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Autonomous rehabilitation at stroke patients home for balance and gait: safety, usability and compliance of a virtual reality system

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ABSTRACT

BACKGROUND: New technologies, such as telerehabilitation and gaming devices offer the possibility for patients to train at home. This opens the challenge of safety for the patient as he is called to exercise neither with a therapist on the patients' side nor with a therapist linked remotely to supervise the sessions.

AIM: To study the safety, usability and patient acceptance of an autonomous telerehabilitation system for balance and gait (the REWIRE platform) in the patients home.

DESIGN: Cohort study

SETTING: Community, in the stroke patients' home

POPULATION: 15 participants with first-ever stroke, with a mild to moderate residual deficit of the lower extremities.

METHOD: Autonomous rehabilitation based on virtual rehabilitation was provided at the participants' home for twelve weeks. The primary outcome was compliance (the ratio between days of actual and scheduled training), analysed with the two-tailed Wilcoxon Mann-Whitney test. Furthermore safety is defined by adverse events. The secondary endpoint was the acceptance of the system measured with the Technology Acceptance Model. Additionally, the cumulative duration of weekly training was analysed.

RESULTS: During the study there were no adverse events related to the therapy. Patients performed on average 71% (range 39 to 92%) of the scheduled sessions. The Technology Acceptance Model Questionnaire showed excellent values for stroke patients after the training. The average training duration per week was 99 ±53min.

CONCLUSION: Autonomous telerehabilitation for balance and gait training with the REWIRE-system is safe, feasible and can help to intensive rehabilitative therapy at home.

CLINICAL REHABILITATION IMPACT: Telerehabilitation enables safe training in home environment and supports of the standard rehabilitation therapy.

Trial registration: URL: https://clinicaltrials.gov

Unique identifier: NCT02192125. Registered 30 May 2014. (Retrospectively registered)

Key words:

Stroke, Rehabilitation, Virtual reality, Telerehabilitation, Gait

Background

A key factor for successful neurorehabilitation after stroke is intensive training.[1] Intensity is defined by the time spent in training and the training demand, i.e., its complexity, level of difficulty and challenge for the trainee. This is optimized for being inpatient.[2] After being discharged home, most stroke patients still suffer from residual impairment that requires additional therapy to improve further or to prevent deterioration.[3] This additional therapy could be offered in outpatient centres or at patients' home (domiciliary therapy), which requires a large organization effort and strain.[4] Besides this, economical support of outpatient rehabilitation by service providers has become very limited due to budget cuts.[3, 5, 6] Moreover, in most cases, outpatient therapy does not reach intensity sufficient to produce meaningful effects.[1, 7, 8]

Information and communication technologies (ICT) have the potential to improve this situation[9-13] by enabling video/audio communication between healthcare professionals and the patient at home. Results generally show a fragmentation in protocols and not enough evidence for a benefit for the patients.[13] Moreover, economical gains are limited, as a therapist has still to be present remotely.

A different approach to telerehabilitation has been offered by commercial gaming devices like the Nintendo balance board and the Microsoft Kinect, used to track human motion in real-time with an acceptable accuracy.[14, 15] In combination with powerful game engines like Panda3D and Unity3D, they have been recently explored to provide autonomous rehabilitation at the patient's home in the form of games.[8, 16, 17]

These studies have shown that such approach can be effective in improving patient's motor ability and motivating, and even more effective than standard rehabilitation.[18] However, such approach opens the challenge of safety for the patient as he is called to exercise neither with a therapist on the patients' side nor with a therapist linked remotely to supervise the sessions. Recent pilot clinical studies have reported adverse events (e.g. Prosperini, Fortuna[19] – occurrence of knee or lower back pain that limited compliance) that have caused patients dropping out of the studies.

Recently, inside the European Commission funded project REWIRE, a platform that integrates inside the game engine a continuous monitoring of patient's motion is provided[20]: motion data are analysed in real-time, to diminish the risk for occurrence of therapy related adverse events. This allows preventing maladaptation and/or joints overloading, thereby making therapy unsupervised by the therapist, safe for the patient. This real-time analysis is

used to provide immediate on-line feedback by the system about movement quality and suggestions to correct it. At the end of each training session, a summary feedback on how well the exercise was carried out (online tutor) as well as on how much progress was achieved is provided to the patient.

Such approach would allow one step forward in telerehabilitation as it would allow safe exercising at home. Here, we present the usability results of such at home autonomous therapy system (the REWIRE platform[1]).

Methods

Description of the platform

The REWIRE autonomous telerehabilitation platform is aimed at allowing patients to continue intensive rehabilitation at home under asynchronous remote monitoring by clinicians working at the hospital. The platform consists of three hierarchical components: 1. Patients Station, 2. Hospital Station and 3 Networking Station:

1. *Patient Station*, computer installed at patient's home and a TV screen, to play rehabilitative balance exer-games (video games that are also a form of exercise) and to collect game information and motion data. The Patient Station in this study has been configured for posture rehabilitation and it includes a force plate (Tymo plate, Tyromotion, Graz, Austria), a 3D camera (Kinect, Microsoft Inc, Redmond USA) and a host computer connected to a TV screen,[20] to the Kinect camera via USB port and to Tymo plate through Bluetooth wireless connection.

Control of the Patient Station software is implemented by gesture tracking, therefore no keyboard or mouse input is required.[21, 22] Exer-games are pre-selected by a clinician at the Hospital Station and, each day at training start, they are proposed to the patient by the Virtual Therapist, embedded insight the game engine, are presented to the patient. The patient is free to choose which game to start with.

The patient exercises in front of the TV screen and the movement is tracked by the Kinect camera [23] and used to animate the avatar. For some exer-games, a force plate is used to track the Centre of Pressure;[24] this is projected down to the virtual floor of the game to provide feedback to the patient. In the exer-game, the patient sees himself as an avatar moving and interacting in real-time with the virtual game environment (Fig. 1d, and Fig. 2). The Virtual Therapist guides the patients through each therapy session, including advices and encouragement during the exer-games; at the end of each daily session it summarises the results.

[1] http://www.rewire-project.eu

The Virtual Therapist is endowed with an artificial intelligence engine based on a fuzzy control system.[20] This analyses motion and pressure data during the training sessions and is able to inform the patient about wrong movements that are potentially harmful and may lead to maladaptation or strain injuries.[19, 25] The fuzzy system is instructed by clinicians before starting the therapy. The correctness of the posture maintained while performing the exercise is clearly shown in real-time through a meaningful colour code painted over the 3D avatar (Fig. 1). Each body segment colour could change from an intense green (correct posture) to a red colour (wrong posture) passing through the spectrum colours (yellow and orange). If a wrong posture is detected, the exer-game is paused and the Virtual Therapist avatar pops-up and explains the correct way to perform the movements required by the game (Fig. 2).[22] To this aim, a simple face animation of the Virtual Therapist is used to improve engagement and compliance.[26] In the extreme cases, when the movement are dangerous, the system forces the shutdown and sends a message to the therapist (this never occurred in the pilot studies). Music, selected by the patient, is played during the game to avoid isolation and increase compliance.

A set of eleven exer-games have been designed starting from therapists' specifications according to pre-specified guidelines[27] to implement exercises to train body alignment, weight shifting, stepping, raising legs and sit to stand (see Pirovano, Mainetti for detailed description of the exer-games).[20, 22] The Patient Station logs the gaming data: the motion of the patient's skeleton, the time course of the Center Of Pressure and the interaction with game elements are recorded and sent to the Hospital Station at the end of each session for assessment by a clinician.

2. The *Hospital Station* installed in the rehabilitation center to configure, schedule and review therapy sessions by a clinician. The *Hospital Station* is a cloud-based service that allows therapists, through a Web graphical interface, to schedule and personalize the rehabilitation sessions and revise rehabilitation results, any time, from anywhere, also outside the hospital. It has been designed with therapists to maximize compliance and it is organized in two main modules: therapy schedule and therapy assessment. The modules are structured through a set of hierarchical interfaces to maximize ease of use. The scheduler is based on a calendar: it allows defining the mix of exercises that the patient is required to carry out daily. Such exercises can be grouped into sessions to make assignment easier.

A critical aspect specific of exer-games for rehabilitation is the regulation of the degree of difficulty: this should be adapted to the actual patient capabilities. When an exercise is too easy, it has little effect, if the exercise is too difficult, it may become frustrating. The Hospital

Station allows regulating for each exer-game its speed, range of motion and/or accuracy. To simplify the exercises, a set of pre-defined difficulty levels is offered to the therapist. The regulation of the difficulty enables implementing a progressive therapy schedule as a continuous learning stimulus.[28, 29] The exer-game parameters are for instance the amplitude of apples falling from a tree (amplitude control), the speed of a tractor moving in the virtual field (velocity control).

The assessment module shows the patient's performance, through a specific Web interface integrated inside the Hospital Station. It shows a summary table of the compliance with the therapy along with a detailed description of patient's performance. The movements executed during each session can also be played back through a skeleton to better understand how the exercise was performed along with the time course of the Center of Pressure on the floor plane. The same Web interface allows regulating monitoring. Maximum value of specific parameters, is defined (e.g. spine bending, knee flexion, displacement of the Center of Pressure), thus defining for those parameters a range of admissible values. The range is mapped on a continuous scale from 0 to 4. The interval of values [0-2) is associated to correct movement (green avatar), the interval [2-3) to warning level (yellow avatar), the interval [3-4) to dangerous movement (red avatar, the exer-game is paused). If the value is equal or above 4, the exercise is interrupted for safety reasons, the system shuts down and a message is sent the hospital.

3. The *Networking Station*, at the health provider site, mines the data to discover common features and trends of rehabilitation treatment among hospitals and regions.

Moreover, analysing over time the recovery curve of each patient and the mix of exercises provided, it could determine which exercises could be most effective for particular groups of patients.

Therapy scheduling

At the beginning of the therapy program, the therapist defined a weekly set of exercises to be performed daily and tailored them to the patient status choosing the adequate level of difficulty and activates specific monitoring. Each session was composed of a mix of exercises that often involve equilibrium, coordination and increase of lower limbs muscle strength.[3] The sessions were scheduled to last between 10 to 40 minutes per day depending on the patients' capacity and the therapist knowledge of performing each exercise. Based on the data collected by the Patient Station during the prior week and on the qualitative report from the weekly visit by the therapist to the patient's home, the clinician could update inside the Hospital Station

the program for the following week by adjusting game mix selection, difficulty level, monitoring, and session duration.

Installing the REWIRE telerehabilitation platform at home and follow-up

Swiss participants were trained on the PS for one day at the hospital. Spanish participants received this training during the last two weeks of their outpatient program. Afterwards, the Patient Station was installed at the patient's home, and the autonomous home training was continued for three consecutive months.

When a problem occurred, the patient contacted the therapist by telephone. If the problem could not be solved in the first line, a therapist or technician visited the patient. In case the problem persisted, a remote connection through TeamViewer software (GFI Software, Luxemburg) was established with the technical team in the University of Milan to solve problems.

Design of the study

The pilot cohort study was designed to evaluate safety, feasibility and compliance of the REWIRE intervention in stroke patients. This study was performed in the stroke patients homes and assessment where performed at the Centre for Neurology and Rehabilitation cereneo (Vitznau, Switzerland) and at the Virgen del Rocìo University Hospital (Seville, Spain). Patients recruited had already completed their outpatient rehabilitation program and did not receive any rehabilitation training any more. The study followed "Good Clinical Practice" guidelines[30] and was approved by the responsible ethics committees for each site.

Participants

First-time stroke patients with a mild to moderate residual deficit of the lower extremities were recruited (Functional Ambulatory Categories[31, 32] ≥3; Berg- Balance-Scale (BBS)[33] ≥21). All patients were willing to train at home with an autonomous telerehabilitation system for balance and gait (the REWIRE platform). Exclusion criteria were presence of aphasia, dementia, severe neglect or other neurological disease.

Outcome measures

Outcome was assessed at baseline, before the intervention and after the intervention, by a trained therapist. The primary safety outcome was related adverse events (e.g. pain, falls) or serious adverse event during the study period. The acceptance of the intervention was evaluated through the compliance defined by the ratio between days of actual and scheduled training. The reason for skipping a scheduled session was recorded by the supporting therapist. Additionally the cumulative duration of weekly training was analysed.

Safety measure, defined in the system during the sessions was evaluated through the mean

value of monitoring occurring during the training sessions, ranging from 0 (correct movement) to 4 (dangerous movement).

Patients' acceptance of the telerehabilitation program was measured using the Technology Acceptance Model (TAM) questionnaire.[34-37] TAM is one of the most commonly used measures of user acceptance and usage of technological devices along the following dimensions: perceived ease of use, perceived usefulness and attitude toward using and behavioural intention to use the system.[38] The TAM questionnaire has been tailored to the REWIRE intervention by taking also into account the patient's involvement in the program, knowledge on disability and satisfaction. It comprises 24 items (see Appendix A) that are rated in a seven-point Likert-scale, whereby a score of one refers to "I do not agree at all" and a score of seven refers to "I agree entirely". Patients receiving autonomous telerehabilitation training evaluated their acceptance after the initial two weeks of training and again after three months.

Statistics

For statistical analysis we used Prism version 6 (GraphPad Prism, La Jolla, USA). Descriptive statistics is reported as median ± interquartile range [IQR]. Two-sided P values less than 0.05 were considered significant. The two-tailed Wilcoxon Mann-Whitney test was used to compare the average weekly training duration in patients with higher risk of falling against patients with lower risk of falling, based on the Berg Balance Scale (BBS).

Results

Recruited Participants

16 subjects with first-ever stroke (3 to 74 months post stroke) and mild to moderate impairments in balance and gait (BBS: 47 [43; 53]) were recruited between April 2014 and February 2015. All subjects gave informed consent (6 in Switzerland and 9 in Spain). Baseline demographics and baseline functional parameters are shown in Table 1.

Safety and System Usage

One patient decided to quit after the hospital training, because of lack of appropriate infrastructure at home and technical problems with the system. Therefore, the data from that participant was not included. 15 patients completed a minimum of 12 weeks training. No adverse events (e.g., pain or injury) occurred. Furthermore, the clinicians perceived no risky or critical situations while the patients trained at home with the REWIRE system.

Monitored data showed that patients trained below level 3 most of the time (>75% of the training sessions). The overall maximum monitoring score did not exceed 3.04 points: a score close to level 3 was observed 29 out of 900 times during training sessions. In none of the

patients the system interrupted the therapy for security reasons (monitoring level 4 or above, Fig. 3a).

On average, patients completed 71% (range 39% and 92%) of the scheduled sessions (Fig. 3b). One participant had to travel abroad for work and interrupted training for 3 weeks. Other reasons for low compliance were technical issues or the requirement of more support from a clinician.

Patients used the REWIRE system on 3.58 ±1.59 (Switzerland 3.63 ±1.87, Spain 3.55 ±1.38) days per week. Sessions were scheduled on 5.11 ±1.63 (Switzerland 6.22 ±1.6, Spain 4.38 ±1.19) days per week. The average training duration per week was 99 ±53 min (Switzerland 88 ±54min/ Spain 107 ±50 min) (Fig. 4a). It did not change over the course of the twelve weeks of training ($p = 0.5962$).

The average training duration per training day was 28 ±15 min (Switzerland 24 ±11 min/ Spain 30 ±7 min) (Fig. 4b). Six patients with high fall risk (BBS ≤45)[39, 40] did use the system for similar amounts of time as compared with low risk subjects (BBS >45) ($p= 0.5328$) (Fig. 4c).

The TAM questionnaire showed high acceptance of the REWIRE system already at the beginning of the study (Tab. 2) and scores improved slightly but not significantly during the three months of training ($p = 0.197$). All patients reported that they would have continued to use the REWIRE system after the trial, if the system would have been made available to them.

Discussion

This pilot study demonstrates that the REWIRE autonomous telerehabilitation system to train balance and gait is feasible and safe in stroke patients who live in their home and are able to walk independently. Safety is a major concern when training at home, as the patient is not supervised by a therapist in a one-to-one setting. Harmful movements could induce or aggravate high tone for patients with paresis or overload joints and induce pain.[19, 25] Falls are of concern during balance training. The REWIRE platform therefore continuously monitored the patient movement using an intelligent engine working on the data from the 3D camera and a pressure board.

The early warning to the patient, provided when slight deviations from correct movements were occurring (yellow or orange colour) prevented more dangerous movements that would harm the patient. This preventive measure enabled a therapy that in no case had to be interrupted for security concerns nor led to serious adverse events. These results are in contrast to previous balance training studies,[19, 25] with related adverse events occurring. The system allowed movement pattern variability among subjects, as a certain movement may be

harmful for some but not for other patients and the possibility to regulate and program them was rated as an important feature by all clinician.

Adequately setting the monitors was made possible because the therapist could evaluate the exercise safety while the patient performed supervised training in the clinic. The therapist then defined individual movement parameters and associated monitoring levels.

The compliance with the system was good. The average duration of 99 minutes per week, with training performed on 3.6 days/week is promising. This result compares well with other studies of home-based rehabilitation, in which durations of 105 min/week[41] and 85 min/week[42] was reported. Patients who used the REWIRE system less had a higher risk of falling, which could be due to fear of falling when using the system unassisted.

Patients used the REWIRE system at the hospital, before starting autonomous training at home. They were satisfied and motivated in using the system. Only a slight change in TAM was observed over the 3-months training period: TAM had possibly reached an already high value at the beginning of training. While high acceptance may be the result of a selection bias with patients open to technology being more likely to consent to the trial, acceptance may have been positively influenced by designing the REWIRE-system intuitively to be used via gestures avoiding keyboard and mouse.

The REWIRE system provides valid scenarios that stimulate movement and behaviors that are relevant for daily life. This is implemented within a safe environment, which can be shaped in accordance to individual requirements and levels of ability. The responsive virtual environment allows patients to explore independently, increasing their sense of autonomy and independence in directing their own therapeutic experience. The controllability of virtual environment allows for consistency in the way therapeutic protocols are delivered and performance is recorded, enabling an accurate valuation of a patient's performance over time.

Conclusions

Autonomous telerehabilitation for balance and gait training with the REWIRE-system is safe, feasible and can enable intensive rehabilitative therapy at home. Patients were satisfied with and motivated in using the system. The efficacy of the REWIRE therapy with respect to improving balance and reducing impairment should be investigated in future randomized trials.

List of abbreviations

BBS Berg Balance Scale

ICT Information and communication technologies

NIHSS National Institutes of Health Stroke Scale

REWIRE	Rehabilitative Wayout In Responsive Home Environments
TAM	Technology Acceptance Model
TuG	Timed up and go

Declarations

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Declaration of Conflicting Interests

Andreas R. Luft is scientific advisor for Hocoma AG (Volketswil), which develops rehabilitation technology. The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Authors' Contributions

J.H. contributed to the conception of the work, the acquisition, analysis and interpretation of data, and writing the manuscript. N.A.B. contributed to the design of the game engine and of the exer-games, and writing the manuscript. A.S. developed the hospital station and contributed in analysis of the data. E.V. contributed to the definition of the hospital station development. B.F., M.J.Z., M.B., C.E., A.M.C. and C.L.P.C. participated in the definition of requirements of the REWIRE system for healthcare environment, coordinated pilot in Virgen del Rocío University Hospital and evaluated the results. A.D., R.M. and M.P. participated in the tuning of the REWIRE platform and exercises, they were involved in data acquisition and pilot evaluation. A.R.L initiated the study, assisted in the acquisition of data, and contributed to writing the manuscript. F.J.S and B.H. was involved in the study design and pilot results evaluation.

All authors read, revised, and approved the final manuscript.

Availability of data and supporting materials

The data supporting the conclusions of this article are included within the article.

Consent for publication

The individual in Figure 2 consented to the publication of the photograph.

Ethics Approval and Consent to Participate

The study followed GCP-guidelines and was approved by the local Cantonal ethics committee "Nordwest- und Zentralschweiz" (EKNZ: 2014-061) and by the ethical committee from Virgen del Rocío Hospital in Seville, Spain (CEI code 2012PI/216). All subjects gave written informed consent in accordance with the declaration of Helsinki.

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Tables:

Table 1: Baseline Characteristics

Table 2: Change in Technology Acceptance Model Questionnaire.

Figures:

Figure 1: Patient station components and deployment for one patient. a) Microsoft Kinect Camera; b) Laptop; c) Tyromotion Balance Board; d) Screenshot of one of the exer-games: “animal hurdler”. Notice the green spot under the avatar: this shows the position of the center of pressure (CoP) that indicates the resulting of all forces exerted on the ground. In a healthy postural control, the CoP lies in between the feet when standing vertical.

Figure 2: Playing patient. A patient playing fruit catcher game is bending his spine on the right too much and he is advised by the virtual therapist.

Figure 3: a) Game Performance. Mean and standard deviation of the monitoring level for each patient. 0-2 = green, no safety concern, 2-3 = yellow, the patient receives a warning, 3-4 = red, the exercise is interrupted and the virtual therapist shows the patient how to move correctly, >4 = application shuts down for severe safety concerns. **b) Compliance in percentage**. Percentage of executed relative to scheduled sessions.

Figure 4: System Usage. a) Minutes trained per week per subject, mean and standard deviation b) Minutes trained per day c) Daily training in patients with high versus low fall risk (BBS – Berg Balance Scale).

Table 1: Baseline Characteristics

Characteristic	Switzerland Median, IQR*	Spain Median, IQR*	Combined Median, IQR*
Number of participants	6	9	16
Age (years)	53 [48; 58.5]	56 [52; 67]	56 [48.5; 63.5]
Months after stroke	32 [20; 55]	7 [6; 7]	7 [6; 31.5]
Sex (female/male)	3/3	2/6	5/9
NIHSS†	4.5 [2.5; 6]	3 [2; 7]	4 [2; 6]
BBS‡	51.5 [46.5; 53.5]	44 [41; 49]	47 [43; 53]
Barthel Index	97.5 [95; 100]	75 [74; 90]	92.5 [75; 95]

* Interquartil Range

† National Institutes of Health Stroke Scale (0-42 points)

‡ Berg Balance Scale (0-56 points)

Table 2: Change in Technology Acceptance Model Questionnaire. 7 Point Likert-scale: 1="I do not agree at all" to 7 = "I agree entirely"

Domain	Swiss mean ± standard deviation		Spain mean ± standard deviation		Combined mean ± standard deviation	
	Pre-intervention	*Post-intervention*	*Pre-intervention*	*Post- intervention*	*Pre-intervention*	*Post-intervention*
Perceived Ease of Use	5.5 ±1.58	6.11 ±1.37	6.04 ±1.21	6.09 ±1.28	5.8 ±1.17	6.11 ±0.96
Perceived Usefulness	5.94 ±1.25	6.67 ±0.66	5.91 ±1.01	5.91 ±1.17	5.93 ±0.92	6.24 ±0.85
Attitude Toward Using	4.33 ±2.79	4.43 ±2.74	6.33 ±0.8	6.38 ±0.87	5.51 ±0.92	5.54 ±1.06
Behavioral Intention to Use	6.11 ±1.47	6.36 ±1.36	5.7 ±1.33	5.5 ±1.8	5.89 ±0.88	5.89 ±1.19
TAM total	5.54 ±1.91	5.96 ±1.83	5.98 ±1.13	5.96 ±1.36	5.8 ±0.68	5.97 ±0.73

Appendix A

Questionnaire. Technology acceptance model

Perceived Ease of Use

1. I found the exer-games easy to use.
2. Learning to use the exer-games would be easy for me.
3. My interaction with the exer-games was clear and understandable.
4. I think the messages displayed by the REWIRE system would be clear.
5. I think it would be easy to acquire the skills required to use the exer-games
6. I found the lifestyle devices easy to use.
7. In general, I think the REWIRE system will be easy to use.

Perceived Usefulness

8. Using the exer-games would enhance my effectiveness in training.
9. Using the exer-games would improve my training performance.
10. Using the exer-games would increase my productivity in training.
11. I found the exer-games useful.
12. Using the lifestyle devices would improve the follow up of my rehabilitation.
13. In general, the REWIRE system may help to improve the rehabilitation.

Attitude Toward Using

14. I dislike the idea of using the exer-games. (R)
15. I have a generally favorable attitude toward using exer-games.
16. I believe it is (would be) a good idea to use these exer-games for my training.
17. Using the exer-games is a foolish idea. (R)
18. In general, I think that my family/friends would support the use of the REWIRE system.

Behavioral Intention to Use

19. I intend to use the exer-games in my further training.
20. I will use the exer-games often.
21. I intend to use the exer-games frequently for my training.
22. I intend to use the lifestyle devices when it is necessary for my rehabilitation.
23. I intend to take part in the patients' community.
24. I intend to use the REWIRE system when it is available at my hours

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Reported on page
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1-2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	1-2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3-4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	7
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7-8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*7-8*
Bias	9	Describe any efforts to address potential sources of bias	7
Study size	10	Explain how the study size was arrived at	8
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8
		(*b*) Describe any methods used to examine subgroups and interactions	8
		(*c*) Explain how missing data were addressed	n.a
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	8-9

		(*e*) Describe any sensitivity analyses	8

Continued on next page

Results			**Reported on page**
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8
		(b) Give reasons for non-participation at each stage	n.a.
		(c) Consider use of a flow diagram	n.a.
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8
		(b) Indicate number of participants with missing data for each variable of interest	n.a.
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	9
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	*8-9*
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	*n.a.*
		Cross-sectional study—Report numbers of outcome events or summary measures	*n.a.*
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	8-9
		(*b*) Report category boundaries when continuous variables were categorized	8
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	n.a.
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	n.a.
Discussion			
Key results	18	Summarise key results with reference to study objectives	9
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	9
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	9
Generalisability	21	Discuss the generalisability (external validity) of the study results	10
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	11

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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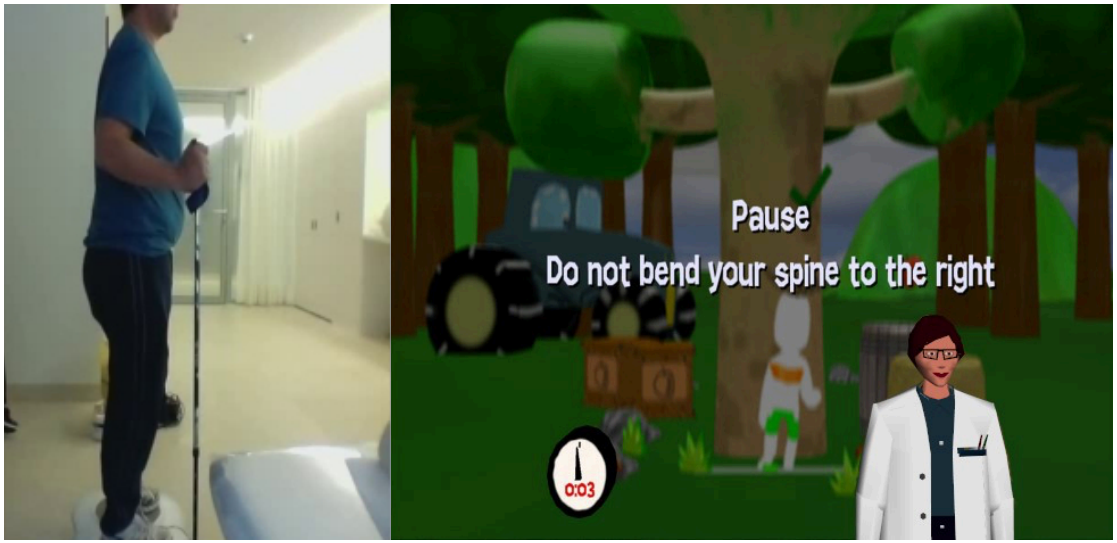

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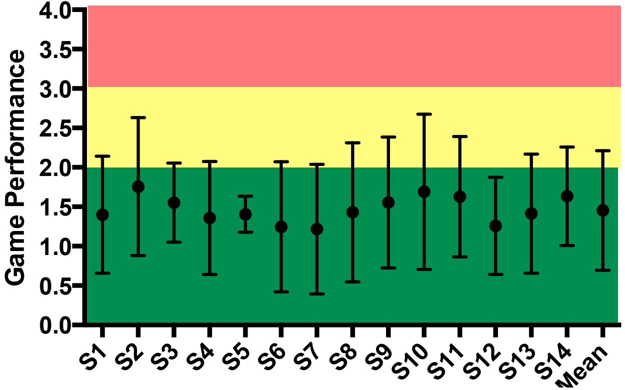

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