Multiple Sclerosis and Related Disorders 19 (2018) 25–29

Contents lists available at ScienceDirect

Multiple Sclerosis and Related Disorders

journal homepage: www.elsevier.com/locate/msard

Serious games for arm rehabilitation of persons with multiple sclerosis. A randomized controlled pilot study☆

Johanna Jonsdottir[a,*], Rita Bertoni[a], Michael Lawo[b], Angelo Montesano[a], Thomas Bowman[a], Silvia Gabrielli[c]

[a] IRCCS Don Gnocchi Foundation Onlus, Milan, Italy
[b] Universität Bremen-TZI – Center for Computing and Communication Technologies, Am Fallturm 1, 28359 Bremen, Germany
[c] Fondazione Bruno Kessler, Via Sommarive 18, Trento, Italy

A R T I C L E I N F O

Keywords:
Multiple Sclerosis
Rehabilitation
Upper extremity
Virtual Reality
Kinect
Serious games

A B S T R A C T

Objectives: The feasibility and preliminary evidence for efficacy of a serious games platform compared to exergame using the Wii for arm rehabilitation in persons with multiple sclerosis (MS) was investigated.
Methods: A pilot single-blind randomized (2:1) controlled in clinic trial was carried out. Sixteen persons with MS participated (age years 56.8 (SD 12.3), MS-onset years 19.4 (SD 12.3), EDSS 6.5). Ten participants used a serious games platform (Rehab@Home) while 6 participants played with the commercial Wii platform, for four weeks (40 min, 12 sessions/4 weeks). Feasibility and user experience measures were collected. Primary outcomes were the 9 Hole Peg Test (9HPT) and the Box and Block test (BBT). Secondary outcomes were the EQ-5D visual analogue scale (EQ-VAS) and the SF-12. Nonparametric analysis was used to verify changes from pre to post rehabilitation within group and treatment effect was verified with Mann-Whitney *U* test. P value was set at 0.10 and clinical improvement was set at 20% improvement from baseline.
Results: Serious games were perceived positively in terms of user experience and motivation. There were clinically significant improvements in arm function in the serious games group as measured by 9HPT (38–29.5 s, P = 0.046, > 20%) and BBT 32–42 cubes, P = 0.19, > 20%) following the 12 gaming sessions while the exergame group did not improve on either test (9HPT 34.5–41.5 s, P = 0.34; BBT 38,5 to 42 cubes, P = 0.34). Only the exergame group perceived themselves as having improved their health. There was a significant between groups treatment effect only in perception of health (EQ-VAS) (Z = 1.93, P = 0.06) favouring the exergame group.
Conclusions: Virtual reality in a serious gaming approach was feasible and beneficial to arm function of persons with MS but motivational aspects of the approach may need further attention.

1. Introduction

Multiple Sclerosis (MS) is a degenerative neurological disorder affecting more than two million people worldwide leading to chronic disability and reduced quality of life (Browne et al., 2014; Pugliatti et al., 2006). Along with limitations in mobility, persons with MS frequently present with limitations in reaching and grasping, that consequently impacts on their daily independence (Bertoni et al., 2015; Cattaneo et al., 2017). Rehabilitation aimed at reducing the limitations resulting from the neurological deficit can be a costly long-term process because of the disease's long duration, the higher prevalence and incidence among young adults and the subsequent early loss of productivity (Moccia et al., 2016; Stawowczyk et al., 2015). Not all patients that need this kind of support can have access to continuous rehabilitation leading to non optimal recovery and functionality. Further, lack of motivation is a common problem in long-term rehabilitation often leading to reduced or no adherence to exercise regimes suggested by clinicians. One solution could be to provide a motivational technological solution for rehabilitation of the arms of persons with MS (Lohse et al., 2014, 2013a; Hung et al., 2016; Pollock et al., 2014). Gaming through virtual reality is already being used in neurorehabilitation. Two distinctive approaches exist: Gaming through serious games, that refers to games that are conceived and developed with the expressed purpose of being rehabilitative of a limited function; and gaming through exergames, that refers to the use of games already existing as entertainment for the general population but then applied in

☆ Retrospectively registered: ClinicalTrials.gov Identifier: NCT02764372.
* Correspondence to: 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).

http://dx.doi.org/10.1016/j.msard.2017.10.010
Received 28 August 2017; Received in revised form 9 October 2017; Accepted 15 October 2017

the context of rehabilitation. According to two recent reviews on interactive gaming technology, serious and exergaming could both be promising approaches to facilitate rehabilitation of balance, mobility and arms for persons with neurological disorders (Laver et al., 2011; Taylor and Griffin, 2015). While the Wii console combined with the Balance board has been used in balance rehabilitation for persons with MS with mostly beneficial results, until now the feasibility and efficacy research of virtual reality paradigms for arm rehabilitation has been primarily carried out on persons with stroke or Parkinson's Disorder (Lozano-Quilis et al., 2014; Brichetto et al., 2013; Prosperini et al., 2013; Nilsagård et al., 2013).

The Rehab@Home serious games system was developed within a European Union grant framework (FP7) to support upper arm rehabilitation of persons with neurological disorders. The final product used Kinect (Hondori and Khademi, 2014) with serious games where the rehabilitation objective was to promote fine and gross arm and shoulder movements while interacting within a virtual environment.

The objective of this study was to assess the feasibility of using the final therapeutic gaming system (Rehab@Home), to augment upper extremity neurorehabilitation services and to provide preliminary evidence of clinical efficacy of the gaming approach in increasing arm performance and health related quality of life of persons with MS.

2. Methods

A pilot single-blind randomized controlled trial was carried out with inpatients and outpatients in a rehabilitation center setting. Twenty eight persons with Multiple sclerosis and resultant upper extremity deficits were screened for eligibility from a convenience sample at Foundation Don Gnocchi Onlus, Milan, in a period of 7 months in 2015–2016. Sixteen individuals met inclusion criteria and were recruited and subsequently randomized (ratio 2:1), by a person external to the study, to an experimental group that played serious games and a control group that played exergames (Fig. 1). Participants included persons with MS established according to McDonald's criteria (Polman et al., 2011) with upper extremity motor deficits but able to flex shoulder and elbow at least 45 degrees, able to comprehend and follow directions, while persons with MS wearing pace-makers, epilepsy and with other comorbidities of the arm were excluded.

The project was approved by the center's Ethics Board (Comitato Etico, IRCCS Fondazione Don Carlo Gnocchi Onlus, Milan) and all participants signed informed consent forms. The rights of human subjects were protected.

2.1. Interventions

Both groups received their usual rehabilitation services, as well as, game playing. The training was done in the clinic by physical therapists trained in using virtual reality. The intervention group received Serious Games-based upper extremity therapy for a total of 12 sessions (4–5 sessions, 40 min, per week) and the control group played the same amount of time with commercial exergames requiring arm movements, available with the Nintendo Wii Console™.

The serious games were played using Kinect (Microsoft website, 2016). The system consisted of a camera and a depth sensor. 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. Six arm rehabilitation games were available to be played and all had adjustable difficulty levels and required different activity of arms and hands (Fig. 2). With increase in ability the games were made progressively more demanding. The exercises consisted in purposeful arm movements in virtual space and in opening and closing of hand to grasp virtual objects. Objective of the games were to improve movement coordination, reaction speed and timing, hand-eye coordination and spatial awareness. The serious games were carried out in a virtual home and garden environment requiring activities such as, putting away cans in a cupboard or capturing flowers while avoiding being stung by bees. Games were played in sitting or standing, depending on the participants' balance ability.

The exergames group played various games of their choice available from the Nintendo Wii gaming console. Playing required holding or gripping the controller and pressing the main buttons A and B during gaming. Games came from the Nintendo Wii package that offers games enabling users to work on timing, dexterity, hand-eye coordination, perceptual skills and spatial awareness. Games were played in sitting or standing, depending on the participants' balance ability.

2.2. Outcome measures

All participants were evaluated by a physical therapist blinded to group assignment using validated clinical scales for functional arm abilities and perception of health administered before and after the twelve sessions of the serious games or exergames playing. Feasibility measures (number and duration of sessions attended) were collected for both groups and user experience indicators (motivation, user satisfaction) were collected for the serious games group (White et al., 2012;

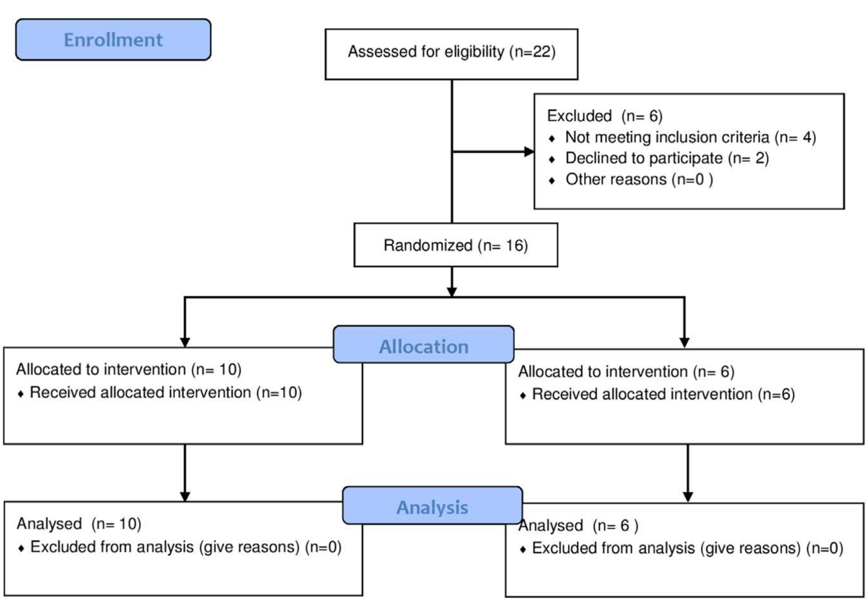

Fig. 1. Flow diagram for enrollment and assignment in the study.

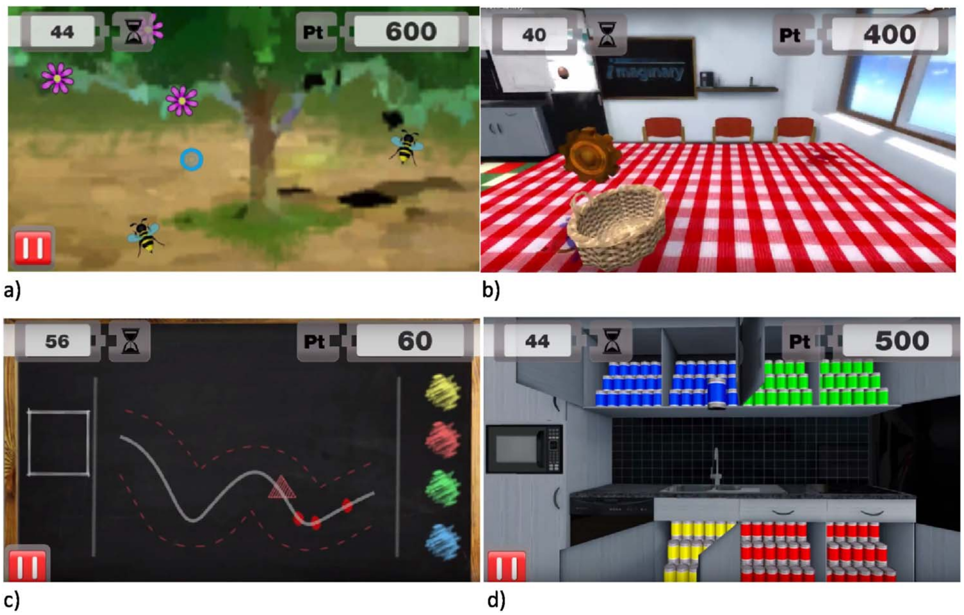

Fig. 2. Serious games scenarios. legend: Four serious game scenarios requesting patients to purposefully grasp, move and avoid objects using arm and hand movements: a) touch flowers and avoid bees; b) move basket on the table to capture falling objects; c) move shapes from left to right following a trajectory; d) move colored cans to the right kitchen shelf.

Bullinger, 1991). Primary outcomes at the activity level were the 9 hole peg test (9HPT) and the Box and Block test (BBT) (Lin et al., 2010; Goodkin et al., 1988). Secondary outcomes were the EQ-5D visual analogue scale (EQ-VAS) (Golicki et al., 2015) and the short form SF-12 (Ware et al., 1996). The healthy population reference score for SF-12, for both mental and physical domains, is equal to or above 50 points.

2.3. Data analysis

Due to the pilot nature of this study descriptive and nonparametric analyses of datawere carried out. The Wilcoxon test was used to verify changes from pre to post rehabilitation within group for primary and secondary measures and treatment effect was verified with the Mann-Whitney *U* test. Statistical significance was set at P ≤ 0.10, and clinical significance was set at a change ≥ 20% from the original score.

3. Results

All participants completed their protocol (mean age 56.8 (SD 12.3) years old, MS-onset years 19.4 (SD 12.3), 4 males/12 females, EDSS 6.5 (IQR 6.5–7.0)) and no adverse events or negative outcomes were encountered during the treatment period. There were no statistical differences in age or onset of MS, nor in any of the baseline measures of function and perception of health state between the serious games group and the exergames group, except on the EQ-VAS scale where the exergames group had a significantly worse perceived health status (P < 0.10) (Table 1).

3.1. Primary outcomes

Participants in the serious games group had a clinically and statistically significant increase in velocity of fine pinch, grasping and releasing movements of the treated hand as measured by the 9HPT, Mdn 38 s (IQR 29.4–57.7) to 29.5 s (IQR 26.5–57.1), P = 0.046, while the exergame group did not improve, Mdn 34.5 s (IQR 23.2–77.2) to 41.5 s (IQR 24.9–70.6), P = 0.34. Five participants in the serious games group improved more than 20% on the 9HPT and none in the exergames group.

Regarding the BBT, the number of cubes moved increased clinically significantly, but not statistically, from pre to post game playing in the serious games group from Mdn 33 cubes (IQR 27–44) to 42 cubes, (IQR 31–46), P = 0.19, but not in the exergames group, Mdn 38,5 cubes, (IQR 27–47) to 42 cubes, (IQR 35–52), P = 0.34. Four subjects in the serious games group improved more than 20% while one subject in the exergames group improved more than 20%.

There was no significant between groups treatment effect for either test.

For a sample size calculation of a future randomized study the mean change of the two groups on the 9HPT and the higher standard deviation of the two groups (Exergames group SD 7.84) were used, type 1 error was set at 5% and power at 80%. The resultant sample size for a future randomized study was 29 persons per group.

3.2. Secondary outcomes

There was a significant increase in perception of health (EQ-VAS) in the exergames group only, from 42.5, (IQR 30–45) to 75, (IQR 50–80), P = 0.046, while the serious games group that had baseline values that were already within normal range did not change, from 62,5 (IQR 50–80), to 65 (IQR 45–85), P = 0.77. Changes were observed in the mental domain of the SF-12 in both groups, serious games: 51.6 (IQR 39.1–59.3) to 56.8 (IQR 40.3–61.4), P = 0.109 and exergames: 44.3 (IQR 27.8–58.6) to 55.4 (IQR 51.4–65.7), P = 0.03. Only the exergames group had a significant improvement in the physical domain of the SF-12, serious games: 25.5 (IQR19.9–33.8) to 30.5 (IQR 25.8–34.2), P = 0.44 and exergames: 26.8 (IQR 24.2–35.1) to 34.4 (IQR 31–36.6), P = 0.07.

There was a significant between groups treatment effect only in perception of health (EQ-VAS) (Z = 1.93, P = 0.06).

As for feasibility, the User Experience of persons using the REHAB@HOME serious games system, measured after each of the 12 consecutive sessions was positive, ranging from 4 to 4.64 (1–5 Likert scale, 5 = most positive) for motivation and from 3 to 4.86 for satisfaction.

4. Discussion

To our knowledge this is the first study to be conducted on arm rehabilitation using a virtual gaming environment for persons with MS. Our results show that the serious games developed were positively accepted by participants with MS, with clinically important improvements in fine and gross hand function in response to the serious games' intervention while the exergame group improved less. Noteworthy, only the exergames group perceived themselves as having improved their health. Altogether the study provides initial support for the

Table 1
Subject demographics and characteristics.

	Age (Years)	F/M	Disease duration (years)	EDSS	Group	Box & blocks	Eq. 5D VAS - Health
Case 1	40	F	13	6.0	E	35	45
Case 2	70	F	11	6.5	E	54	52
Case 3	37	F	18	7.5	E	24	25
Case 4	60	F	29	6.5	E	47	40
Case 5	48	F	18	7.0	E	42	45
Case 6	63	F	15	7.0	E	27	30
Mean and (SD)	53.5 (13,3)		17.3 (6.3)			38.2 (11.6)	39.5 (10.1)
Case 7	57	M	36	6.5	S	9	30
Case 8	59	F	11	5.5	S	53	80
Case 9	60	F	12	6.5	S	38	65
Case 10	64	F	26	7.0	S	33	50
Case 11	57	F	12	7.5	S	24	50
Case 12	35	F	13	7.0	S	44	80
Case 13	55	M	27	6.5	S	48	25
Case 14	54	F	13	6.5	S	33	70
Case 15	58	M	28	8.0	S	27	60
Case 16	55	F	29	6.5	S	30	80
Mean and (SD)	55,4 (7.7)		20.7 (9.3)			33.9 (12.7)	59.0* (20.1)

SD = standard deviation; F = female; M = male; MS = multiple sclerosis; EDSS = Expanded Disability Status Scale; E = exergames; S = Serious games.
* = Significant difference between groups at baseline, $P < 0.10$.

appropriateness of deploying gamebased rehabilitaton technologies within plans of care in persons with MS. This is important because MS is a neurodegenerating disorder, often affecting young people that will need rehabilitation over a lifetime

The positive feedback on the feasibility of the serious games approach and the motivation to use the platform in the present study is in line with findings by other feasibility studies carried out in the context of virtual reality and serious (Laver al.,2011; Lohse et al., 2013b). Lack of motivation is a common problem in long term rehabilitation leading to reduced or no adherence to exercise regimes suggested or prescribed by clinicians. Training with virtual reality can provide tailored environments and the opportunity to solve motor problems in a gaming environment, with the potential of enhancing adherence to long-term plans of care (Lohse et al., 2013b).

Regarding the effect of the serious game approach to arm rehabilitation, there were clinically important improvements in arm function with over 20% (9 blocks) increase in blocks moved on the BBT. This improvement exceeds the one reported by Siebers et al. (2010) regarding a change of 4 blocks after 2 weeks' virtual training in persons with spasticity after stroke. For persons with MS there are no reference values from virtual reality training, but a 20% increase in hand function in response to rehabilitation is considered clinically relevant[23], (Schwid et al., 2002). The serious games group also improved their fine hand function, as denoted by a statistically and clinically relevant change of more than 20% on the 9HPT. The improvement found is comparable or superior to that found in persons with MS following robot training of similar intensity (Carpinella et al., 2012; Lamers et al., 2016). It is likely that the tailored approach of the serious games enabled an adaptation to the level of individual ability and thus adequate challenge to increase arm and hand function. In contrast, the exergame group had only a 9% improvement on the BBT and actually increased the time taken to complete the 9HPT indicating little effect on arm function from the exergaming approach. Contrarily, in a study on persons with stroke using the Wii for arm training Paquin et al. (2015) found significant improvement in gross and fine hand functions after 8 weeks of training. It is possible that both the length of the intervention and the different study population played a role in the differences seen in that study and the exergame group in the present study.

Perceived health status was lower at baseline in the exergames group than in the serious games group, but in the post-evaluation phase the exergame group perceived their health status as better with respect to the serious games group. This perceived improvement in wellbeing with non concomitant clinical improvement in arm function indicates that there may be a motivational aspect to exergames, but that the exergames may not have enough components that are globally useful for the rehabilitation of hand function. These findings further suggest that the serious games approach, that appears more effective in improving function, might have to look to exergames for improving participants' level of engagement. However, it should be considered that at baseline the health values of the serious games participants were already in the normal range and so there is a possible ceiling effect in perception of health.

In neurological rehabilitation therapeutic exercises must be repeated many times to improve general function (Langhorne et al., 2011). The use of virtual reality and gaming in rehabilitation is an interesting solution that could enable persons with neurological disorders to perform repetitive-task training as part of continuity of care without decreasing motivation (Celinder and Peoples, 2012). The motivation factor and the fact that active gaming elicits more arm movement repetitions than traditional physical therapy emphasizes the need for further developing the serious gaming approach and testing its effect on functional ability of persons with chronic neurological disorders (Peters et al., 2013).

4.1. Limitations

This pilot study investigated the feasibility and effect of serious games specifically developed for augmenting arm functioning in persons with neurological disorders. Although the results presented are promising and provide initial evidence on the effect of the serious games approach in rehabilitation for persons with MS, the study is limited by the small sample size, so efficacy and validity of the approach will have to be further explored in a larger-scale randomized controlled trial. Moreover, the virtual reality gaming approach is especially interesting for continuity of care so the serious games developed would need to be tested in the home environment in future studies.

4.2. Conclusions

Overall it can be concluded that the devices and serious games proposed to persons with multiple sclerosis were positively accepted and could be played by all participants. The solution deployed was positively received in terms of user experience and motivation to use, with the participants using the serious games showing also global improvements in functional abilities of the treated arm. Study findings thus support the feasibility of using a serious games-based rehabilitation as a supplement to usual care for persons with MS in a clinical context with implications for potential role in continuity of care arm rehabilitation.

Competing interests

The authors have declared that no competing interests exist.

References

Bertoni, R., Lamers, I., Chen, C.C., Feys, P., Cattaneo, D., 2015. Unilateral and bilateral upper limb dysfunction at body functions, activity and participation levels in people with multiple sclerosis. Mult. Scler. 21, 1566–1574.

Brichetto, G., Spallarossa, P., de Carvalho, M.L., Battaglia, M.A., 2013. The effect of Nintendo® Wii® on balance in people with multiple sclerosis: a pilot randomized control study. MultScler 19, 1219–1221.

Browne, P., Chandraratna, D., Angood, C., TremlettH, Baker, C., Taylor, B.V., Thompson, A.J., 2014. Atlas of multiple sclerosis 2013: a growing global problem with widespread inequity. Neurology 83 (11), 1022–1024. http://dx.doi.org/10.1212/WNL.0000000000000768. (PMCID: PMC4162299).

Bullinger, H.J., 1991. Human aspects in computing: design and use of interactive systems and work with terminals. Advances in Human Factors/Ergonomics. Elsevier (ISBN: 044488775X, 9780444887757).

Carpinella, I., Cattaneo, D., Bertoni, R., et al., 2012. Robot training of upper limb in multiple sclerosis: comparing protocols with or without manipulative task components. IEEE Trans. Neural Syst. Rehabil. Eng. 20 (3), 351–360.

Cattaneo, D., Lamers, I., Bertoni, R., Feys, P., Jonsdottir, J., 2017 Jul. Participation restriction in people with multiple sclerosis: prevalence and correlations with cognitive, walking, balance, and upper limb impairments. Arch. Phys. Med. Rehabil. 98 (7), 1308–1315. http://dx.doi.org/10.1016/j.apmr.2017.02.015. (Epub 2017 Mar 21).

Celinder, D., Peoples, H., 2012. Stroke patients' experiences with Wii Sports® during inpatient rehabilitation. Scand. J. Occup. Ther. 19 (5), 457–463.

Golicki, D., Niewada, M., Buczek, J., Karlińska, A., Kobayashi, A., Janssen, M.F., Pickard, A.S., 2015. Validity of EQ-5D-5L in stroke. Qual. Life Res. 24 (4), 845–850.

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

Hondori, H.M., Khademi, M., 2014. A review on technical and clinical impact of Microsoft Kinect on physical therapy and rehabilitation (Article ID 846514). J. Med. Eng. Volume, 16 pages. http://dx.doi.org/10.1155/2014/846514.

Hung, Ya-Xuan, et al., 2016. What do stroke patients look for in game-based rehabilitation: a survey study. Medicine (Baltimore). 95 (11), e3032.

Lamers, I., Maris, A., Severijns, D., Dielkens, W., Geurts, S., Van Wijmeersch, B., Feys, P., 2016. Upper limb rehabilitation in people with multiple sclerosis: a systematic review. Neurorehabil Neural Repair. 30, 773–793. http://dx.doi.org/10.1177/1545968315624785. (Epub 2016 Jan 7).

Langhorne, P., Bernhardt, J., Kwakkel, G., 2011. Stroke rehabilitation. Lancet 377 (9778), 1693–1702.

Laver, K.E., George, S., Thomas, S., Deutsch, J.E., Crotty, M., 2011. Virtual reality for stroke rehabilitation. Cochrane Database Syst. Rev. (9)), CD008349.

Lin, K.C., Chuang, L.L., Wu, C.Y., Hsieh, Y.W., Chang, W.Y., 2010. Responsiveness and validity of three dexterous function measures in stroke rehabilitation. J. Rehabil. Res Dev. 47 (6), 563–571.

Lohse, K., Shirzad, N., Verster, A., Hodges, N., Van der Loos, H.M., 2013a. Video games and rehabilitation: using design principles to enhance engagement in physical therapy. J. Neurol. Phys. Ther. 37 (4), 166–175 (1).

Lohse, K., Shirzad, N., Verster, A., Hodges, N., Van der Loos, H.M., 2013b. Video games and rehabilitation: using design principles to enhance engagement in physical therapy. J. Neurol. 37 (4), 166–175.

Lohse, K.R., Hilderman, C.G., Cheung, K.L., Tatla, S., Van, der Loos, H.F., 2014. Virtual reality therapy for adults post-stroke: a systematic review and meta-analysis exploring virtual environments and commercial games in therapy. PLoS One 28 (9)(3) (:e93318).

Lozano-Quilis JA, Gil-Gómez H., Gil-Gómez JA, Albiol-Pérez S., Palacios-Navarro G., Fardoun HM, and Mashat AS. Virtual Rehabilitation for Multiple Sclerosis Using a Kinect-Based System: Randomized Controlled Trial Monitoring. JMIR Serious Games. Editor: Gunther Eysenbach. Reviewed by Roberto Llorens and Pedro Gamito. 2014;2: e12. PMCID: PMC4307818.

Microsoft website, 2016 Kinect for Xbox One, 〈http://www.xbox.com/en-US/xbox-one/accessories/kinect/〉.

Moccia, M., Palladino, R., Lanzillo, R., Triassi, M., Brescia Morra, V., 2016. Predictors of the 10-year direct costs for treating multiple sclerosis. Acta. Scand. 0, 1–12. http://dx.doi.org/10.1111/ane.12630.

Nilsagård, Y.E., Forsberg, A.S., von Koch, L., 2013. Balance exercise for persons with multiple sclerosis using Wii games: a randomised, controlled multi-centre study. Mult. Scler. 19, 209–216.

Paquin, K., Ali, S., Carr, K., Crawley, J., McGowan, C., Horton, S., 2015. Effectiveness of commercial video gaming on fine motor recovery in chronic stroke within community-level rehabilitation. Disabil. Rehabil. 37 (23), 2184–2191. http://dx.doi.org/10.3109/09638288.2014.1002574. (Epub 2015 Jan 14).

Peters, D.M., McPherson, A.K., Fletcher, B., McClenaghan, B.A., Fritz, S.L., 2013. Counting repetitions: an observational study of video game play in people with chronic poststroke hemiparesis. J. Neurol. Phys. Ther. 37, 105–111.

Pollock, A., Farmer, S.E., Brady, M.C., Langhorne, P., Mead, G.E., Mehrholz, J., van Wijck, F., 2014. Interventions for improving upper limb function after stroke. Cochrane Database Syst. Rev. 12 (11), CD010820. http://dx.doi.org/10.1002/14651858.CD010820.pub2.

Polman, C.H., Reingold, S.C., Banwell, B., et al., 2011. Diagnostic criteria for multiple sclerosis: 2010 Revisions to the McDonald criteria. Ann. Neurol. 69, 292–302.

Prosperini, L., Fortuna, D., Giannì, C., Leonardi, L., Marchetti, M.R., Pozzilli, C., 2013. Home-based balance training using the Wii balance board: a randomized, crossover pilot study in multiple sclerosis. Neurorehabilit. Neural Repair 27, 516–525.

Pugliatti, M., Rosati, G., Carton, H., Riise, T., Drulovic, J., Vécsei, L., et al., 2006 Jul. The epidemiology of multiple sclerosis in Europe. Eur. J. Neurol. 13 (7), 700–722.

Schwid, R., Goodman, A.D., McDermott, M.P., Bever, C.F., Cook, S.D., 2002. Quantitative functional measures in MS: what is a reliable change? Neurology 58, 1294–1296.

Siebers, A., Oberg, U., et al., 2010. The effect of modified constraint-induced movement therapy on spasticity and motor function of the affected arm in patients with chronic stroke. Physiother. Can. 62 (4), 388–396.

Stawowczyk, E., Malinowski, K.P., Kawalec, P., Moćko, P., 2015. The indirect costs of multiple sclerosis: systematic review and meta-analysis. Expert Rev. Pharm. Outcomes Res. 15 (5), 759–786. http://dx.doi.org/10.1586/14737167.2015.1067141. (Epub 2015 Jul 18).

Taylor, M.J.D., Griffin, M., 2015. The use of gaming technology for rehabilitation in people with multiple sclerosis. Mult. Scler. J. 21 (4), 355–371. http://dx.doi.org/10.1177/1352458514563593.

Ware, J.E., Kosinski, M., Keller, S.D., 1996. A 12-Item Short-Form Health Survey: construction of scales and preliminary tests of reliability and validity. Med. Care 34 (3), 220–233.

White, G.N., Cordato, D.J., O'Rourke, F., Mendis, R.L., Ghia, D., Chan, D.K.J., 2012. Validation of the stroke rehabilitation motivation scale: a pilot study. Asian J. Gerontol. Geriatr. 7, 80–87.