni et al., 2015; Lamers et al., 2015; Sampson et al., 2016; Jonsdottir et al., 2018; Carpinella et al., 2012).

Recently, the use of new rehabilitation techniques to improve arm and hand functioning in persons with MS is increasing (Jonsdottir et al., 2018; Carpinella et al., 2012; Feys et al., 2009). Virtual reality and the use of serious games has been shown to be a feasible rehabilitation strategy to improve upper limb function in persons with neurological disorders and importantly, lends itself well as continuity of rehabilitation at home (Lamers et al., 2016; Spooren et al., 2012; Jonsdottir et al., 2018; Feys et al., 2009). Acting in a virtual environment can simulate real life objects and events and offers several advantages, such as, the possibility to perform meaningful tasks with many repetitions in an engaging setting. This approach can continuously adapt to the person's ability while giving multiple types of feedback and may thus enhance motor learning (Laver et al., 2015; Levin et al., 2015). Notably, these technologies enable the individuals to become more active in their lifelong healthcare process (Amann, 2017).

Jonsdottir et al. (2018) recently applied the virtual reality paradigm to arm and hand training of persons with MS with promising results. The study findings supported the feasibility of using virtual reality and serious games in upper limb rehabilitation, however, the efficacy was verified only for the most affected treated arm. While upper limb impairment due to MS is often unilateral at the beginning of the disease it does become increasingly bilateral with three fourths of persons moderately to severely affected by MS showing involvement of both arms (Bertoni et al., 2015). It is important to understand if arm rehabilitation even when applied unilaterally has an effect also on the other arm. Aim of this work is to further investigate the feasibility and efficacy of a serious games approach for upper limb rehabilitation in a sample of persons with MS and verify if there is a transfer of skills from the treated arm to the non-treated arm.

## 1. Methods

Twenty-two persons with MS were screened for eligibility from a convenience sample at Foundation Don Gnocchi Onlus, Milan, between September 2016 and June 2017. Inclusion criteria included persons with MS on the basis of the McDonald criteria (Polman et al., 2011) with upper extremity motor deficits but able to flex shoulder and elbow at least 45°, able to comprehend and follow directions (≥24 Modified Minimental SE). Subjects were excluded if they wore pace-makers, were epileptic or had other comorbidities of the arm.

Eighteen persons reporting upper limb difficulties and meeting study criteria were recruited for the study. All subjects signed an informed consent to the protocol approved by the local ethical committee (Comitato Etico, IRCCS Fondazione Don Gnocchi Milan). All rights of human subjects were observed.

### 1.1. Evaluation

Evaluations were done by a therapist blind to the purpose of the study, pre and post the twelve sessions of the serious games, using validated clinical scales.

Primary outcomes, used to measure fine movements of the hand and gross upper limb function, were the Nine Hole Peg Test (9HPT) (Lin et al., 2010) and the Box and Blocks Test (BBT) (Goodkin et al., 1988).

The 9HPT has been shown to be reliable and valid for persons with MS. In this study we took the time it took to insert all 9 pegs and remove them, the mean of two trials was used as outcome. A 20% change in test score is commonly used to define clinically meaningful worsening (Shirley Ryan λbilitylab website, 2014). Cut off values for abnormal scores were derived for the 9HPT by a mean score of healthy reference values of males and females (Oxford Grice et al., 2003) and adding two standard deviations resulting in a cut off value of 26,5 s. Study participants with values over the cutoff scores were categorized as having abnormal fine hand movements.

The BBT has excellent reliability and validity for persons with MS (Platz et al., 2005; Mathiowetz et al., 1985). The test quantifies limitations in arm function by the person's ability to grasp, transport, and release blocks in a timeframe of 1 min. Established norms range from 75,1 to 78,9 depending on age and sex. Better performance is indicated by a higher number of blocks moved. Cut off value for abnormal scores were derived for the BBT using the mean score of healthy values of males and females and adding two standard deviations, resulting in a cut off score ≥ 55 blocks. Study participants with values under the cutoff score were categorized as having abnormal hand and arm function.

Secondary outcome measured the perception of quality of life and the quality of health and were the short form SF12 (Ware et al., 1996) and the EQ-5D visual analogue scale (EQ-VAS) (Golicki et al., 2015). The normative reference values for both mental and physical domains of SF-12 is ≥ 50 points. The EQ-VAS is a scale ranging of 0 - 100 with 100 corresponding to perfect perceived health of the moment. Normative values in an age matched healthy Spanish population was 74,2 (Garcia-Gordillo et al., 2016).

Depression was evaluated with Beck's Depression Inventory Fast screening tool (BDI-FS) (Benedict et al., 2003). The BDI-FS is a seven-item questionnaire with scores ranging from 0–21 points with higher scores indicating more depressive symptoms. The test's validity has been verified and found to be good for persons with MS. Cutoff values are ≥ 4 points for mild depression, ≥7 to 9 points for moderate depression, and for severe depression > 9 points.

### 1.2. Intervention

Participants received their usual rehabilitation services, as well as, game playing. Each participant received 12 supervised sessions (3 to 5 times per week) of serious games (Fig. 1), lasting 45 min each, aimed at improving the most affected upper limb.

The treated arm was generally the one that had worse results on the 9HPT. When there weren't clear differences between the arms the subjects were asked to indicate the arm that they perceived as worse and that arm was treated.

The serious games were played using the Kinect (Microsoft website, 2016), a system consisting of a camera and a depth sensor. The rehabilitation approach was developed in a user-centered framework as part of a European Project (Rehab@Home,see Jonsdottir 2017 (Jonsdottir et al., 2018) and chapters (Jonsdottir et al., 2018; Ascolese et al., 2018)) and subsequently it has been further developed and new games added (Rehability, Imaginary srl). The gaming environment included a calibration of individual active range of motion and so the virtual environment could be adapted to the participant's ability irrespective of disability level. All participants played six arm rehabilitation games requiring different activities of arms and hands, and progressively more demanding levels resulting in a customized training load. The activities required grasping virtual objects by opening and closing hand and the moving of objects along trajectories in virtual space by means of arm movements. The scenarios of the serious games were various; the subjects had to touch flowers and avoid bees, move a basket on a table to capture falling objects, move shapes from left to right following a trajectory, move colored cans to the right kitchen shelf and so on (See Fig. 1 for an example of a game setup). The aim of the games was to improve coordination, reaction speed and timing, hand-eye coordination and spatial awareness. The progression of the task difficulties was according to levels of spatial accuracy, speed and complexity of attention required. Feedback was given to the player at the end of each game in the form of points achieved. Further, during the game positive achievements were rewarded with an enthusiastic sound and failures with a disappointing sound. Participants could play the games in sitting or standing, depending on their balance ability.

**Fig. 1.** An example of a Serious games scenario.
The subject had to move colored cans to one of four kitchen shelfs using hand and arm movements of grasping, moving and releasing.

### 1.3. Data analysis

Descriptive statistics and non parametric analyses of data were carried out. Wilcoxon matched pair test was applied to assess changes from baseline to post treatment in both treated (T) and non treated (NT) arms, and in participation measures. Difference in treatment effect between arms was verified with the Mann-Whitney U test and repeated measures ANOVA analysis. Statistical significance was set at $P = 0.05$. Effect sizes were calculated as Cohen's $D_z$ that is appropriate for dependent groups. Effects sizes were considered small if they were $<0.2$, small between 0.2 and 0.5, and moderate between 0.5 to 0.8, and high above 0.8 according to Cohen's classification (Turner and Bernard, 2006).

## 2. Results

Eighteen persons with MS (mean age 56.1 (range 28–73) years; mean disease duration 17.6 (range 4–35) years) reporting upper limb difficulties were recruited. The group had moderate to severe disability as described by a median EDSS value of 7 (range 4–8) . Eleven persons were in a relapse remitting phase while 7 persons were in a progressive phase (Table 1).

All participants completed the study protocol and no adverse events were encountered during the treatment period.

In all subjects the dominant arm was the right. After classification of the more affected arm according to criteria the non dominant arm was treated in half of the sample while in the other half the treated arm was the dominant arm. All results will be reported for treated and non-treated-arm regardless of side.

On average the sample was not depressed at baseline, however, 6 participants were above the cut off scores for mild depression (mild depression $\geq 4$ points on BDI-FS), one of those was severely depressed with 10 points ($>9$ points on BDI-FS). Following treatment 2 persons still had mild depression and the participant with severe depression at baseline had changed to moderate depression.

### 2.1. Primary outcomes

#### 2.1.1. 9 Hole Peg Test

At baseline 22,5% ($N = 4$) of the sample did not have abnormal scores on the 9HPT in either arm, 22,5% ($N = 4$) had abnormal scores unilaterally and 55% ($N = 10$) of the sample had abnormal scores

**Table 1**
Individual and group demographics and characteristics.

| | Age (Years) | F/M | Disease duration (Years) | EDSS | 9HPT T-arm | 9HPT NT- arm | EQ5D VAS Health | SM Type |
|---|---|---|---|---|---|---|---|---|
| Case 1 | 57 | M | 35 | 6.5 | 293,2 | 32,9 | 30 | RR |
| Case 2 | 59 | F | 10 | 5.5 | 26,9 | 17,0 | 80 | RR |
| Case 3 | 60 | F | 11 | 6.5 | 34,8 | 31,6 | 65 | RR |
| Case 4 | 64 | F | 25 | 6.5 | 50,0 | 40,5 | 50 | RR |
| Case 5 | 57 | F | 11 | 7.5 | 38,8 | 38,3 | 50 | SP |
| Case 6 | 35 | F | 12 | 7 | 25,2 | 26,9 | 80 | SP |
| Case 7 | 55 | M | 26 | 6.5 | 24,1 | 22,3 | 25 | RR |
| Case 8 | 54 | F | 12 | 6.5 | 41,2 | 45,0 | 70 | RR |
| Case 9 | 58 | M | 27 | 8 | 80,3 | 37,9 | 60 | SP |
| Case 10 | 55 | F | 28 | 6.5 | 34,6 | 31,5 | 80 | SP |
| Case 11 | 57 | M | 35 | 6.5 | 32,7 | 30,5 | 50 | SP |
| Case 12 | 73 | M | 15 | 6 | 32,1 | 25,1 | 50 | RR |
| Case 13 | 55 | F | 11 | 6.5 | 20,2 | 16,8 | 80 | PP |
| Case 14 | 59 | M | 23 | 6.5 | 74,8 | 29,9 | 75 | SP |
| Case 15 | 28 | F | 5 | 8 | 59,2 | 49,3 | 60 | RR |
| Case 16 | 70 | F | 11 | 6.5 | 24,1 | 18,8 | 35 | RR |
| Case 17 | 52 | F | 4 | 6.5 | 24,3 | 24,8 | 50 | RR |
| Case 18 | 62 | F | 16 | 4 | 25,8 | 28,4 | 100 | RR |
| Median | 57 | | 13,5 | 7 | 33.6 | 30.2 | 60 | |
| (IQR) | (55–59.7) | | (11–25.7) | (6–8) | (25.4–47.8) | (24.8–36.6) | (50–78.7) | |
| Mean | 56.1 | | 17.6 | 6.5 | 52.4 | 30.4 | 60.6 | |
| (SD) | (10.5) | | (9.7) | (1.9) | (62.6) | (9.2) | (20.0) | |

F = female; M = male; EDSS = Expanded Disability Status Scale; 9HPT = Nine Hole Peg Test; EQ VAS = EuroQol visual analogue scale; IQR = interquartile range; SD = standard deviation.

**Table 2**
Pre and post values of primary and secondary outcomes ($N = 18$).

| | PRE Median | IQR | POST Median | IQR | Change from pre to post *p*-value | Cohen's $D_z$ |
|---|---|---|---|---|---|---|
| 9HPT- T arm | 33.6 | 25.4/47.8 | 28.0 | 23.9/47.2 | 0.011* | 0.577 |
| 9HPT- NT arm | 30.2 | 24.8/36.6 | 25.6 | 22.2/32.5 | 0.149 | 0.309 |
| BBT - T arm | 38 | 38.8/44.8 | 45 | 31.5/49.3 | 0.030* | 0.546 |
| BBT - NT arm | 41 | 33.5/48.3 | 45 | 38.0/54.8 | 0.088 | 0.391 |
| EQ-5D VAS | 60 | 50/80 | 70 | 50/85 | 0.380 | |
| SF-12 MCS | 46.35 | 38.6/59 | 54.1 | 40.3/61.1 | 0.015* | |
| SF-12 PCS | 28.65 | 21.9/33.8 | 29.8 | 25.8/35.1 | 0.310 | |

IQR = interquartile range; 9HPT = Nine Hole Peg Test; BBT = Box and Block; EQ VAS = EuroQol visual analogue scale, SF12 MCS = Short-Form 12 Health Survey Mental Component Score; SF12 PCS = Short-Form 12 Health Survey Physical Component Score; T arm = treated arm; NT arm = non treated arm.
* = Significant difference at post treatment. $P < 0.05$.

bilaterally (Table 1). Following treatment 44% ($N = 8$) did not have abnormal scores, 12% had abnormal scores unilaterally and 44% had abnormal scores bilaterally on the 9HPT.

At baseline there were statistically significant differences between treated and nontreated arms on the 9HPT with the T-arm being worse ($P = 0.005$). Following rehabilitation there were still statistically significant differences between arms ($P = 0.002$) (Table 2).

After the serious games training, participants improved the velocity of fine hand movements bilaterally as measured by the 9HPT, however, there was a statistically significant improvement only in the treated-arm that went from Mdn 33.6 s (IQR 25.4–47.8) at baseline to 28 s (IQR 23.9–47.2), ($P = 0.011$) an improvement of 17% from baseline value. The nontreated-arm instead improved from Mdn 30.2 s (IQR 24.8–36.6) to 25.6 s (IQR 22.2–32.5) ($P = 0.15$), a change of 15% that brought the performance of the nontreated-arm to the level of healthy age-matched normative values. The difference in change between arms was not significant ($P = 0.407$) (Table 3). This was further verified with a repeated measured ANOVA that revealed no interaction for time per treatment ($F(1,33) = 0.449$, $P = 0.508$) while there was a time effect ($F = 6.868$, $= P = 0.013$).

On average both the treated-arm and the nontreated-arm were nearer the cut off score for normative values of age-matched subjects after rehabilitation. At baseline the dexterity of the treated-arm was at 79% of normative values and after rehabilitation it was at 95% while in the nontreated-arm dexterity was at 88% of normative values at baseline and at 100% after rehabilitation (Fig. 2).

On an individual level, 5 persons improved their dexterity in response to treatment in a clinically meaningful way (≥ 20%) in response to treatment while in the nontreated-arm 7 people improved in a clinically important way.

A sample size calculation for a study powered to detect a difference between arms was carried out. The difference of adjusted means post intervention (without outlier) was 2,3 s on the 9HPT, with a standard deviation of 8 s and 10 s respectively for the treated and the non treated arm. A type 1 error set at 5% and power at 80% resulted in a sample size needed of 245 persons (with 490 arms) for a future study interested in differentiating between a treatment effect of a serious games in virtual reality and a crossover effect. Regarding efficacy of a VR treatment versus a control treatment, a similar study had established that a sample size of 29 persons per group was needed (Jonsdottir et al., 2018). Thus, the influence of a crossover effect of treatment between arms seen in the present study results in a much bigger sample size needed to demonstrate a significant difference in change between arms of the same person.

**Table 3**
Difference in median change scores for Treated and Non-treated arm at activity level post intervention.

| | T arm | NT arm | *p*-value |
|---|---|---|---|
| 9HPT sec (% of change)* | −3.0 (−9%) | −1.1 (−4%) | 0.407 |
| BBT nr (% of change)# | 2.5 (6%) | 1.5 (4%) | 0.408 |

9HPT = Nine Hole Peg Test; BBT = Box and Block; T arm = treated arm; NT arm = non treated arm.
* A negative value means an improvement.
# a positive value means an improvement.

### 2.1.2. Box and Block Test

Regarding the BBT, at baseline all participants had abnormal values in the treated-arm and 83% also had abnormal values in the nontreated-arm (15/18). After rehabilitation 89% of the participants still had abnormal values in the treated-arm (16/18) and 67% in the nontreated-arm (12/18).

At baseline there were statistically significant differences between arms in number of cubes moved ($P = 0.012$) with the treated-arm moving less cubes. Following rehabilitation the difference between arms was still statistically significant ($P = 0.006$) (Table 2).

For both arms the number of cubes moved increased following the serious games intervention but only in the treated-arm was the change statistically significant, ($P = 0{,}043$), from Mdn 38 cubes (IQR 38.8–44.8) to 45 cubes (IQR 31.5–49.3), a change of 18%. With the nontreated-arm, the participants improved the score of BBT from 41 cubes (IQR 33.5–48.3) to 45 cubes (IQR 38.0–54.8, $P = 0{,}12$) a change of 10% (See Table 2 for baseline, results and effect sizes). The difference in change between arms was not significant ($P = 0.408$) (Table 3). This was further verified with a repeated measured ANOVA that revealed no interaction time per treatment ($F(1,33) = 0.1658$, $P = 0.686$) while there was a significant time effect ($F(1,33) = 8.798$, $P = 0.005$).

After the VR training on average both the treated and the nontreated-arm were nearer the cut off score for normative values of age-matched subjects after rehabilitation. In the treated-arm the participants were at 69% of normative values at baseline and after rehabilitation they were at 75% while in the nontreated-arm they were at 78% of normative values at baseline and at 83% after rehabilitation (Fig. 2).

The change in treated and nontreated-arm was not statistically different ($P = 0.408$) (Table 3).

Regarding arm function, 6 persons improved in a clinically meaningful way (≥4 blocks) in the treated-arm, and 3 persons in the arm non-treated (Siebers and Oberg, 2010).

### 2.2. Secondary outcomes

Participants increased their perception of health (EQ-VAS) after the serious game rehabilitation, from 60 (IQR 50–80) to 70 (IQR 50–85) however the change was not significant ($P = 0.38$). There was a significant improvement in the mental domain of the SF-12 from 46.35 (IQR 38.6–59) to 54.1 (IQR 40.3–61.1)($P = 0.015$) (Table 2), while no changes were observed in the physical domain of the SF-12 (from 28.65 (IQR 21.9–33.8) to 29.8 (IQR 25.8–35.1)).

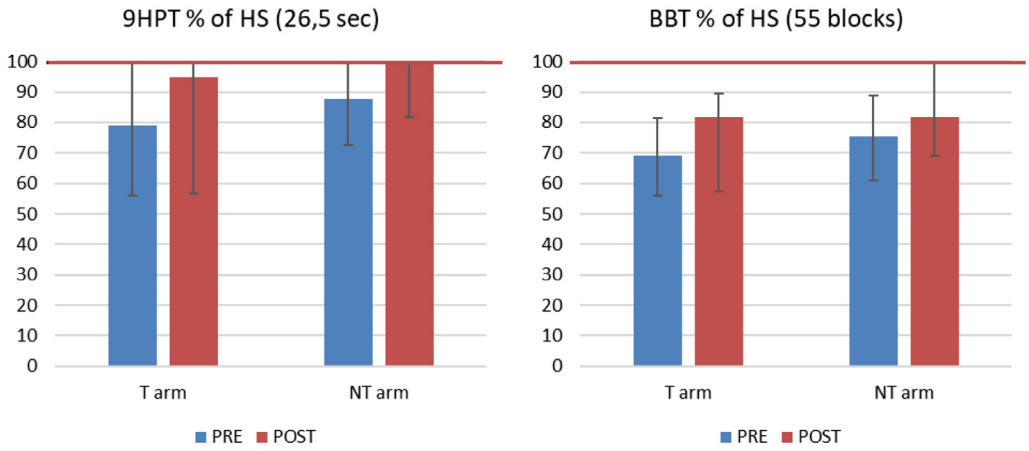


**Fig. 2.** Percentage performance (means and standard deviations) on the 9HPT and BBT relative to normative values of age-matched healthy subjects (HS) 9HPT = Nine Hole Peg Test; BBT = Box and Block; HS = healthy subjects; T arm = treated arm; NT arm = non treated arm. 100% and thick line imply performance of age matched healthy persons plus 2 standard deviations.

## 3. Discussion

The aim of this study was to verify the feasibility and efficacy of a serious games approach to supervised upper limb rehabilitation of the more affected arm in persons with MS and the cross-over effect to the nontreated-arm. The intervention was safe and well accepted with improvement in dexterity and arm function in the treated and non treated arm, as well as, a positive impact on the mental domain of perceived health.

All but two participants required unilateral or bilateral walking aid and four of the participants were wheelchair bound. In accordance with the literature for this disability level most of our participants were below normative values of healthy age-matched persons both in dexterity and in arm function (Oxford Grice et al., 2003; Mathiowetz et al., 1985). Almost 80% of the sample had abnormal values in the treated arm on the 9HPT with respect to healthy age-matched subjects while 55% had abnormal values bilaterally. Instead on the BBT, that measures more gross hand and arm function, the whole sample had abnormal values for the treated arm and more than 80% of them had abnormal values bilaterally. This relatively more severe disability in arm function compared to dexterity in our sample is similar to that found in the study of Goodkin et al. (1988) suggesting that gross motor arm function may be affected earlier in the disease course than finer movements.

### 3.1. Primary outcome

#### 3.1.1. Dexterity and arm function

After twelve sessions with the VR serious games there was a trend for both arms to be improved in dexterity and arm function although only in the treated arm was the change statistically significant with both dexterity and arm function improving approximately 18%, a near clinically significant change. There was a cross over effect of the intervention for the nontreated arm of 15% and 10% respectively for dexterity and arm function. These effects were confirmed by moderate effect sizes ($>0.5$) for the treated arm and small effect sizes for the nontreated arm. It has to be considered that before treatment the nontreated arm was nearer normative value for dexterity of healthy age matched subjects and that after the intervention the dexterity in the nontreated arm arrived at the normative cut off value indicating a ceiling effect for improvement. The treatment effect found in the treated arm is a confirmation of findings from a prior pilot study (Jonsdottir et al., 2018) that investigated the use of VR serious games for arm rehabilitation in persons with MS.

Most studies investigating the use of rehabilitation to improve arm and hand functioning in persons with MS have considered only the arm that was treated and results are often inconclusive. A study of Kamm et al. (2015) reported no change in 9HPT in a sample of persons with MS after Feldenkrais bodywork that included arm training. In line with these results Feys and colleagues (Feys et al., 2015) found no significant changes for any clinical measure in neither intervention nor a control group following robot therapy. Taken together these studies demonstrate the difficulty in changing upper limb function in persons with MS.

There are studies reporting improved dexterity following rehabilitation (Carpinella et al., 2010; Gijbels et al., 2011). Among those a pilot study by Carpinella and colleagues (Carpinella et al., 2010) using robotic therapy for the more affected limb reported improvement (20%) similar to those achieved in the present study. They also reported a cross over effect of 10% to the nontreated arm in persons with MS of similar disability levels to the present study, adding support for a crossover effect to the nontreated arm following rehabilitation requiring unilateral arm movements.

It is evident from the study results and reporting of others that both arms tend to be affected in persons with MS, in particular in arm function (Bertoni et al., 2015; Solaro et al., 2019). Consequently it would be fundamental to test and report performance of both arms, even when the intervention is unilateral.

Further, in the study population that was moderately to severely affected in mobility there was a tendency for dexterity, as measured by the NHPT, to have a ceiling effect, especially in the less affected arm. Future studies should consider using both NHPT and the BBT when describing functioning of the arm in persons with similar characteristics since the BBT appears to be more sensitive to changes in upper limb function due to disease progression.

### 3.2. Secondary outcomes

Participants increased their perception of overall health (EQ-VAS) after the serious game rehabilitation by 17%, from 60 to 70. This improvement in perceived health,was in line with an improvement in perceived mental functioning as measured by the SF-12. In accordance with findings of other authors (Jonsdottir et al., 2018; Patti et al., 2003) perception of mental health at baseline was near values of healthy subjects. Following the serious games intervention there was a significant improvement bringing the participants within normal range. The use of an engaging and entertaining intervention most likely played some role in improving self-perception of mentally related health.

Instead the overall perception of the physical health, as measured by the physical domain of the SF-12, was low at baseline and did not respond to treatment. This low perceived physical health is again in line with findings from Patti and colleagues (Patti et al., 2003) that found the domain of physical functioning on the SF-36 to be markedly low in persons with EDSS scores similar to those of the present study.

It should be considered though that the VR serious games treatment was only directed at improving upper limb function while the participants all had moderately to severely reduced mobility. It is possible that

the improvement in upper arm function was not relevant enough for the participants to influence the overall perceived physical health.

### 3.3. General discussion and limitations

Multiple Sclerosis is a chronic neurological disease that can lead to significant motor and cognitive disability and consequently persons with MS need a lifetime continuity of rehabilitation. The integration of innovative technologies in their continuity of care could have a significant impact on the short and long term efficacy of their disease management. In the present study the virtual reality approach was beneficial in improving the more affected arm and there was a trend for improvement also in the less affected, nontreated arm. This is important considering that a large number of ADL are performed bilaterally. The scarcity of studies considering both arms after upper limb rehabilitation in persons with MS is preoccupying since it has been shown that bimanual activities such as changing clothes, washing hands, washing plates etc. are performed more frequently than unimanual activities in daily life (Kilbreath and Heard, 2005). Further, impaired upper limb function in general has been associated with decreased odds of employment and decreased participation in community activities (Cattaneo et al., 2017; Johansson et al., 2007).

VR and user interfaces appear to be a favorable method of motor learning and life-long training for persons with MS. The participants in the present study were motivated during the training and most expressed being willing to continue this approach in their house. A rehabilitation approach including VR applied in the home of persons with MS would allow more people to have intensive training with possible decreased costs of treatment.

Given this potential of the virtual reality approach to rehabilitation in continuity of care the present results are promising for maintaining and/or improving bilateral arm and hand function in persons with MS throughout their disease course.

There are limitations to this study. First of all there was no control group receiving other treatments and so a superiority of the experimental intervention was not verified. However, since MS is a progressive disorder an improvement in arm and hand function is an important result of this study. Nonetheless, these results should be further verified in bigger random controlled studies and a longer-term follow-up evaluation to explore the retention of improved performance of treated arm would be needed. Second, the intervention effects on arm and hand use in daily life were not verified with patient reported outcomes specific to arm activities. Finally, in this study we treated only the more affected arm with some translation of effect onto the less affected arm, however, future studies using the virtual reality approach should preferably include also bilateral activities.

## 4. Conclusion

An in clinic intervention with a serious-games virtual reality approach positively influenced arm recovery in persons moderately to severely affected by Multiple Sclerosis, improving mainly the treated arm but with beneficial effects also on the nontreated arm. The persons were motivated during the intervention and expressed willingness to use the approach in continuity of care. The adoption of technological virtual reality solutions is promising for promoting motor learning and training in persons with MS over the whole disease course and in diverse situations of life.

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