Virtual Reality to Improve Postural Control in Patients with Schizophrenia: Study Protocol for a Single-Blind Parallel Group Randomised Controlled Trial

Mara Cunha, Raquel Simões de Almeida(✉), Ângela Fernandes, and António Marques

Center for Rehabilitation Research - Psychosocial Rehabilitation Lab., School of Health of P.PORTO, Rua Dr. António Bernardino de Almeida, 400, 4200-072 Porto, Portugal
afa@ess.ipp.pt

Abstract. Impairment in postural control is prevalent in patients with schizophrenia, and often limit occupational performance. Virtual reality (VR) has proven its benefits for improving postural control and among schizophrenia population. Remarkably, the effectiveness of a VR game-based intervention on postural control in this population has never been evaluated. The primary aim of this study is to examine the effects and impact of VR on postural control parameters in patients with schizophrenia. This is a single-blinded, randomised controlled trial with two parallel groups. Thirty-four patients with schizophrenia are randomly assigned to the virtual reality group (VR) or the inactive control group (CG). The intervention consists of 3 30 min sessions for 4 weeks. Assessments are performed at baseline, post-intervention and 1-month follow-up. The primary outcome is postural control. The center of pressure (COP) displacement and velocity in anteroposterior (AP) and mediolateral (ML) directions are measured by PhyisoSensing pressure platform. This study protocol comprises parameters that are thought to be crucial to the success of the intervention. There are used objective and quantitative measures to evaluate the outcomes for effectively plan postural control interventions in schizophrenia with more reliable and valid results. The results of the study will be useful to clarify the effect of VR on postural control in patients with schizophrenia and provide insight into the validity of this approach as an intervention technique. It is expected that the results confirm the positive findings supporting the therapeutic prospects of VR.

Keywords: Virtual reality · Postural control · Schizophrenia · Physical rehabilitation

1 Introduction

Schizophrenia is a chronical severe mental disorder that affects 20 million people worldwide. [1] Postural abnormalities are prevalent in patients with schizophrenia [2–5] and

Á. Rocha et al. (Eds.): WorldCIST 2021, AISC 1368, pp. 384–400, 2021.
https://doi.org/10.1007/978-3-030-72654-6_38

affect occupational performance [6, 7]. The first mentions to schizophrenia in the classical literature described the condition as dementia praecox, but Bleuler [8] rejected these assumptions. He stated that schizophrenia "is not a disease in the strict sense but appears to be a group of diseases […]" [9]. This is in line with recent findings.

Besides the core psychiatric symptoms, neurological soft signs (e.g., sensory integration, motor coordination, sequencing of complex motor acts, and primitive reflexes) were identified in people with schizophrenia. [10–12] This appears to be consistent with investigations that report motor functional abnormalities [13, 14]. Although motor symptoms had been documented in the preneuroleptic era, [15] some studies have continued to exclusively associate schizophrenia motor symptoms with antipsychotic treatment effects [16, 17]. Currently, it is believed that motor abnormalities can be either intrinsic or antipsychotic drug induced [18–20]. This paradigm shift should have promoted research in this field, considering the need for a better understanding of motor symptoms in schizophrenia. Instead, they were broadly undervalued [14, 21].

The evolution of neuroimaging techniques has led to a new and deep understanding of the motor symptoms, its etiology and impact on individuals. [4, 22, 23] As a result, postural control appears as a more comprehensive and complex concept linked to cerebellar dysfunctions [2, 20, 22, 24, 25]. The hypothesis of the importance of the cerebellum for postural control dates back to the 1940s [26] and is now getting the attention of the scientific community. Imaging studies reveal that changes in the volume of the cerebellum are correlated with poor postural control and sensory integration issues [27–31].

Postural control aims to maintain an antigravity posture and balance, adjusting the position and orientation of the corporal segments to interact with external perturbations. To guarantee the immobilization of the center of mass, despite the external factors, it is crucial to build a postural body scheme based on orientation and stability, integration of multisensory inputs, and development of anticipatory reactions to recover balance or postural stability [7, 32–35]. Without the interaction of postural control and limb movement, it would not be possible to execute voluntary movements to complete daily life tasks and activities [36–38]. Thus, it may threaten the individual's independence, affecting active and safe involvement in everyday occupations [7, 29, 36–41]. Given the meaning of occupation to the process of Occupational Therapy [42] and its central role in human life, [43] factors that limit engagement in occupation must be analysed. Therefore, tools for the assessment and intervention of postural control in schizophrenia play an important role.

The gold standard method to assess postural control is force-plate posturography, with COP being a valid and reliable parameter that calculates several spatiotemporal metrics. [44–46] Several studies have assessed postural sway using posturography in patients with psychotic disorders. However, there is not a standard for assessment conditions. It varies between a statistic and dynamic, eyes open and closed, open base and closed base, hard or soft surface, and dual or single task [47].

Few interventions on people with schizophrenia have specifically targeted postural control and none of them has used virtual reality (VR) as the intervention of interest. [48, 49] The therapeutic use of VR in mental health has not extended its potential beyond the psychosocial, phobias and symptoms-focused interventions [50, 51]. Nevertheless,

virtual reality has been proving to be an effective and rising intervention in schizophrenia physical rehabilitation [52–56]. Studies using VR exercises revealed positive changes in the COP parameters, balance, mobility, postural stability and other postural control variables [48, 57, 58]. It is suitable and safe to use either in people with schizophrenia or psychosis [59, 60]. VR creates an immersive, controlled and real-time experience, gamifying the therapeutic environment. The patient feels like interacting in a parallel world, being allowed to have an active role in his rehabilitation process [61]. This sense of reality promotes skills acquisition and retention and induces functional recovery, which represents a big advantage for the intervention goals [62]. Nevertheless, it is unknown whether skills are transferable to the real world or not [61, 63, 64].

Considering the disruptive contribution of VR interventions and the concomitant lack of evidence regarding its application on postural control in schizophrenia, this study sets out to determine the clinical effects of VR treatment on postural control in people with schizophrenia.

Aims. The study aims to determine the effectiveness of a virtual reality game-based intervention for improvement of postural control in patients with schizophrenia.

The primary hypothesis is that:

– Compared to the control group (CG), VR intervention will lead to an improvement in postural control by decreasing COP displacement and velocity in anteroposterior (AP) and mediolateral (ML) directions (post-intervention, 1 month).

The secondary hypotheses are:

– The benefits of VR will be maintained at follow-up (1 month).
– Intervention effects are correlated with body mass index (BMI), age and physical activity.

Trial Design. The trial is designed as a single-blind parallel-group randomized controlled trial that investigates the efficacy of a game-based virtual reality intervention on postural control among people with schizophrenia. This is a quantitative, experimental and analytical study. It intends to gather and analyse numerical data by using statistical methods to predict the strength of the relationship between intervention and outcomes, comparing two study arms. [65–68] Participants will be randomly assigned to the VR group or inactive control group by an independent person who is not involved in the recruitment, assessments, or intervention. Assessments of outcome variables will be carried out at baseline, after 12 sessions and 1 month (follow-up) by an occupational therapist, blinded to treatment allocation. A summary of the trial design can be seen in Fig. 1. Flow chart of the study protocol. The protocol is described according to the Standard Protocol Items: recommendations for Interventional Trials (SPIRIT) Checklist for clinical trials [69].

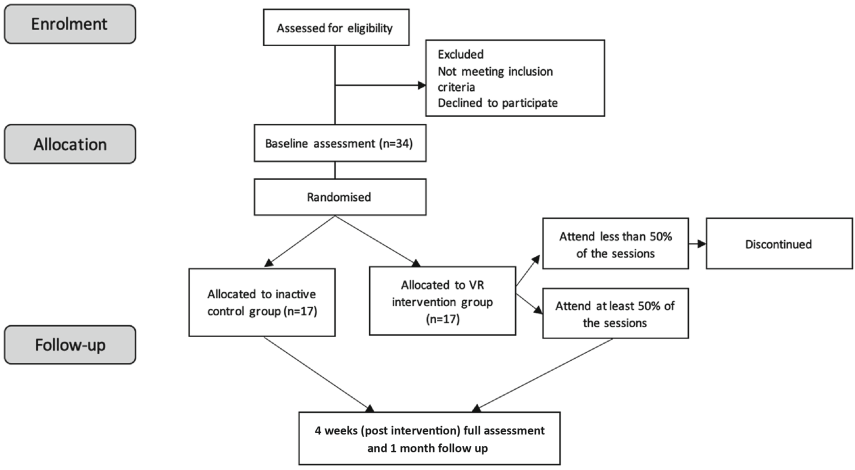

Fig. 1. Flow chart of the study protocol.

2 Methods

2.1 Participants

The trial participants will be patients with schizophrenia. The recruitment methods will be via direct patient contact and seeking referrals to the trial from relevant clinical teams (outpatient mental health services, clinics). A convenience non-probability sampling method was chosen due to its ready availability and cost-effectiveness. Nevertheless, caution must be taken regarding the statistical representativeness of this type of sampling [70]. With the clinical team's approval, if willing to take part of the study, patients are approached by the research team to give them more information and verify if they met the inclusion criteria (eligibility screening). After the confirmation of their participation, written informed consent is obtained from all participants and anonymity is assured. The study will take place in Physical Rehabilitation Laboratory at Porto School of Health.

Patients eligible for the trial must meet the following inclusion criteria: (1) adults aged 18 to 64, inclusive, (2) clinical primary diagnosis of schizophrenia according to DSM-5 criteria, (3) being clinically stable, (4) following simple verbal cues, and (5) ability to walk and move without physical assistance. Patients are excluded if they: (1) have a severe cognitive deficit (<10 points) rated by Mini-Mental State Examination [71], (2) have a neuromusculoskeletal disorder or other comorbidities that may limit global body movements, (3) present signals of overmedication, and (4) are receiving concomitant interventions. All data collection will be coded with numbers to maintain participant's confidentiality, and records containing personal identifiers will be stored separately.

The estimated sample size was calculated using the G*Power 3.1 version. The calculation was based on the primary hypothesis. Hence, to test between-group and within-time difference, it will be used a linear mixed model design (mixed ANOVA) at level $\alpha = 0.05$, estimating a medium effect size of $f = 0.25$, according to Cohen's benchmarks [72], to achieve a power of $1 - \beta = 0.8$. The required sample size (n) amounts to 28

participants with equal allocation to each arm of the trial. Enrolling more subjects to the study is a recommended dropout compensation technique [73]. According to Forte Research [74], the average dropout rate (d) across clinical trials is 18%. Thus, the total sample size should be, approximately, $n/(1 - d) \approx 34$ [73].

Allocation. A blocked randomization will be generated by r software using a 1:1 allocation ratio. The randomization sequence designating the allocation group for each participant is concealed in sealed opaque envelopes. These are only seen by the occupational therapist providing the intervention. The research assessor is blinded to treatment allocation, but due to the nature of the study, participants and therapist cannot be blinded.

Intervention. Participants in the inactive control group are not receiving any intervention so that the absolute effects of the intervention of interest can be estimated [75]. According to the Declaration of Helsinki [76] "the use of no intervention is acceptable if it is necessary to determine the efficacy or safety of an intervention". However, CG will have post-trial access to the intervention if proved to be effective.

The VR group will begin the intervention right after the assessment phase. VR group will participate in 3 sessions with 30-min per week for 4 weeks (12 sessions) of a VR game intervention with Beat Saber. The software is freely available on Steam and no alterations were made to the original game content for the intervention. The game will run through the Steam software on a computer connected to a head-mounted display (HMD) and motion controllers. During the intervention sessions, a mental health occupational therapist will be in the VR CAVE with the participant. The therapist will help the participant to put on the HMD and start the game.

The Beat Saber is a rhythm game that combines motor coordination with cognitive flexibility. The goal is to slash the beats of the selected song, represented by small cubes of two different colors, as they come at the person. Each cube indicates which saber (motion controller) to use, according to the color, and the direction to match. Also, in some game levels, participants must move from left to right to avoid the oncoming obstacles. The game can be individualized in terms of difficulty, for example by adjusting game level, music selection, the amount of real-time verbal feedback or simultaneous tasks. A first exploratory session should be performed to set the appropriate game level for each participant and promote their adaptation. The following sessions start at the last level played. The game progress should consider consistency session to session on a certain level. The therapist records the setting and performance of each participant. Intervention can be modified in response to harms or participant's request. This may involve pauses and game management, for example by selecting the appropriate game level (even if it does not correspond to the actual participant's game level). The intervention will be discontinued if the participant attends less than 50% of the VR sessions or starts any concomitant intervention during the trial. The research team will not provide any treatment other than the intervention of interest.

To promote adherence to the intervention, the therapist can give relevant information so that participants understand their key role in the trial and its contribution to themselves. Additionally, researchers can strengthen their relationship with participants or their clinical teams, by sending timely emails about intervention schedule and assessments or with research-related information [77, 78].

Outcomes. The groups are assessed at baseline to compare demographic and clinical features between CG and VR group and assure two similar comparison study arms. If the two groups have similar characteristics at baseline, the difference in outcomes can thus be attributed to the intervention given to the experimental group [79]. To determine the effect of VR intervention, mean changes from baseline in body sway parameters are analysed. The variables of interest are mean AP and ML COP displacement and mean COP velocity because these are broadly used time-dependent parameters to assess postural function [44, 80, 81]. The participants are asked to stand barefoot on the pressure platform and are requested to perform 8 different conditions varying in visual input, the base of support and single or dual-task (n-back task): (1) eyes open, base open, single task (EOBOST); (2) eyes open, base open, dual task (EOBODT); (3) eyes open, base closed, single task (EOBCST); (4) eyes open, base closed, dual task (EOBCDT); (5) eyes closed, base open, single task (ECBOST); (6) eyes closed, base closed, single task (ECBCST); (7) eyes closed, base open, dual task (ECBODT) and (8) eyes closed, base closed, dual task (ECBCDT). Data is recorded for three trials in each condition, during 60 s, of which will be analysed the most stable 30 s. There will be a 60 s break between each trial. The primary outcomes are assessed at baseline, post-intervention and 1-month follow-up (Table 1).

Table 1. Standard Protocol Items for Interventional Trials (SPIRIT) schedule of enrolment, interventions, and assessments.

	Study Period					
	Enrolment	Allocation	Post-allocation			Follow-up
Timepoint	-t1	0	t1 (baseline)	Intervention (4 weeks)	t2 (post-intervention)	t3 (1-month post-intervention)
ENROLMENT:						
Eligibility screen	X					
Informed consent	X					
Allocation		X				
INTERVRENTIONS:						
VR group				← →		
Control group				← →		
ASSESSMENTS:						
Demographic and clinical variables			X			
Outcome variables			X		X	X

3 Data Collection and Management

Demographic and clinical measurements are assessed by a sociodemographic questionnaire containing the information presented in Table 2. This is a structured questionnaire that focuses on specific questions, limiting the range of responses. This is a way of reducing rater and participant bias by avoiding interaction-dependent responses [82]. Postural

control is assessed using PhysioSensing by Sensing Future Technologies. It is a balance and pressure platform indicated for physical or vestibular rehabilitation and sports medicine that quantifies COP, sway, weight distribution and pressure map. The 19.0.1.0 version software records data at a sampling rate of 100 Hz and exports all the measurements. Participants are assessed using the Body Sway protocol that can be personalized with multiple conditions. The results provide a pressure map, three statokinesigrams, two stabilograms and two spectral analyses (anteroposterior and mediolateral). A clinical report with raw COP data can also be generated. The COP parameters obtained are ellipse area, COP displacement, mean COP in both directions and its standard deviations, mean velocity, and root mean square. The COP is an important posturography parameter [83], and can be clinically monitored using a pressure mapping system [84] like PhysioSensing. As shown in a systematic review [47], a great number of studies uses posturography to assess postural sway in psychotic disorders, making it relevant to assess our target population. Furthermore, this tool ensures validity and reproducibility [85]. Using such an objective instrument for data collection and experienced assessors contributes to reducing rater bias [82].

Table 2. Baseline demographic and clinical variables

Demographic variables
Age
Gender
Anthropometric variables
Height (cm)
Weight (kg)
BMI (kg/m^2)
Clinical Variables
Regular medications
Co-morbidities
Time since diagnosis (years)
Psychiatric hospitalization report, prior 12 months
Psychiatric hospitalization report, prior 6 months
Others
Hours of physical activity per week
Type of physical activity (aerobic, strength, flexibility, balance)

To maximize participant retention, efforts must be made to follow the participant during the entire study period. They should be timely informed about the schedule and assessments using all available contact methods. Local services who interact with the study population should also be informed about the study, to collaborate in the retention process, showing their support to participants. When scheduling the follow-up visits, first visits must be planned for those demonstrating late or missed appointments to allow time for rescheduling if needed. The team members are required to explain the importance of participant's involvement and compliment their valuable contribution and

effort dedicated to the study. In case of withdrawal, the participant must be welcomed back if he wishes to have any further contact. Guarantee participant's confidentiality is also a method of retention. [86–88] In this study, data is collected in the appropriate paper forms and then coded and entered electronically by double data entry. The paper forms are kept in a locked cabinet for at least 10 years after completion of the study [89]. All data management is under the responsibility of the researcher.

4 Statistical Methods

Descriptive statistics to describe patient's characteristics will be presented by means, medians and standard deviations for continuous numeric variables, and by frequency tables for qualitative data. To compare baseline values within randomized groups, an inferential analysis will be presented. If data are close to a normal distribution, determined by the Shapiro-Wilk test, and groups have equal variance, it will be used an independent samples t-test for quantitative or ordinal data. If these assumptions are not met, it will be used the non-parametric equivalent, the Mann-Whitney U test. A chi-squared test (X2) is used to compare the distributions of qualitative variables.

The primary hypothesis will be tested using a repeated measures mixed effect analysis of variance (ANOVA), with time (pre-intervention, post-intervention, follow-up) as the within-subjects factor and VR (experimental vs control group) as the between-subjects factor. The mixed-effect model will have the outcome as the response variable, randomised group, baseline scores, and time points as fixed effects, as well as the interaction between time and randomized group, to estimate the intervention effect at all moments. To improve individual predictions, a patient-specific random intercept is considered [90]. To use a repeated measures design, four assumptions [91] need to be satisfied: 1) the independent variable must be categorical with 3 or more levels, and the dependent variable must be on interval or ratio scale; 2) observations from different participants must be independent of each other; 3) data must follow approximately normal distribution and should not have outliers; 4) variances of the differences between all pairs of repeatedly measured dependent variables are equal (sphericity). If repeated measures test assumptions are not violated, a repeated-measures ANOVA reduces statistical error, increasing the value of the F-statistic, which leads to an increased test power to identify significant differences between means [92, 93]. Also, fitting a mixed effect model to the repeated measures increases analysis flexibility (e.g., accounting for missing data) [94]. For the first secondary hypothesis, to compare the effect of VR in the experimental group at post-intervention and follow-up, a paired-samples t-test is conducted if data are normally distributed, observations are independent, and variances between the two samples are the same. In alternative, it is used the non-parametric equivalent Wilcoxon signed-rank test. For the other secondary hypothesis, before performing the Pearson r correlation coefficient, data must be analysed in a scatterplot to determine if there is a possible linear relationship. If it exists, Pearson's correlation can be performed only if variables are normally distributed. The non-parametric equivalent to measure the degree of relationship between physical activity (hours per week), BMI and age, and postural control (COP measures) is the Spearman rank correlation (ρ). For all tests, results are considered significant when P value < 0.05.

Both per-protocol (PP) and intention-to-treat (ITT) analysis are conducted. In the PP analysis, to estimate the VR effect under optimal conditions, patients who do not complete the study protocol (e.g., follow-up loss) are excluded. Whereas the ITT analysis includes every subject randomized unless no treatment has been applied or there are no existing data following randomization. Depending on the context (e.g., data missing at random or not), different approaches can be implemented to deal with missing data. It may vary between complete case analysis, simple/multiple imputations, impute to a constant value or last observation carried forward [95, 96].

The principal investigators have full access to the final data sets which will be protected with a password. Other team members should only access the files by request. Participant's confidentiality is settled by attributing a code to any identifying participant information.

Given the low-risk profile and relative short duration of the intervention, we do not plan to execute an interim analysis.

5 Supervising and Monitoring

Due to the size and nature of this study, a data monitoring committee was not assumed to be mandatory. There is no planned interim analysis. Adverse events occurring in the trial period related or not to the VR treatment (e.g., sickness, dizziness, pain, falls, nausea, headaches) are registered [76] and, in case of a serious adverse event, intervention will be discontinued to the participant.

6 Discussion

For the author's knowledge there are currently no published studies on postural control with VR as a treatment for patients with schizophrenia. This study is important because consistent findings prove altered postural control in patients with schizophrenia, which is expected to affect their daily living [2, 3, 5–7, 97]. With this intervention positive results are expected, supporting the advantage of the therapeutic prospects of this technology. It is believed that VR can be a protective factor from dropouts and improve patient's adherence as the VR game-based intervention is based on a goal-directed task and has a lot of potential to provide a dynamic, active, and non-monotonous treatment, therefore contributing to the effectiveness of the intervention [51, 98–102]. The multiplicity of game options and the real time feedback provided increase motivation and it is crucial to skills transfer [103]. This is also a dual task-based intervention that could improve both motor and cognitive performance, which is particularly interesting given the role of attentional resources to regulate posture [104–107]. Plus, the VR environment is rich in multisensory stimulation. It offers a realistic experience [108] that focuses on the extrinsic factors of postural control, inducing postural responses and repetition that can result in an effective method for postural stability training [109, 110]. But the richness of the VR intervention also establishes a duality. While on the one hand it has many potential benefit ingredients, on the other, using an inactive control group does not permit making inferences about what specific ingredients contribute to the effectiveness of the intervention. To fill the gap between estimating absolute and relative treatment

effects, this study should provide effect size estimates [111]. Other implication of a no treatment control is the unblinding of the subjects. This can result in expectation bias as the intervention group may expect benefit, and control group expect lack of benefit, influencing outcomes [112]. This is more relevant in trials with subjective outcomes. Other concerns may be due to ethical considerations. A control group should not be left untreated if a standard or accepted treatment exists. Otherwise, it is recommended a placebo control [112].

Confounding bias is also extremely important in studies of efficacy and could represent limitations of the study [113]. It should be guaranteed that postural control improvement is due to the intervention, and that other reasons could not account for a difference. To deal with confounding, all potential confounding factors (e.g., time of the day of the assessment, energy/concentration/fatigue levels, changes in medication) must be measured, assessed and reported [113].

Other potential limitation of this study protocol is the loss to follow-up, that can severely compromise the validity of the study [114]. But this study protocol has elaborated precautions to minimize this situation.

Regarding the chosen assessment method, there should be careful while interpreting the results because the low frequency (100 Hz) of the pressure platform may lead to missing and less accurate data [115]. Still, it allows the creation of a personalized protocol to quantify several characteristics of postural control [116]. Other advantage of the pressure platform is that it is easy to use because it is portable, allowing its use in settings other than the laboratory.

With regards to the study results, according to a study, it is expected that males achieve better results than females in the same time frame because some females require more training to accomplish effects of VR [110]. However, VR gender specific effects are not frequently reported in literature. Furthermore, neither baseline postural control measures do not even indicate gender-based differences, but rather age-related changes [7, 117–120]. Other differences may be related with physical activity [56] and BMI [121–123]. The efficacy of the intervention depends not only on the training intensity but also on task-specificity, feedback and motivation [124]. Unfortunately, reviewed VR studies show great variability of training intensity, duration and frequency [54, 125]. Further research is necessary to find whether the amount of training planned in this study protocol is the optimal dosage of training to achieve the desired outcomes for this population.

In conclusion, the present study provides a useful base to learn and examine implementation issues of VR in schizophrenia and determine the effectiveness of VR to postural control in this population.

7 Additional File

Author's Information
Not applicable.

Competing Interests
The authors declare that they have no competing interests.

Author's Contributions. AM is the chief investigator and had overall responsibility for the trial design. AF, AM, RSA have conceived the study idea and contributed to the development of the study. They have contributed to the treatment design and advised on virtual reality intervention. AF has provided statistical expertise. MC has drafted the trial protocol and manuscript. AF and RSA have critically reviewed and contributed to the refinement of the manuscript, which was reviewed and approved by AF, AM, and RSA.

Funding. Not applicable.

Availability of Data and Materials
Not applicable.

Ethics Approval and Consent
The study protocol was submitted to the approval of all the institutions taking part in the study. Written informed consent will be obtained from all people who agree to take part in the study.

Consent for Publication
Yes.

References

1. James, S.L., Abate, D., Abate, K.H., Abay, S.M., Abbafati, C., Abbasi, N., et al.: Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet **392**(10159), 1789–1858 (2018)
2. Kent, J.S., Hong, S.L., Bolbecker, A.R., Klaunig, M.J., Forsyth, J.K., O'Donnell, B.F., et al.: Motor deficits in schizophrenia quantified by nonlinear analysis of postural sway. PLoS One **7**(8), e41808 (2012)
3. Koreki, A., Tsunoda, K., Suzuki, T., Hirano, J., Watanabe, K., Kashima, H., et al.: Clinical and demographic characteristics associated with postural instability in patients with schizophrenia. J. Clin. Psychopharmacol. **31**(1), 16–21 (2011)
4. Picard, H., Amado, I., Mouchet-Mages, S., Olié, J.-P., Krebs, M.-O.: The role of the cerebellum in schizophrenia: an update of clinical, cognitive, and functional evidences. Schizophr. Bull. **34**(1), 155–172 (2008)
5. Marvel, C.L., Schwartz, B.L., Rosse, R.B.: A quantitative measure of postural sway deficits in schizophrenia. Schizophr Res. **68**(2–3), 363–372 (2004)
6. Mackenzie, L., O'Toole, G.: Occupation Analysis in Practice. Wiley, Hoboken (2011)
7. Teng, Y.-L., Chen, C.-L., Lou, S.-Z., Wang, W.-T., Wu, J.-Y., Ma, H.-I., et al.: Postural stability of patients with schizophrenia during challenging sensory conditions: implication of sensory integration for postural control. PloS One **11**(6), e0158219-e (2016)
8. Fusar-Poli, P., Politi, P.: Paul Eugen Bleuler and the birth of schizophrenia (1908). Am. J. Psychiatry **165**(11), 1407 (2008)
9. Bleuler, E.: Textbook of Psychiatry. Arno Press, New York (1976)
10. Varambally, S., Venkatasubramanian, G., Gangadhar, B.N.: Neurological soft signs in schizophrenia - the past, the present and the future. Indian J. Psychiatry. **54**(1), 73–80 (2012)
11. Bachmann, S., Schröder, J.: Neurological soft signs in schizophrenia: an update on the state- versus trait-perspective. Front. Psychiatry **8**, 272 (2018)
12. Papiol, S., Fatjó-Vilas, M., Schulze, T.G.: Neurological soft signs in patients with schizophrenia: current knowledge and future perspectives in the post-genomics era. Transl. Dev. Psychiatry **4**(1), 30071 (2016)

13. Wolff, A.L., O'Driscoll, G.A.: Motor deficits and schizophrenia: the evidence from neuroleptic-naïve patients and populations at risk. J. Psychiatry Neurosci. **24**(4), 304–314 (1999)
14. Walther, S., Strik, W.: Motor symptoms and schizophrenia. Neuropsychobiology **66**(2), 77–92 (2012)
15. Reiter, P.J.: Extrapyramidal motor disturbances in dementia praecox. Acta Psychiatrica et Neurologica (KjøBenhavn) **1**, 287–304 (1926)
16. Ayd, F.J., Jr.: A survey of drug-induced extrapyramidal reactions. JAMA **175**, 1054–1060 (1961)
17. Crane, G.E., Naranjo, E.R.: Motor disorders induced by neuroleptics: a proposed new classification. Arch. Gen. Psychiatry **24**(2), 179–184 (1971)
18. Compton, M.T., Fantes, F., Wan, C.R., Johnson, S., Walker, E.F.: Abnormal movements in first-episode, nonaffective psychosis: dyskinesias, stereotypies, and catatonic-like signs. Psychiatry Res. **226**(1), 192–197 (2015)
19. Friedman, J.H.: Historical perspective on movement disorders. J. Clin. Psychiatry. **65**(Suppl 9), 3–8 (2004)
20. Peralta, V., Cuesta, M.J.: Motor features in psychotic disorders. I. Factor structure and clinical correlates. Schizophr Res. **47**(2–3), 107–116 (2001)
21. Hirjak, D., Thomann, P.A., Kubera, K.M., Wolf, N.D., Sambataro, F., Wolf, R.C.: Motor dysfunction within the schizophrenia-spectrum: a dimensional step towards an underappreciated domain. Schizophr. Res. **169**(1), 217–233 (2015)
22. Bernard, J.A., Mittal, V.A.: Cerebellar-motor dysfunction in schizophrenia and psychosis-risk: the importance of regional cerebellar analysis approaches. Front. Psychiatry **5**, 160 (2014)
23. Turner, R., Schiavetto, A.: The cerebellum in schizophrenia: a case of intermittent ataxia and psychosis–clinical, cognitive, and neuroanatomical correlates. J. Neuropsychiatry Clin. Neurosci. **16**(4), 400–408 (2004)
24. Strik, W.K., Dierks, T., Gaebel, W., Falkai, P., Rössler, W.: Biologische Psychopathologie: Kohlhammer Verlag (2010)
25. Apthorp, D., Bolbecker, A.R., Bartolomeo, L.A., O'Donnell, B.F., Hetrick, W.P.: Postural sway abnormalities in schizotypal personality disorder. Schizophr. Bull. **45**(3), 512–521 (2018)
26. Holmes, G.: The cerebellum of man1. Brain J. Neurol. **62**(1), 1–30 (1939)
27. Ho, B.C., Mola, C., Andreasen, N.C.: Cerebellar dysfunction in neuroleptic naive schizophrenia patients: clinical, cognitive, and neuroanatomic correlates of cerebellar neurologic signs. Biol. Psychiatry **55**(12), 1146–1153 (2004)
28. Nasrallah, H.A.: Neurologic comorbidities in schizophrenia. J. Clin. Psychiatry **66**(Suppl 6), 34–46 (2005)
29. Varambally, S., Venkatasubramanian, G., Thirthalli, J., Janakiramaiah, N., Gangadhar, B.N.: Cerebellar and other neurological soft signs in antipsychotic-naive schizophrenia. Acta Psychiatr Scand. **114**(5), 352–356 (2006)
30. Ioffe, M.: Cerebellar Control of Posture, pp. 1221–1240 (2013)
31. Yanagihara, D.: Role of the cerebellum in postural control. J. Phys. Fit. Sports Med. **3**(2), 169–172 (2014)
32. Ivanenko, Y., Gurfinkel, V.S.: Human postural control. Front. Neurosci. **12**, 171 (2018)
33. Nashner, L.M., Shupert, C.L., Horak, F.B., Black, F.O.: Organization of posture controls: an analysis of sensory and mechanical constraints. Prog. Brain Res. **80**, 411–418 (1989). Discussion 395–397
34. Massion, J., Alexandrov, A., Frolov, A.: Why and how are posture and movement coordinated? Prog. Brain Res. **143**, 13–27 (2004)

35. Bouisset, S., Do, M.C.: Posture, dynamic stability, and voluntary movement. Neurophysiol. Clin. **38**(6), 345–362 (2008)
36. Melo, P.S., Ferreira, T.P., Santos-Pontelli, T.E.G., Carneiro, J.A.O., Carneiro, A.A.O., Colafêmina, J.F.: Comparação da oscilação postural estática na posição sentada entre jovens e idosos saudáveis. Brazilian J. Phys. Therapy **13**, 549–554 (2009)
37. Oba, N., Sasagawa, S., Yamamoto, A., Nakazawa, K.: Difference in postural control during quiet standing between young children and adults: assessment with center of mass acceleration. PLOS ONE **10**(10), e0140235(2015)
38. Nag, P.K., Nag, A., Vyas, H., Shah, P. (eds.) Postural control in different load handling tasks (2014)
39. Tsuji, Y., Akezaki, Y., Mori, K., Yuri, Y., Katsumura, H., Hara, T., et al.: Factors inducing falling in schizophrenia patients. J. Phys. Ther. Sci. **29**(3), 448–451 (2017)
40. Vancampfort, D., Probst, M., De Herdt, A., Corredeira, R.M.N., Carraro, A., De Wachter, D., et al.: An impaired health related muscular fitness contributes to a reduced walking capacity in patients with schizophrenia: a cross-sectional study. BMC Psychiatry **13**(1), 5 (2013)
41. Vancampfort, D., Probst, M., Scheewe, T., De Herdt, A., Sweers, K., Knapen, J., et al.: Relationships between physical fitness, physical activity, smoking and metabolic and mental health parameters in people with schizophrenia. Psychiatry Res. **207**(1), 25–32 (2013)
42. Occupational therapy practice framework: domain and process (3rd edition). Am. J. Occup. Therapy **68**(Supplement_1), S1–S48 (2017)
43. Kielhofner, G.: Model of Human Occupation: Theory and Application: Lippincott Williams & Wilkins (2008)
44. Paillard, T., Noé, F.: Techniques and methods for testing the postural function in healthy and pathological subjects. BioMed Res. Int. **2015**, 891390 (2015)
45. Huurnink, A., Fransz, D.P., Kingma, I., van Dieën, J.H.: Comparison of a laboratory grade force platform with a Nintendo Wii Balance Board on measurement of postural control in single-leg stance balance tasks. J. Biomech. **46**(7), 1392–1395 (2013)
46. Duarte, M., Freitas, S.M.: Revision of posturography based on force plate for balance evaluation. Brazil. J. Phys. Therapy **14**(3), 183–192 (2010)
47. Fujino, H., Imura, O.: Postural sway and clinical characteristics in patients with psychotic disorders: a review. Psychiatr Q. **86**(4), 603–614 (2015)
48. Ikai, S., Uchida, H., Suzuki, T., Tsunoda, K., Mimura, M., Fujii, Y.: Effects of yoga therapy on postural stability in patients with schizophrenia-spectrum disorders: a single-blind randomized controlled trial. J. Psychiatr Res. **47**(11), 1744–1750 (2013)
49. Erdem, E.U., Akbaş, E., Ünver, B.: Pilates-based training for postural stability in patients with schizophrenia. Exercise Medicine **3** (2019)
50. Park, M.J., Kim, D.J., Lee, U., Na, E.J., Jeon, H.J.: A literature overview of virtual reality (VR) in treatment of psychiatric disorders: recent advances and limitations. Front. Psychiatry **10**, 505 (2019)
51. Uvais, N.A.: Virtual reality applications in Schizophrenia. Ind. Psychiatry J. **24**(2), 210 (2015)
52. Ayed, I., Ghazel, A., Jaume, I.C.A., Moya-Alcover, G., Varona, J., Martinez-Bueso, P.: Vision-based serious games and virtual reality systems for motor rehabilitation: a review geared toward a research methodology. Int. J. Med. Inform.**131**, 103909 (2019)
53. Gutierrez, R.O., Galan Del Rio, F., Cano de la Cuerda, R., Alguacil Diego, I.M., Gonzalez, R.A., Page, J.C.: A telerehabilitation program by virtual reality-video games improves balance and postural control in multiple sclerosis patients. NeuroRehabilitation **33**(4), 545–54 (2013)
54. Chen, L., lo, A., Mao, Y.-R., Ding, M., Lin, Q., Li, H., et al.: Effect of virtual reality on postural and balance control in patients with stroke: a systematic literature review. BioMed. Res. Int. **2016**, 1–8 (2016)

55. Zanona, A.F., de Souza, R.F., Aidar, F.J., de Matos, D.G., Santos, K.M.B., Paixao, M.D.C., et al.: Use of virtual rehabilitation to improve the symmetry of body temperature, balance, and functionality of patients with stroke sequelae. Ann. Neurosci. **25**(3), 166–173 (2019)
56. Prasertsakul, T., Kaimuk, P., Chinjenpradit, W., Limroongreungrat, W., Charoensuk, W.: The effect of virtual reality-based balance training on motor learning and postural control in healthy adults: a randomized preliminary study. Biomed. Eng. Online **17** (2018)
57. Jo, G., Rossow-Kimball, B., Park, G., Lee, Y.: Effects of virtual reality exercise for Korean adults with schizophrenia in a closed ward. J. Exerc. Rehabil. **14**(1), 39–48 (2018)
58. Gatica-Rojas, V., Cartes-Velasquez, R., Albornoz-Verdugo, M.E., Soto-Poblete, A., Monteiro-Junior, R.S., Elgueta-Cancino, E.: Effects of a Nintendo Wii exercise program versus Tai Chi Chuan on standing balance in older adults: aA preliminary study. J. Phys. Ther. Sci. **31**(1), 1–4 (2019)
59. Macedo, M., Marques, A., Queirós, C.: Virtual reality in assessment and treatment of schizophrenia: a systematic review. J. Bras. Psiquiatr. **64**, 70–81 (2015)
60. Freeman, D.: Studying and treating schizophrenia using virtual reality: a new paradigm. Schizophr. Bull. **34**(4), 605–610 (2008)
61. Artemisa, R.D., Barbosa, F., António, M., Irene, P.C., de Liliana, S., Alexandre, C.-C.: Realidade virtual na reabilitação: Por que sim e por que não? uma revisão sistemática = Virtual reality and rehabilitation: why or why not? a systematic literature review. Acta Med. Port. **25**(6), 414–421 (2012)
62. Teo, W.-P., Muthalib, M., Yamin, S., Hendy, A.M., Bramstedt, K., Kotsopoulos, E., et al.: Does a combination of virtual reality, neuromodulation and neuroimaging provide a comprehensive platform for neurorehabilitation? – A narrative review of the literature. Front. Hum. Neurosci. **10**(284) (2016)
63. Kim, A., Schweighofer, N., Finley, J.M.: Locomotor skill acquisition in virtual reality shows sustained transfer to the real world. J. Neuroeng. Rehabil. **16**(1), 113 (2019)
64. Bossard, C., Kermarrec, G., Buche, C., Tisseau, J.: Transfer of learning in virtual environments: a new challenge? Virtual Reality **12**(3), 151–161 (2008)
65. Babbie, R.: The Practice of Social Research. Cengage Learning (2012)
66. McNabb, D.E.: Research Methods in Public Administration and Nonprofit Management. Unknown Publisher (2002)
67. Sheard, J.: Chapter 18 - quantitative data analysis. In: Williamson, K., Johanson, G. (eds.) Research Methods, 2nd edn. , pp. 429–452 Chandos Publishing (2018)
68. Lennon-Dearing, R., Neely, B.: Quantitative Research, pp. 3–21 (2013)
69. Chan, A.-W., Tetzlaff, J.M., Gøtzsche, P.C., Altman, D.G., Mann, H., Berlin, J.A., et al.: SPIRIT 2013 explanation and elaboration: guidance for protocols of clinical trials. BMJ Brit. Med. J. **346**, e7586 (2013)
70. Sim, J., Wright, C.: Research in Health Care: Concepts. Nelson Thornes, Designs and Methods (2000)
71. Folstein, M.F., Folstein, S.E., McHugh, P.R.: "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J. Psychiatr. Res. **12**(3), 189–198 (1975)
72. Cohen, J.: Chapter 8 - F tests on means in the analysis of variance and covariance. In: Cohen, J. (ed.) Statistical Power Analysis for the Behavioral Sciences. Academic Press, pp. 273–406 (1977)
73. Sakpal, T.V.: Sample size estimation in clinical trial. Perspect Clin. Res. **1**(2), 67–69 (2010)
74. Hosley, M.: Retention in clinical trials – keeping patients on protocols. Forte Research [Internet]. Forte, editor: Forte (2020). https://forteresearch.com/news/infographic/infographic-retention-in-clinical-trials-keeping-patients-on-protocols/. Accessed 30 June 2020

75. Higgins, J., Thomas, J., Li, T., Page, M., Welch, V., Chandler, J., et al.: Collecting data. In: Higgins, J., Thomas, J., Li, T., Page, M., Welch, V., Cumpston, M., et al. (eds.) Cochrane Handbook for Systematic Reviews of Interventions. Cochrane (2019)
76. World Medical: A world medical association declaration of Helsinki. Ethical principles for medical research involving human subjects. Bull. World Health Organ. **79**(4), 373–374 (2001)
77. Smith, D.L.: Patient nonadherence in clinical trials: could there be a link to postmarketing patient safety? Drug Inf. J. **46**(1), 27–34 (2012)
78. Robiner, W.N.: Enhancing adherence in clinical research. Contemp. Clin. Trials **26**(1), 59–77 (2005)
79. Elkins, M.: Assessing baseline comparability in randomised trials. J. Physiother. **61** (2015)
80. Duarte, M., Freitas, S.M.S.F.: Revisão sobre posturografia baseada em plataforma de força para avaliação do equilíbrio. Braz. J. Phys. Therapy **14**, 183–192 (2010)
81. Rocchi, L., Chiari, L., Cappello, A.: Feature selection of stabilometric parameters based on principal component analysis. Med. Biol. Eng. Comput. **42**(1), 71–79 (2004)
82. Bias, A.: In: Berman, N.G., Parker, R.A. (eds.) Planning Clinical Research, pp. 217–226. Cambridge University Press, Cambridge (2016)
83. Rossi, S., Patanè, F., Scalise, L., Marchionni, P., Cappa, P.: Centre of pressure in dynamic posturography: a comparison among systems based on a pressure matrix and a force platform. Meas. Sci. Technol. (2010)
84. Cook, A.M., Polgar, J.M.: Assistive Technologies- E-Book: Principles and Practice. Elsevier Health Sciences (2014)
85. Fernando, F.A.P.: Fiabilidade e validade do instrumento Physiosensing na avaliação do equilíbrio em pessoas com deficiência intelectual (2014)
86. Abshire, M., Dinglas, V.D., Cajita, M.I.A., Eakin, M.N., Needham, D.M., Himmelfarb, C.D.: Participant retention practices in longitudinal clinical research studies with high retention rates. BMC Med. Res. Methodol. **17**(1), 30 (2017)
87. Zweben, A., Fucito, L.M., O'Malley, S.S.: Effective strategies for maintaining research participation in clinical trials. Drug Inf. J. **43**(4) (2009). https://doi.org/10.1177/009286150904300411.
88. MTN: Participant Retention. Study Specific Procedures: MTN (Microbicide Trials Network) (2011)
89. Smith, P.G., Morrow, R.H., Ross, D.A.: Field Trials of Health Interventions: A Toolbox. Oxford University Press (2015)
90. Gałecki, A., Burzykowski, T.: Linear Mixed-Effects Models Using R: A Step-by-Step Approach. Springer, New York (2013)
91. Verma, J.P.: Repeated Measures Design for Empirical Researchers. Wiley, Hoboken (2015)
92. Beins, B.C., McCarthy, M.A.: Research Methods and Statistics in Psychology. Cambridge University Press, Cambridge (2018)
93. Beins, B.C., McCarthy, M.A.: Research Methods and Statistics. Cambridge University Press, Cambridge (2017)
94. Brown, H., Prescott, R.: Applied Mixed Models in Medicine. Wiley, Hoboken (2014)
95. Deke, J., Puma, M.: Coping with missing data in randomized controlled trials (2013). https://www.hhs.gov/ash/oah/sites/default/files/ash/oah/oah-initiatives/for-grantees/assets/copingwithmissingdata.pdf.
96. General principles for dealing with missing data. In: Higgins, J., Deeks, J., Altman, D. (eds.) Cochrane Handbook for Systematic Reviews of Interventions Version 510: The Cochrane Collaboration (2011)
97. Ikai, S., Uchida, H., Suzuki, T., Tsunoda, K., Fujii, Y., Mimura, M.: Postural sway and flexibility in patients with schizophrenia-spectrum disorders: a cross-sectional study. Asian J. Psychiatr. **19**, 14–18 (2016)

98. Sveistrup, H.: Motor rehabilitation using virtual reality. J. Neuroeng. Rehabil. **1**(1), 10 (2004)
99. Proffitt, R., Lange, B.: Considerations in the efficacy and effectiveness of virtual reality interventions for stroke rehabilitation: moving the field forward. Phys. Ther. **95**(3), 441–448 (2015)
100. Alfonsson, S., Olsson, E., Hursti, T.: Motivation and treatment credibility predicts dropout, treatment adherence, and clinical outcomes in an internet-based cognitive behavioral relaxation program: a randomized controlled trial. J. Med. Internet Res. **18**, e52 (2016)
101. Dias, P., Silva, R., Amorim, P., Lains, J., Roque, E., Pereira, I., et al.: Using virtual reality to increase motivation in poststroke rehabilitation. IEEE Comput. Graph. Appl. **39**, 64–70 (2019)
102. Perez-Marcos, D., Bieler-Aeschlimann, M., Serino, A.: Virtual reality as a vehicle to empower motor-cognitive neurorehabilitation. Front. Psychol. **9**(2120) (2018)
103. Beek, P.J., Roerdink, M.: Evolving insights into motor learning and their implications for neurorehabilitation. In: Kwakkel, G., Cohen, L.G., Selzer, M.E., Miller, R.H., Clarke, S. (eds.) Textbook of Neural Repair and Rehabilitation: Volume 2: Medical Neurorehabilitation 2. 2 ed. Cambridge University Press, Cambridge, pp. 95–104 (2014)
104. Lanzarin, M., Parizzoto, P., Libardoni, T.d.C., Sinhorim, L., Tavares, G.M.S., Santos, G.M.: A influência da dupla tarefa no controle postural de adultos jovens. Fisioterapia e Pesquisa **22**, 61–68 (2015)
105. Blanchard, Y., Carey, S., Coffey, J., Cohen, A., Harris, T., Michlik, S., et al.: The influence of concurrent cognitive tasks on postural sway in children. Pediatric Phys. Therapy **17**(3) (2005)
106. Palluel, E., Nougier, V., Olivier, I.: Postural control and attentional demand during adolescence. Brain Res. **1358**, 151–159 (2010)
107. Bustillo-Casero, P., Cebrian-Bou, S., Cruz-Montecinos, C., Pardo, A., García-Massó, X.: Effects of a dual-task intervention in postural control and cognitive performance in adolescents. J. Mot. Behav. **52**(2), 187–195 (2020)
108. Tinga, A.M., Visser-Meily, J.M.A., van der Smagt, M.J., Van der Stigchel, S., van Ee, R., Nijboer, T.C.W.: Multisensory stimulation to improve low- and higher-level sensory deficits after stroke: a systematic review. Neuropsychol. Rev. **26**(1), 73–91 (2016)
109. Chander, H., Kodithuwakku Arachchige, S.N.K., Hill, C.M., Turner, A.J., Deb, S., Shojaei, A., et al.: Virtual-reality-induced visual perturbations impact postural control system behavior. Behav. Sci. (Basel) **9**(11), 113 (2019)
110. Fransson, P.-A., Patel, M., Jensen, H., Lundberg, M., Tjernström, F., Magnusson, M., et al.: Postural instability in an immersive Virtual Reality adapts with repetition and includes directional and gender specific effects. Sci. Rep. **9**(1), 3168 (2019)
111. Karlsson, P., Bergmark, A.: Compared with what? An analysis of control-group types in Cochrane and Campbell reviews of psychosocial treatment efficacy with substance use disorders. Addiction **110**(3), 420–428 (2015)
112. Monsen, E.R., Van Horn, L., Association, A.D.: Research: Successful Approaches: American Dietetic Association (2007)
113. Skelly, A.C., Dettori, J.R., Brodt, E.D.: Assessing bias: the importance of considering confounding. Evid. Based Spine Care J. **3**(1), 9–12 (2012)
114. Dettori, J.R.: Loss to follow-up. Evid. Based Spine Care J. **2**(1), 7–10 (2011)
115. Besancon, M.F., Conzemius, M., Derrick, T., Ritter, M.J.: Comparison of vertical forces in normal Greyhounds between force platform and pressure walkway measurement systems. Veter. Compar. Orthop. Traumatol. **16**, 153–157 (2003)
116. PhysioSensing (2019). https://www.physiosensing.net/assessment. Accessed 2 July 2020
117. Hageman, P.A., Leibowitz, J.M., Blanke, D.: Age and gender effects on postural control measures. Arch. Phys. Med. Rehabil. **76**(10), 961–965 (1995)

118. Ozcan Kahraman, B., Kahraman, T., Kalemci, O., Salik, S.Y.: Gender differences in postural control in people with nonspecific chronic low back pain. Gait Posture **64**, 147–151 (2018)
119. Buragadda, S., Melam, G., Alhusaini, A.: I I, Kachanathu S. Gender differences in static and dynamic postural stability parameters in community dwelling healthy older adults **22**, 1259–1264 (2014)
120. Virk, S., McConville, K.M.: Virtual reality applications in improving postural control and minimizing falls. Conf. Proc. IEEE Eng. Med. Biol. Soc. **2006**, 2694–2697 (2006)
121. Greve, J., Alonso, A., Bordini, A.C., Camanho, G.L.: Correlation between body mass index and postural balance. Clinics (Sao Paulo) **62**(6), 717–720 (2007)
122. Błaszczyk, J., Cieślińska-Świder, J., Plewa, M., Zahorska-Markiewicz, B., Markiewicz, A.: Effects of excessive body weight on postural control. J. Biomech. **42**, 1295–1300 (2009)
123. Ku, P.X., Abu Osman, N.A., Yusof, A., Abas, W.: Biomechanical evaluation of the relationship between postural control and body mass index. J. Biomech. **45**, 1638–1642 (2012)
124. Darekar, A., McFadyen, B.J., Lamontagne, A., Fung, J.: Efficacy of virtual reality-based intervention on balance and mobility disorders post-stroke: a scoping review. Journal of neuroengineering and rehabilitation **12**, 46 (2015)
125. Lohse, K.R., Hilderman, C.G.E., Cheung, K.L., Tatla, S., Van der Loos, H.F.M.: Virtual reality therapy for adults post-stroke: a systematic review and meta-analysis exploring virtual environments and commercial games in therapy. PloS one **9**(3), e93318-e (2014)