

Title: Effects of sensory cueing in virtual motor rehabilitation. A review

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Abstract

Objectives. To critically identify studies that evaluate the effects of cueing in virtual motor rehabilitation in patients having different neurological disorders and to make recommendations for future studies.

Methods. Data from MEDLINE®, IEEEExplore, Science Direct, Cochrane library and Web of Science was searched until February 2015. We included studies that investigate the effects of cueing in virtual motor rehabilitation related to interventions for upper or lower extremities using auditory, visual, and tactile cues on motor performance in non-immersive, semi-immersive, or fully immersive virtual environments. These studies compared virtual cueing with an alternative or no intervention.

Results. Ten studies with a total number of 153 patients were included in the review. All of them refer to the impact of cueing in virtual motor rehabilitation, regardless of the pathological condition. After selecting the articles, the following variables were extracted: year of publication, sample size, study design, type of cueing, intervention procedures, outcome measures, and main findings. The outcome evaluation was done at baseline and end of the treatment in most of the studies. All of studies except one showed improvements in some or all outcomes after intervention, or, in some cases, in favor of the virtual rehabilitation group compared to the control group.

Conclusions. Virtual cueing seems to be a promising approach to improve motor learning, providing a channel for non-pharmacological therapeutic intervention in different neurological disorders. However, further studies using larger and more homogeneous groups of patients are required to confirm these findings.

Keywords: virtual cueing, virtual motor rehabilitation, human computer interaction, disorders

1 Introduction

In the last few years, the main causes of neurological disorders in the world are Acquired Brain Injury (ABI) [1], Parkinson's disease (PD) [2], and Multiple Sclerosis disease (MS) [3]. ABI is an acute injury in the encephalon which leads to permanent neurological impairment in the subject and produces a detriment to functional abilities and quality of life [4]. Based on initial diagnosis, ABI is classified by traumatic (Traumatic Brain Injury (TBI) [5]) or non-traumatic (Stroke [6]) incidents. This type of injury leads to motor disabilities such as postural control impairments, balance disorders, patient mobility, and upper extremity functionality [7]. From 1997 to 2007, the number of deaths from TBIs in the US was around 53,014 patients, with an average incidence of 18.4 per 1,000,000 individuals [8], 1.1 million emergency department visits, 235,000 hospitalizations, and 50,000 deaths [9].

The incidence of stroke is considerable in the US and EU countries (France, Italy, Spain, UK, and Germany). Based on the data collected by Zhang et al. [10], the incidence of stroke in the six countries of interest ranges between 114 cases per 100,000 people per year in France for

1 first ever stroke to 350 cases per 100,000 people per year in Germany for all stroke, while
2 prevalence estimates ranged from 1.5% in Italy and 3% in the UK and the US. The incidence in
3 Northeastern China was between 441 and 486 cases per 1,000,000, and in Southern China it
4 was between 81 and 136 cases per 1,000,000 [11].
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6 PD is a progressive degenerative disorder that produces motor disturbances showing
7 dyskinesia and motor fluctuations [2]. Due to neural damage in the brain [12], the motor
8 symptomatology of PD patients is resting tremor [13], muscle rigidity [14], bradykinesia [15],
9 postural control [16], and balance disorder [17]. The non-motor disturbances of PD patients are
10 cognitive impairments [18] (memory impairment) and sleep and mood disorders [19]. According
11 to Dorsey et al. [20] the projected number of people with PD in the world's 10 most populous
12 nations over age 50 will range between 8.7 and 9.3 million by 2030 (doubling 2005 figures).
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17 MS is an inflammatory disease of the central nervous system (CNS) with progressive
18 neurodegeneration effects [21]. The physical disorders are fatigue, spasticity, weakness,
19 impaired mobility [22], coordination, balance disorders, and vision problems [3], whereas the
20 non-physical disorders are cognitive dysfunction (attention deficits, memory loss, information
21 processing) [23], reducing the MS patients' quality of life. The incidence of MS is based on
22 latitude [24], with a standardized rate of 7.3 per 1,000,000 person-year in the US [25], an
23 incidence in Canada of 298.3 per 1,000,000 people per year [26] in 2005, an annual incidence in
24 the Patagonia region of 1.4 per 100,000 people per year [27], and an incidence for both sexes
25 in Europe from 1.14 to 7.93 per 100,000 people per year [28] in the period of 1985-2009.
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31 The purpose of this methodological review is to determine the effects of cueing in motor virtual
32 rehabilitation in a broader sense, regardless of the pathology of patients.
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35 1.1 Cueing and Virtual Rehabilitation 36

37 Cueing is defined as using external temporal or spatial stimuli to facilitate the initiation and
38 continuation of movement (gait) [29]. Horstink et al. [30] distinguish between cues and stimuli,
39 stating that 'cues give information on how an action should be carried out and are hence more
40 specific than simple stimuli'. According to Cools [31], cues are 'contextual or spatial stimuli
41 which are associated with behavior to be executed, through past experience'. Albiol et al. [32]
42 proposed an alternative definition of Virtual Reality Motor Cues (VR Motor Cues), which
43 includes 'those mechanisms in a virtual environment designed with the specific purpose of
44 inducing the user to perform a specific motor activity'.
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50 There are many types of external cues such as visual, auditory, and somatosensory cues. In
51 traditional motor rehabilitation, visual cues have normally used a series of strips placed on the
52 floor in a transverse line for the patients to walk over [33][34][35]. Auditory cues do not
53 necessarily add realism to the scene, but they do increase the sense of presence [36].
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57 The field of Virtual Reality (VR) technologies has experienced great advances and benefits in
58 Traditional Motor Rehabilitation (TMR) in patients with Neurological Diseases. Virtual
59 rehabilitation introduces a new form of intervention that has many advantages over traditional
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rehabilitation approaches. This technology provides the capability to create an environment in which the intensity of feedback and training can be systematically manipulated and enhanced in order to create the most appropriate, individualized motor learning paradigm [37]. The programs become more interesting and enjoyable than traditional tasks [38][39] and they are especially appropriate for systems targeted to non-clinic environments (e.g., a patient's home). This reduces reducing the cost of providing care in remote areas while at the same time improving access to a higher quality of care in these remote areas. Different studies have demonstrated that virtual rehabilitation could be beneficial for patient rehabilitation [40][41][42][43][44][45].

The capacity of Virtual Motor Rehabilitation (VMR) to create customizable, interactive, and multisensory 3-D stimuli offers clinical intervention and assessment that are more accurate than TMR approaches [46]. VR has great potential to create very precise training environments that allow performance measurement, data analysis, and recording to monitor the progress of subjects. The practical advantages of using VMR include safety, time, space, equipment, cost efficiency, and enjoyable therapeutic sessions [47].

One of the strengths of virtual reality as a training tool in clinical environments is related to the multi-sensory experience that it provides. The visual, auditory, and tactile cues that are added to the environment improve the virtual experience.

1.2 Real versus Virtual Cueing

Some studies on real cueing suggest that it can have an immediate and powerful effect on gait performance in people with Parkinson's disease, showing improvements in walking speed, step length, and step frequency. [48][49]. Nevertheless, the influence of cueing has mainly been studied in single-session experiments in laboratory settings [50]. Results show a short-term correction of gait and gait initiation but generalization to activities of daily living (ADL) is limited. Willems et al. [51] also demonstrated that the use of rhythmical auditory cues improved stride length and walking velocity. Withall et al. [52] demonstrated that bilateral arm training with rhythmic auditory cueing improves motor function in the hemiparetic arm. Later, in a review about cueing applied to the Freezing of Gait in patients with Parkinson's disease [53], the results showed that the immediate effects of cues have no consistent impact but that longer periods of cued training may be beneficial. Suteerawattananon et al. [35] conducted a study that showed that either visual or auditory cues significantly improved gait performance in PD, not only separately but also when combined. They conclude that cueing may be one of the strategies for reducing gait difficulties in patients with PD and should be incorporated in clinical scales to assess gait and balance difficulties.

Nevertheless, in the literature, we find that cueing does not always improve motor functions such as gait [54][55][56], nor does a single type of cue improve gait for all the patients suffering from Parkinson's Disease. In fact, the study conducted by Nieuwboer et al. [29] trained Parkinson Patients with their preferred modality of cue only.

Several studies have developed cue-based prototypes to enhance VR-based rehabilitation. The research presented by Park et al. [57] is a novel approach to the development of a body-weight supported treadmill interface (BWSTI) system associated with a VR system to investigate Freezing of Gait (FoG) in patients with Parkinson's disease. The authors found that the system can safely and realistically reproduce real-world, overground walking conditions, being able to evoke FOG in the laboratory with the help of visual cues. Visual stimuli that might cause FOG were shown to them while the speed adaptation controller adjusted treadmill speed to follow the subjects' intention. With regard to tactile cues, the sense of touch is indispensable for many routine tasks, working in close coordination with vision, hearing, and the motor control system. Real-time tactile feedback applied to the working arm could help patients correct motion errors during rehabilitation [58].

There is little evidence in methodological reviews from the point of view of virtual motor cues. Cueing has mostly been studied in the rehabilitation of Parkinson Patients (traditional and/or virtual), mainly oriented to the problematic of gait and balance in this kind of pathology. The study performed by Lim et al. [49] focused on the effects of external rhythmical cueing on gait in patients with Parkinson's Disease. As a clinical message, the authors concluded that there was strong evidence that rhythmical auditory cueing enhances walking speed. However, generalization of reported effects measured in a gait laboratory to gait-related ADLs and patients' own home situations remains unclear. Baram conducted a review focused on the improvement of gait in movement disorder patients with the help of virtual sensory feedback [59]. The author performed a series of studies including visual feedback, auditory feedback, and combined visual and auditory feedback for the following pathologies: Parkinson's Disease, Senile Gait, Multiple Sclerosis, Cerebral Palsy and patients having had previous strokes. Even though certain studies found that open-loop sensory stimulation resulted in gain and balance improvement, other studies have questioned the effectiveness of monotone sensory cues.

2.- Materials and methods

2.1. Search Strategy. In order to gather all the information, we searched different databases electronically: (Medline through Pubmed, IEEE Electronic Library, Science Direct, Cochrane library) from inception until February 2015. The major search terms were virtual rehabilitation, cueing, and virtual cues. Depending on the search engine, subject headings and keywords based on the search terms were used to identify relevant articles). **To summarize, we attempted to obtain publications that contain interventions based on virtual motor rehabilitation and that also used virtual cueing, rregarless of the type of cue (visual, auditory, or tactile/haptic). Some examples of search words were: virtual rehabilitation, virtual motor cues, virtual cueing, virtual reality motor cueing, and combinations of these terms. Fig. 1 presents some example search queries that we used for searching in Medline (using the PubMed interface).**

	All fields	Cueing [mh]
AND	All fields	Virtual cues [majr]
	All fields	virtual motor cues
OR	All fields	virtual motor cueing
	All fields	Virtual Rehabilitation
AND	All fields	Virtual cueing
	All fields	Virtual Rehabilitation [mh]
AND	All fields	Virtual cueing [majr]
	All fields	virtual motor cues/RH
OR	All fields	virtual motor cueing/RH
	All fields	Virtual Cueing [mh]
OR	All fields	Virtual cues [mh]
AND	All fields	Motor rehabilitation

Fig. 1. Sample search queries used for article retrieval from Medline.

In an attempt to identify further relevant studies, we searched conference proceedings of international workshops on Virtual Reality/Rehabilitation. Reference lists from the identified publications were also reviewed to identify additional research articles of interest.

2.2. Eligibility criteria. We included studies that investigate the effects of cueing in virtual motor rehabilitation. Interventions for upper or lower extremities using auditory, visual, or tactile cues on motor performance in non-immersive, semi-immersive, or fully immersive virtual environments were included. Interventions that met the definition introduced by Schultheis and Rizzo [60] were considered to be virtual reality: “an advanced form of human-computer interface that allows the user to interact with and become immersed in a computer-generated environment in a naturalistic fashion”. Studies were accepted when they were published in a peer-reviewed journal and they were written in English.

We excluded interventions applied on healthy subjects as well as studies conducted for rehabilitation of cognitively disabled people. We also excluded studies intended for cognitive rehabilitation whether they use or not they used cueing for virtual rehabilitation. Studies related to traditional rehabilitation were also excluded as well as any kind of virtual-reality-based contribution developed for recreational or educational purposes.

2.3. Data Collection. Two review authors (GP and SA) independently reviewed titles and abstracts retrieved from the search in order to determine if they met the predefined inclusion criteria. The full text was checked in cases of uncertainty. A third review author (IG) moderated any disagreement. The full text articles were analyzed in order to extract the type of sensory cue.

3.4. Quality Assessment. The studies were assessed independently by GP and SA. Any disagreements in quality assessment were resolved in consensus meetings by the three authors. We tried to take into account the inclusion criteria stated in the Physiotherapy Evidence

Database (PEDro) [61]. The eligibility criteria were clearly satisfied in six studies [62][63][64][65][66][67]. Due to the nature of treatments, blinding of subjects and clinicians was impossible. That means that it is not possible to fit some of the items in the PEDro scale, such as concealed allocation. The same applies to the items 5, 6, and 7, referring to subject, clinician, and assessor blinding, respectively. With the exception of three studies [68][65][69], the interventions were carried out on a single group. Baseline comparability was achieved in all studies except two cases [65][68], where this criterion was unclear. Finally, due to the novelty of treatments, subject allocation was only randomly performed in two studies [68][69]. These two studies [68][69] were included in PEDro.

3. Results

3.1 Data synthesis. The initial search yielded 547 articles. After removing duplicates, 357 potential articles that investigate the effects of cueing were identified. The authors independently evaluated titles and abstracts taking into account the inclusion and exclusion criteria. Whenever necessary, a more thorough study was carried out in order to discard articles that did not match the established criteria. Finally, the population of our study consisted of 10 articles, with a total number of 153 patients included and selected for quantitative analysis. All of them refer to the impact of cueing in virtual motor rehabilitation, regardless of the pathological condition. After selecting the articles, the following variables were extracted: year of publication, sample size, study design, type of cueing, intervention procedures, outcome measures, and main findings. The details of the search result are summarized in Figure 2.

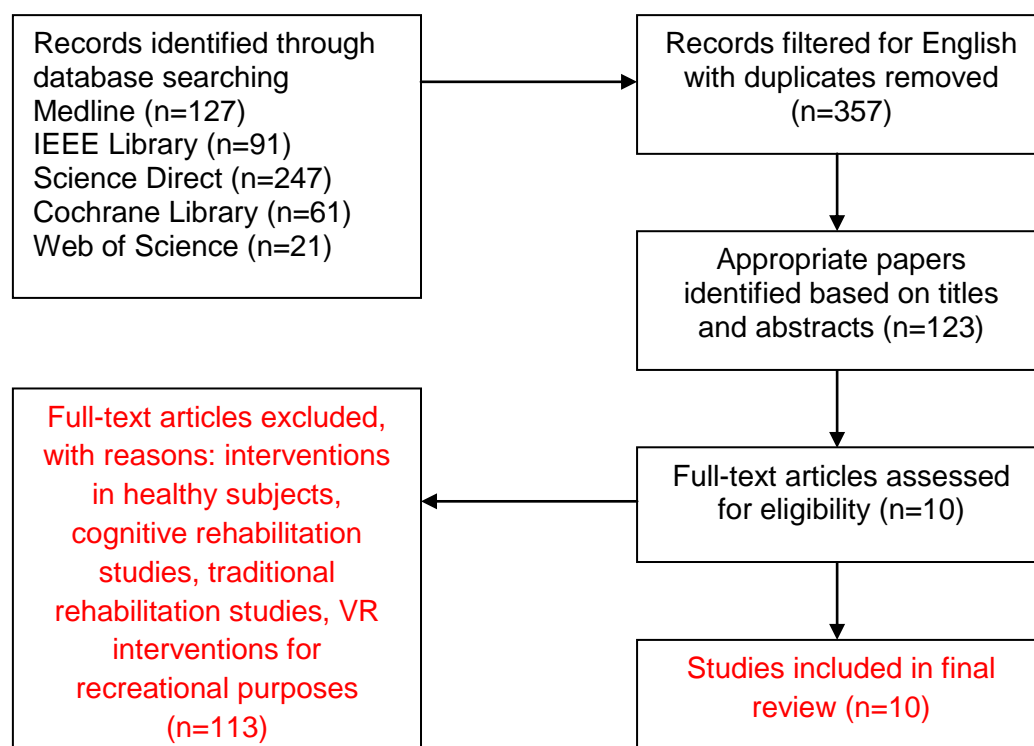


Fig. 2. Consort diagram of study selection.

3.2. *Characteristics of included studies.* Table 1 presents the general characteristics of the different studies: concerning year of publication, sample size, study design, type of cueing, intervention procedures, outcome measures, and main findings.

(a) *Population.* The subjects in five studies were Parkinson's Disease patients [62][63][64][70][71], four were related to Stroke [68][65][66][69], and one study dealt with Traumatic Brain Injury (TBI) patients [67]. The mean age of the subjects was comparable across studies (from 54.3 to 73.3) except the TBI study (37.8). None of the studies reported sample size calculation to achieve the necessary power to detect important differences. The sample sizes were small in all studies (<30). In most of them, the percentage of males was higher than the percentage of females.

(b) *Study design and type of cueing.* Four studies were pre-post designed [63][66][68][71], two of them were designed as pilot studies [64][70], three were comparative studies [62][65][67], and one of them was a randomized control study [69]. Visual cueing was used in all studies. A mixed cueing (auditory and visual) was used in five studies [62][66][68][69][70], and only one study used haptic cueing [67].

(c) *Interventions.* Different VR devices were used across studies. Seven studies conducted immersive or semi-immersive interventions [62][63][64][67][68][70][71], whereas three studies conducted non-immersive interventions [65][66][69]. Seven studies were focused on lower limb rehabilitation [62][63][64][66][69][70][71], and three of them were focused on upper limb rehabilitation [68][65][67]. Head-mounted displays or virtual reality glasses (VGR) were used in six studies [62][63][64][68][70][71]. Espay et al. [62] used a head-mounted micro display and earphones operating in an adaptive closed-loop mode and displaying a life-size checkerboard-tiled floor superimposed in the real world. Kaminsky et al. [64] used a prototype of virtual cueing spectacles (VCS) intended for simulating the kinesia paradoxa to improve gait in PD patients at home and in community settings. It was programmed in such a way that when the subjects looked directly at their feet, they would see stationary horizontal lines of light on the floor in front of them. Caudron et al. [70] used a semi-immersive binocular head-mounted display and 3D-wireless inertial sensors together with eight infrared-emitting cameras. Baram [71] used a head-mounted 3-axis rotational accelerometer, a body-mounted 3-axis translational accelerometer together with head-mounted display, all of which were connected to a wearable computer. Fischer [68] used a cable orthosis with a five-cable glove and a pneumatic hand orthosis containing a single chamber air bladder for the two experimental groups, respectively. The patients also used a PC Glasstron® head-mounted display (PLM-S700; SONY electronics, Inc). On the other hand, in the study of Mirelman et al. [69], the subjects were trained on the Rutgers Ankle Rehabilitation System. Walker et al [66] used a body weight-supported treadmill training (BWSTT) virtual reality system. Liebermann [65] used a 2-D IREX video-capture system, and Dvorkin designed a "virtually minimal" approach using robot-rendered haptics consisting of a three-dimensional haptics/graphics system and a 6-degree of freedom PHANTOM [67].

1 The frequency and duration of interventions varied across studies: from two consecutive days
2 [67] to six weeks [66][68]. Some of the studies did not specify a period of time but rather the
3 number of performed tests [63][65][71]. As far as the experiment settings are concerned, four
4 studies were carried out in clinical environments [62][67][70][71], four studies took place in
5 research laboratories [63][65][66][68], and two studies were developed at home and in
6 community environments [64][69].
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9 The interventions were successfully carried out in most cases. In the study of Griffin et al. [63], 4
10 out of 26 participants were excluded either because of disagreement or because of their
11 extremely impaired walking. Three out of 21 participants did not tolerate the interactive visio-
12 haptic environment in Dvorkin's study [67]. One out of seven participants dropped out of the
13 study conducted by Walker [66], and two participants out of 15 withdrew from Fischer's study
14 [68]. In the study conducted by Espay et al. [62], two patients did not feel comfortable using the
15 glasses and did not train at home.
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20 (d) *Outcome measures.* All of the studies included more than one outcome measure. Those
21 studies related to Parkinson's Disease patients showed measures related to gait functions and
22 balance (freezing of gait frequency, fear of falling, loss of balance, etc.) as well as timing
23 parameters to measure completion tasks (task completion time, velocity, cadence, stride length,
24 etc.). The TBI study included spatial and temporal kinematic parameters (trial time, hand path,
25 distance from target, and velocity). All of the studies except one [65] showed improvements in
26 some or all outcomes after intervention, or, in some cases, in favor of the VR group compared
27 to the control group.
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33 Outcomes in lower limb rehabilitation were good enough due to the introduction of cueing in
34 virtual rehabilitation. Griffin et al. [63] demonstrated that, of the Virtual Reality Glasses (VRG)
35 cues, only the visual-flow stimuli showed an improvement in task completion time with no
36 amelioration of Freezing of Gait (FoG). In conclusion, their results suggest that the provision of
37 visual-flow cues through the VRG can improve some aspects of walking without medication in
38 mid-stage PD. However, no specific VRG stimulus emerged as being effective in the majority of
39 patients. Virtual cueing spectacles (VCS) used in the study of Kaminsky et al. [64] appeared to
40 improve the functional mobility of six idiopathic PD patients by counting the number of LOBs
41 and freezes, as well as the completion of the PDQ-39 questionnaire pre- and post-intervention.
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47 On the other hand, Mirelman et al. [69] found that walking speed and distance walked in chronic
48 hemiparesis patients improved and were retained for 3 months in the experimental group,
49 whereas improvements in the control group were modest without transferring significant
50 functional changes. Walker et al [66] showed that participants made significant improvements in
51 their ability to walk by measuring reasonable increases in functional gait assessment (FGA),
52 Berg balance scale (BBS), and overground walking speed.
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57 Espay et al. [62] demonstrated the effectiveness of interventions with devices using closed-loop
58 sensory feedback. PD patients showed improvements in gait while decreasing freezing. In the
59 same way, the Baram et al. study [71] showed that performance in the completion of a track,
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1 speed and stride length was improved significantly when using a closed-loop display. These
2 devices help the patient to regulate his/her gait since they respond to the patient's own motion.

3 Caudron et al. [70] measured instability and fall parameters by submitting patients to several
4 sequences of pull test. Both visual and auditory cues were given, but only visual cues resulted
5 in improvements in both stabilization and orientation. Auditory cues applied alone did not modify
6 postural responses.
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9 Outcomes for upper limb rehabilitation were quite modest. The participants in the Fischer study
10 [68] demonstrated a decrease in the time to perform some of the functional tasks, although the
11 overall gains were slight. In the same way, in the Dvorkin study [84], patients exhibited attention
12 loss both before and during a movement, but they benefitted from haptic nudge cues.
13 Movement quality in the Lieberman study [65] was not good enough due to the virtual
14 environment.
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20 Table 1. Characteristics of the different studies.
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Author(s) Year of publication	Pathology and sample size	Age Mean (SD) years	Gender (% male)	Design of Study	Type of cueing	Type of VR	VR Intervention	Outcome measures	Conclusions
Espay et al. (2010) [62]	PD/13	73.3 ± 11.7	6/15	Comparative study	AV	Immersive	At-home training exercises to improve gait using virtual augmented reality goggles and earphones operating in an adaptative closed-loop mode	Gait velocity, stride length, and cadence, FoGQ.	Effectiveness of interventions with devices using closed-loop sensory feedback. Improvement of gait in patients with PD while decreasing freezing.
Griffin et al. (2011) [63]	PD/26	64.3 (7.58)	22/26	Pre-post	V	immersive	VR walking exercises with VRG to improve gait and reduce FoG	Measures of gait (task completion time; velocity, cadence, stride length; FoG frequency) and self-rated FoF.	Visual-flow cues through the VRG can improve some aspects of walking without medication in mid-stage PD. No particular VRG stimulus emerged as effective in a majority of the patients
Kaminsky et al. (2007) [64]	Idiopathic PD/6	65.1±12.3	4/6	A single-subject pilot study	V	immersive	Activities of Daily Living (ADL) with VCS	Counts of LOBs and freezes, pre-/post intervention completion of the PDQ-39, observation of baseline and intervention gait, and an interview regarding user satisfaction with VCS.	VCS appeared to improve the functional mobility of all six participants in some way.
Liebermann et al. (2012) [65]	right-handed right-hemiparetic Stroke/16	65.2±9.8	13/16	Comparative study (VR versus non VR conditions)	V	Non-immersive	Seated subjects made 14 reaching movements towards each of three targets in two conditions, a physical environments and a 2-D Virtual environment, using the IREX video-capture system	Motor performance variables: endpoint peak speed, path length, path straightness, movement precision: 3-D absolute root mean square (rms) directional errors; motor pattern variables: final angles of elbow extension and shoulder flexion, sagittal trunk displacement.	Results describe a decrease in overall movement quality due to the Virtual environment in comparison with the physical environment.
Walker et al. (2010) [66]	Stroke/7	54,3	50%	Pre-post	VA	Non-immersive	Twelve treatment sessions of BWSTT with VR	FGA score, BBS score, and overground walking speed.	Participants made significant improvements in their ability to walk. Reasonable increase in FGA, BBS and overground scores.
Dvorkin et al. (2013) [67]	severe TBI/21	37.8 ± 17.9	17/21	Comparative study	VH	Immersive	Exercises to reach targets appearing randomly at various locations in the 3D space.	Spatial and temporal kinematic parameters (total trial time (s), from target appearance to trial completion, hand path, velocity (m/s), and distance from target (m).	The interactive visuo-haptic environments were well-tolerated, but they exhibited attention loss both before (prolonged initiation) and during (pauses during motion) a movement. Compared to no haptic feedback, patients benefitted from haptic nudge cues but not break-through forces.
Fischer et al. (2007) [68]	Stroke- Chronic upper	60±14	9/15	Pre-post-follow up	VA	Immersive	Grasp-and-release training integrating	Biomechanical assessments included grip strength, extension	Participants demonstrated a decrease in time to perform some of the

	extremity hemiparesis/15						virtual reality with mechatronic devices to assist hand opening.	range of motion and velocity, spasticity, and isometric strength.	functional tasks, although the overall gains were slight.
Mirelman et al. (2009) [69]	chronic hemiparesis after stroke/18	Exp. Group: 61.8±9.94 Control Group: 61±8.32	15/18	A single-blind, randomized, control study	VA	Non-immersive	Movements of ankle into dorsiflexion, plantar flexion, inversion, eversion, and a combination of these movements on the Rutgers Ankle Rehabilitation System	Distance (km in 7 Days), number of Steps/Day, average Speed (m/sec), step length (m) and top speed (m/sec).	Walking speed and distance walked improved and were retained for 3 months in the experimental group, whereas improvements in the control group were modest and did not transfer significant functional changes.
Caudron et al. (2014) [70]	Idiopathic PD/17	61.9±8.2	10/17	Pilot study	VA	Semi-immersive	Patients were submitted to several sequences of pull tests. These tests were performed with eyes open, eyes closed and with visual biofeedback. Two verbal instructions were given	Postural reaction peak, final orientation, fall parameter, instability parameter.	Auditory cues did not modify postural responses. Stabilization and orientation improved with the visual cues.
Baram et al. (2002) [71]	PD/14	68.2±8.17	not specified	Pre-post	V	Immersive	Walking a straight track of 10 meters four times, displaying a virtual tiled floor in perpetual motion towards the observer.	The time to complete the track and the number of steps for each path, speed and stride length.	The best effect can be achieved using a closed-loop display, which responds to the patient's own motion and helps him regulate his gait. Performance was improved significantly.

PD: Parkinson's Disease, TBI: traumatic brain injury, A: Auditory cue, V: visual cue, T: tactile cue, H: haptic cue, VR: Virtual Reality, VRG: Virtual Reality Glasses, VCS: Virtual Cueing Spectacles, ADL: Activities of Daily Living, IADL: instrumental ADL, BWSTT= body weight-supported treadmill training, FoG: Freezing of Gait, FoGQ, Freezing Of Gait Questionnaire, FoF: fear of falling, FGA: Functional Gait Assessment, LOB: Loss of Balance, BBS: Berg Balance Scale, PDQ-39, Parkinson's Disease Questionnaire.

4 Discussion

This is the first methodological review carried out to explain the benefits of cueing in virtual motor rehabilitation. Several methodological reviews have been conducted in the field of traditional motor rehabilitation (not virtual cueing), such as the work of Lim et al. [49].

In the literature, it has been shown that sensory cues of different modalities (lines on the floor, rhythmic music, vibratory cues, etc.) lead to improvement in motor problems in different neurodegenerative diseases. Several studies indicated improvements in stride length and walking speed when using visual cues on the floor [72][33], auditory cues [73][74], or vibratory cues [75]. Pongmala et al. [76] conclude that visual, auditory, and somatosensory can improve gait in Parkinson's Disease patients. In [77], the results showed that on-demand cueing seems to be more effective in reducing the duration of freezing episodes than continuous cueing, but that it has little effect on the number of freezing episodes. Yoshizawa et al. [78] developed a virtual reality system for tests and rehabilitation of patients with hemispatial neglect in which a dynamic cue is effective in encouraging patients to their attention to the neglected side. Nevertheless, cueing does not always bring improvements [54][55][56].

Visual cueing has been broadly used in motor rehabilitation experiments. Specifically, visual flow in the direction of walking has mostly been used when using visual cueing in patients with gait impairment. Martin [79] was the first to suggest that the placement of visual cues perpendicular to the direction of gait spaced one step length apart was most effective in improving gait in patients with PD. Many subsequent open-loop studies confirmed this benefit [72][75][80][81]. Nevertheless, these open-loop feedback systems may not have long-term effects unless dedicated training programs are established [82]. Nevertheless, closed-loop feedback systems may lead to long-term learning of motor skills and enhancement of adaptive cerebral plasticity, in particular with the use of visual cueing [83]. Espay et al [62] demonstrated that patients with PD were able to improve gait while decreasing freezing by using closed-loop sensory feedback, through an at-home training program.

The closed-loop system designed by Baram et al [71] responds to the patient's own motion and helps the patient to regulate gait. This provided a great advantage over other systems [84]. In that study, the use of virtual reality cues (superimposed on the real world) helped PD patients to control their gait. Specifically, the best effect was achieved using a closed-loop display. The study revealed that the gait parameters that are most sensitive to anti-Parkinson medication and are improved by brain surgery (such as walking speed and stride length [85][86]) can also be manipulated to a similar extent and without some of the adverse effects by a closed-loop display of virtual visual cues. On average, the performance of PD patients using the device improved (higher speed, longer stride) by about 30%.

In Kaminsky's study [64], the participants reported finding VCS helpful. Its use decreased the length of freezes as well as the number of freezes for some of participants. This is in line with

1 the study by Griffin et al. [63], who demonstrated that the provision of visual-flow cues via virtual
2 reality glasses (VRG) improves some aspects of walking without medication in mid-stage PD.
3 Nevertheless, no particular VRG stimulus emerged as being effective in a majority of patients.
4 In spite of that fact, VRG flexibility may be the strongest point, allowing people with PD to
5 customize the stimuli to build a very effective rehabilitation treatment.
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8 As far as auditory cueing within virtual rehabilitation is concerned, we found that most of the
9 studies provided this stimulus in conjunction with visual cueing. In their study, Mirelman et al.
10 [69] demonstrated that patients belonging to the group trained with a robotic device coupled
11 with the VR experienced greater changes in velocity and distance walked than those patients
12 trained with the robot alone. Improvements did occur in both laboratory and community-based
13 environments. The results obtained support earlier findings that lower extremity training using a
14 robot coupled with VR can improve ambulation for individuals with chronic stroke [87]. Walker
15 [66] also demonstrated that performance in post-stroke patients improved in walking speed and
16 duration by using an auditory and visual cueing system in a treadmill training protocol. This is in
17 line with the study of Yang et al. [88], who found that individuals with post-stroke hemiparesis in
18 the VR treadmill groups improved their gait speed more than those who walked on the treadmill
19 alone. Nevertheless, some limitations arose from the study; these include a small number of
20 subjects, lack of homogeneity of subjects, and lack of a comparison group with random
21 assignment of conditions. In contrast, in their study, Caudron et al. [70] found that auditory cues
22 were not sufficient to improve the postural control in PD patients. Nevertheless, the use of visual
23 cueing through the visualization of the geometry of the patient's body improved components of
24 the postural control of PD patients. In fact, postural responses to pull-tests improved in real time
25 by visualizing visual external cues, and no improvements were detected when verbal cues were
26 applied alone. With regard to balance control, the occurrence of falls was significantly reduced
27 by using visual cueing.
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30 Nevertheless, we have found some limitations within the virtual environment. We found several
31 examples in which cueing did not provide any improvement for upper limb rehabilitation. The
32 study that focused on hand rehabilitation conducted by Fischer [68] incorporated mechatronic
33 devices and virtual reality and showed some degree of efficacy in mainly a severely impaired
34 population. The gains that were observed were quite modest taking into account the upper
35 extremity FM scores and previous studies of robotic or constraint-induced training. Due to the
36 taxing nature of the reach-to-grasp tasks of the study, the intensity of the training program may
37 not have been sufficient to induce changes in hand function and the reaching demands may
38 have overshadowed the hand rehabilitation. Although task-oriented rehabilitation seems to be
39 beneficial, greater repetition of simplified tasks may be preferable for moderately to severely
40 impaired stroke survivors. The authors stated that it is necessary to enhance compensatory
41 skills or incorporate assistive devices rather than focusing on restoring motor control.
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44 In Dvorkin's study [67], in spite of the fact that the interactive visuo-haptic environment was well-
45 tolerated and engaging for patients, they exhibited attention loss both before (prolonged
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initiation) and during (pauses during motion) a movement. As training progressed, the patients increased the number of targets acquired and spontaneously improved through practice. Nevertheless, the mode of haptic feedback should be carefully selected since some modes that increase completion times may distract the patient. In their study, Liebermann et al. [65] found that, in all subjects, movements were slower, shorter, less straight, less accurate, and involved smaller shoulder and elbow joint ranges for target reaches in the 2-D virtual environment compared to the physical environment. That is to say, there was a decrease in overall movement quality due to the virtual environment, which was much more noticeable in the stroke group in comparison with the control group (patients without stroke). The authors stated that people with stroke found it more difficult to perform movements in the virtual environment. Among the possible explanations, one plausible explanation is that people with severe impairment find it more difficult to use perceptual information, failing to evaluate depth from the relative distance between objects in a virtual environment. The results also suggested that the 2-D virtual environment is also challenging for participants since the intended 3-D illusion presented by the 2-D was likely based on cognitive premises [89]. Thus, subjects should be cognitively able to make predictive hypotheses to perceive 3-D objects. Another possible explanation they stated is the fact that there is no stereovision in the video-capture virtual environment and subjects are exposed to planar vision, which could eventually lead to an error in depth estimation.

Implications for Practice

The findings from our review suggest that virtual cueing within motor virtual rehabilitation is a promising intervention when used in patients with motor disorders. Virtual cueing can not only draw attention towards the motor processes by normalizing the internal cueing deficit to prepare the patient for the forthcoming movement but also compensate for defective sensory integration [90]. Greater improvements might be achieved by further customizing the applied cues for every single patient (e.g., by modifying speed, colour, spatial frequency, adding effects such as perspective, etc.) [63].

Nevertheless, in some cases, it is not clear which characteristics of the virtual rehabilitation program are important, at what point in the recovery the program should be applied, or what type of cue should be used to improve the rehabilitation process. For instance, in the study conducted by Nieuwboer et al. [29], Parkinson patients were trained with only their preferred modality of cue. Even though the virtual environment may be well tolerated and engaging for patients, they may suffer from loss of attention, so it is necessary to select the appropriate operation modes within the virtual reality program. There was an interesting reported result about experienced fatigue by the patient. Mirelman et al. [69] outlined an important matter related to fatigue in virtual environments. In their study, the subjects in the robot VR group reported fatigue later than the subjects in the group with the robot alone and required more verbal cues and manual cues to produce movement. Furthermore, the average total training

time for the robot VR group was significantly greater than the group with the robot alone. This outcome suggests that in some cases fatigue could mask improvements in virtual rehabilitation.

Finally, the appropriateness of the use of these techniques depends on the person's rehabilitation goals and preferences. It is hypothesized that one of the reasons virtual rehabilitation is effective is the fact that it is an enjoyable and motivating therapy; however it is true that some studies have shown that patients prefer traditional therapies [91]. In line with this assumption, clinicians using virtual rehabilitation programs should take this into account in order to improve patient rehabilitation processes.

Implications for Research

Our review suggests that there are two important implications for further research. The first question is the number of participants in the studies conducted. Further studies should be done with larger groups of patients in order to study the effects of every single type of intervention, eventually determining the ideal parameters of use. In some cases, differences between groups were not statistically significant due to sample variability in impairments and gait speeds as well as a reduced sample size. Another important question is the long-term efficacy of the different cueing applied. Therefore, longer studies will be necessary. The necessary quantification of the residual benefits in the short and medium term also requires further studies

On one hand, it would be desirable to have more homogeneous samples. On the other hand, it would be of interest for future studies to include different levels of physical disabilities to exploit the benefits of virtual cueing and to obtain more rigorous studies. Kaminsky et al. [64] stated that since the participants were highly active people, the performance of the sample limits the generalization to people that are more severely limited in their activities due to the disease. Furthermore, factors such as medication changes and illness could not be adequately controlled.

Nevertheless, the additive effects in the response to different measured parameters should be studied taking into account the combination of cueing (auditory, visual and tactile/haptic). The contribution of combined sensory cueing versus individual virtual cueing is not yet clear. This is partly due to the fact that many studies precluded the ability to ascertain the effect of single versus dual sensory cueing on gait since subjects are instructed to use both visual and auditory cueing [62][69]. Lim et al. [49] recommended that future studies should evaluate the effects of different types of cueing on gait-related activities in the patient's own home situation, including measurements related to Activities of Daily Living.

5 Conclusions

Virtual cueing provides a channel for non-pharmacological therapeutic intervention in different neurological disorders. Recent studies have focused on finding non-pharmacologic interventions of this type to improve walking in patients with difficulties. Patients with disabilities

appear to be capable of improving motor learning with the help of cueing inside a virtual environment. They are also capable of transferring to equivalent real-world motor tasks in most cases. They are generally enthusiastic about the incorporation of virtual reality into the training program. In some cases, the initial experiences reported in the studies suggest that important modifications in the prototypes should be made before undertaking larger trials. The virtual reality system has usually provided a faster transition between tasks and more opportunity to practice in comparison with a traditional treatment setting. Patients with more advanced disease showed a greater benefit after using the device. This is because greater baseline disability would provide the opportunity for a proportionally larger magnitude of benefit, whereas small baseline disability makes it harder for the intervention to show any beneficial effects.

The development of wearable devices such as inertial sensors or head-mounted display glasses could help patients that have motor impairments improve their rehabilitation processes. One important advantage of virtual reality sensors is their flexibility to allow stimuli to be customized taking into account the characteristics of each patient in order to obtain greater benefits.

Conflict of Interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

Acknowledgement

We thank the Gobierno de Aragón, Departamento de Industria e Innovación, and Fondo Social Europeo for their support.

References

1. Chan V, Zagorski B, Parsons D, Colantonio A. Older adults with acquired brain injury: a population based study. BMC Geriatr. 2013, 13-97.
2. Wirdefeldt K, Adami HO, Cole P, Trichopoulos D, Mandel J: Epidemiology and etiology of Parkinson's disease: a review of the evidence. Eur J Epidemiol. 2011, 26 Suppl 1:S1-58.
3. Wingerchuk DM, Carter JL: Multiple Sclerosis: Current and Emerging Disease-Modifying Therapies and Treatment Strategies. Mayo Clinic Proceedings 2014, 89(2): 225-240.
4. Castellanos-Pinedo F, Cid-Gala M, Duque P, Ramirez-Moreno JM, Zurdo-Hernández JM: Acquired brain injury: a proposal for its definition, diagnostic criteria and classification. Rev Neurol. 2012, 54(6):357-66.
5. Timmons SD: An update on traumatic brain injuries. J Neurosurg Sci. 2012, 56(3):191-202. Review.
6. Adamson J, Beswick A, Ebrahim S: Is stroke the most common cause of disability?. Journal of stroke and cerebrovascular diseases: the official journal of National Stroke Association 2004, 13(4):171-177.
7. Marshall S, Teasell R, Bayona N, Lippert C, Chundamala J, Villamere J, Mackie D, Cullen N, Bayley M: Motor impairment rehabilitation post acquired brain injury. Brain Inj. 2007, 21(2):133-60.
8. Coronado VG, Xu L, Basavaraju SV, McGuire LC, Wald MM, Faul MD, Guzman BR, Hemphill JD: Centers for Disease Control and Prevention (CDC). Surveillance for traumatic brain injury-related deaths--United States, 1997-2007. MMWR Surveill Summ. 2011, 60(5):1-32.
9. Langlois JA, Rutland-Brown W, Wald MM. The epidemiology and impact of traumatic brain injury: a brief overview. J Head Trauma Rehabil. 2006, 21(5):375-8.

10. Zhang Y, Chapman AM, Plested M, Jackson D and Purroy F: The Incidence, Prevalence, and Mortality of Stroke in France, Germany, Italy, Spain, the UK, and the US: A Literature Review. *Stroke Research and Treatment*. 2012, doi:10.1155/2012/436125.
11. Sun H, Zou X, Liu L: Epidemiological Factors of Stroke: A Survey of the Current Status in China. *J Stroke* 2013, 15(2):109-114.
12. Brundin P, Kordower JH: Neuropathology in transplants in Parkinson's disease: implications for disease pathogenesis and the future of cell therapy. *Prog Brain Res*. 2012, 200:221-41.
13. Ruonala V, Meigal A, Rissanen SM, Airaksinen O, Kankaanpää M, Karjalainen PA: EMG signal morphology and kinematic parameters in essential tremor and Parkinson's disease patients. *J Electromyogr Kinesiol*. 2014, pii: S1050-6411(13)00284-8.
14. Shimizu S, Ohno Y: Improving the Treatment of Parkinson's Disease: A Novel Approach by Modulating 5-HT(1A) Receptors. *Aging Dis*. 2013, 4(1):1-13.
15. Campos FL, Carvalho MM, Cristovão AC, Je G, Baltazar G, Salgado AJ, Kim YS, Sousa N: Rodent models of Parkinson's disease: beyond the motor symptomatology. *Front Behav Neurosci*. 2013, 7:175.
16. Mille ML, Creath RA, Prettyman MG, Johnson Hilliard M, Martinez KM, Mackinnon CD, Rogers MW: Posture and locomotion coupling: a target for rehabilitation interventions in persons with Parkinson's disease. *Parkinsons Dis*. 2012, 2012:754186.
17. Oude Nijhuis LB, Allum JH, Nanhoe-Mahabier W, Bloem BR: Influence of perturbation velocity on balance control in Parkinson's disease. *PLoS One* 2014, 9(1):e86650.
18. Costa A, Monaco M, Zabberoni S, Peppe A, Perri R, Fadda L, Iannarelli F, Caltagirone C, Carlesimo GA: Free and cued recall memory in Parkinson's disease associated with amnesic mild cognitive impairment. *PLoS One* 2014, 9(1):e86233.
19. Meireles J, Massano J: Cognitive impairment and dementia in Parkinson's disease: clinical features, diagnosis, and management. *Front Neurol*. 2012, 3-88.
20. Dorsey ER, Constantinescu R, Thompson JP, Biglan KM, Holloway RG, Kieburtz K, Marshall FJ, Ravina BM, Schifitto G, Siderowf A, Tanner CM: Projected number of people with Parkinson disease in the most populous nations, 2005 through 2030. *Neurology* 2007, 68(5):384-6.
21. Nylander A, Hafler DA: Multiple sclerosis. *J Clin Invest*. 2012, 122(4):1180-8.
22. Tullman MJ: A review of current and emerging therapeutic strategies in multiple sclerosis. *Am J Manag Care*. 2013, 19(2 Suppl):S21-7.
23. Achiron A, Barak Y: Cognitive impairment in probable multiple sclerosis. *J Neurol Neurosurg Psychiatry* 2003, 74(4):443-6.
24. Pimentel ML: Multiple sclerosis in the Southern and Northern hemispheres: the month of birth at different latitudes has the same influence on the prevalence and progression of the disease in the Northern and Southern hemispheres? *Arq Neuropsiquiatr*. 2013, 71(9A):569-70.
25. Mayr W, Pittock S, McClelland R, Jorgenson N, Noseworthy J, Rodriguez M: Incidence and prevalence of multiple sclerosis in Olmsted County, Minnesota, 1985–2000. *Neurology* 2003, 61:1373–1377.
26. Hader WJ, Yee IM: Incidence and prevalence of multiple sclerosis in Saskatoon, Saskatchewan. *Neurology* 2007, 69(12):1224-9.
27. Melcon MO, Gold L, Carrá A, Cáceres F, Correale J, Cristiano E, Fernández Liguori N, Garcea O, Luetic G, Kremenchutzky M: Patagonia Multiple Sclerosis Research Project. Argentine Patagonia: prevalence and clinical features of multiple sclerosis. *Mult Scler*. 2008, 14(5):656-62.
28. Alcalde-Cabero E, Almazán-Isla J, García-Merino A, de Sá J, de Pedro-Cuesta J: Incidence of multiple sclerosis among European Economic Area populations, 1985–2009: the framework for monitoring. *BMC Neurol*. 2013, 13-58.
29. Nieuwboer A, Kwakkel G, Rochester L, Jones D, van Wegen E, Willems AM, Chavret F, Hetherington V, Baker K, Lim I: Cueing training in the home improves gait-related mobility in Parkinson's disease: the RESCUE trial. *J Neurol Neurosurg Psychiatry* 2007, 78:134-140.
30. Horstink MWIM, De Swart BJM, Wolters EC, Berger HJC: Paradoxical behavior in Parkinson's disease. In: Wolters EC, Scheltens P eds. *Proceedings of the European Congress on Mental Dysfunction in Parkinson's Disease*. Amsterdam: Vrije Universiteit, 1993.

31. Cools AR, Berger HJC, Buytenhuis EL, Horstink MWIM, Van Spaendonck KPM: Manifestations of switching disorders in animal and man with dopamine deficits in A10 and/or A9 circuitries. In: Wolters EC, Scheltens P eds. *Proceedings of the European Congress on Mental Dysfunction in Parkinson's Disease*. Amsterdam: Vrije Universiteit, 1993.
32. Albiol S, Gil JA, Alcañiz M, Lozano JA: VR Motor Cues: Inducing user movements in virtual rehabilitation systems, in *Proc. Virtual Rehabilitation 2009*, Israel, 1999.
33. Azulay JP, Mesure S, Amblard B, Blin O, Sangla I, Pouget J: Visual control of locomotion in Parkinson's disease. *Brain* 1999, 122: 111-120.
34. Lewis GN, Byblow WD, Walt SE: Stride length regulation in Parkinson's disease: the use of extrinsic, visual cues. *Brain* 2000, 123: 2077-2090.
35. Suteerawattananon M, Morris GS, Etnyre BR, Jankovic J, Protas EJ: Effects of visual and auditory cues on gait in individuals with Parkinson's disease. *J Neurol Sci* 2004, 219:63-69.
36. Hendrix C, Barfield W: The sense of Presence within Auditory Virtual Environments. *Presence: Teleoperators and Virtual Environments* 1996, 5(3):290-301.
37. Jack D, Boian R, Merians AS, Tremaine M, Burdea GC, Adamovich SV, Recce M and Poizner H: Virtual Reality-Enhanced Stroke Rehabilitation. *IEEE Transactions on Neural Systems and Rehabilitation Engineering* 2001, Vol. 9, No. 3.
38. Bryanton C et al.: Feasibility, motivation and selective motor control: virtual reality compared to conventional home exercise in children with cerebral palsy. *Cyberpsychol Behav* 2006, 9:123-8.
39. Thornton M et al.: Benefits of activity and virtual reality based balance exercise programmes for adults with traumatic brain injury. *Perceptions of participants and their caregivers. Brain Injury* 2005, 19:989-1000.
40. Rizzo A and Buckwalter JG: Virtual Reality and cognitive assessment and Rehabilitation: The State of the Art, in *Virtual Reality in Neuro-Psycho-Physiology* 1997, 123-146. Ed. Amsterdam, The Netherlands:IOS.
41. Riva G: Virtual Reality in Psychotherapy: Review, *CyberPsychology & Behavior* 2005, Vol. 8, No. 3, 220-230.
42. Dobkin B: Strategies for stroke rehabilitation. *Lancet Neurol* 2004, 3:528-36
43. Albiol-Pérez S, Gil-Gomez JA, Llorens R, Alcaniz M, Font CC: The role of virtual motor rehabilitation: a quantitative analysis between acute and chronic patients with acquired brain injury. *IEEE J Biomed Health Inform* 2014, 18(1):391-8.
44. Forcano García M, Albiol-Pérez S, Aula Valero MC, Gil-Gómez JA, Solsona-Hernández S, Manzano-Hernández P: Balance virtual rehabilitation in the elderly: The use of the "ABAR" system. *European Geriatric Medicine* 2013, 4:S109.
45. Palacios-Navarro, G. García-Magariño, I., Ramos-Lorente, P. A Kinect-Based System for Lower Limb Rehabilitation in Parkinson's disease Patients: a Pilot Study. *Journal of Medical Systems* 2105, 39 (9) No. 103, 1-10.
46. Lange B, Koenig S, Chang CY, McConnell E, Suma E, Bolas M, Rizzo A. Designing informed game-based rehabilitation tasks leveraging advances in virtual reality. *Disabil Rehabil* 2012, 34(22):1863-70.
47. Holden MK: Virtual environments for motor rehabilitation: review. *Cyberpsychol Behav* 2005, 8(3):187-211.
48. Rubinstein T, Giladi N, Hausdorff J: The power of cueing to circumvent dopamine deficits: a review of physical therapy treatment of gait disturbances in Parkinson's disease. *Mov Disord* 2002, 17:1148-60.
49. Lim I, Van Wegen E, de Goede C, et al.: Effects of external rhythmical cueing on gait in patients with Parkinson's disease: a systematic review. *Clin Rehabil* 2005, 19:695-713.
50. Dibble LE, Nicholson DE, Shultz B, et al.: Sensory cueing effects on maximal speed gait initiation in persons with Parkinson's disease and healthy elders. *Gait Posture* 2004, 19:215-25.
51. Willems AM, Nieuwboer A, Chavret F, Desloovere K, Dom R, Rochester L, Jones D, Kwakkel G, Van Wegen E: The use of rhythmic auditory cues to influence gait in patients with Parkinson's disease, the differential effect for freezers and nonfreezers, an explorative study. *Disabil Rehabil* 2006, 28:721-728.
52. Whittall J, Waller SM, Silver KHC and Macko RF: Repetitive Bilateral Arm Training With Rhythmic Auditory Cueing Improves Motor Function in Chronic Hemiparetic Stroke, *Stroke* 2000, 31:2390-2395.

53. Nieuwboer A: Cueing for freezing of gait in patients with Parkinson's disease: a rehabilitation perspective. *Mov Disord* 2008, 23:S475–S481.
54. Howe TE, Lovgreen B, Cody FWJ, Ashton VJ, Oldham JA: Auditory cues can modify the gait of persons with earlystage Parkinson's disease: a method for enhancing parkinsonian walking performance? *Clin Rehabil* 2003, 17:363–367.
55. Jiang Y, Norman KE: Effects of visual and auditory cues on gait initiation in people with Parkinson's disease. *Clin Rehabil* 2006, 20:36–45.
56. Morris ME, Iansek R, Matyas TA, Summers JJ: The Pathogenesis of gait hypokinesia in Parkinson's disease. *Brain* 1994, 117:1169–1181.
57. Park HS, Yoon JW, Kim J, Iseki K, Hallett M: Development of a VR-based Treadmill Control Interface for Gait Assessment of Patients with Parkinson's disease, IEEE international conference on rehabilitation robotics, Rehab Week Zurich, ETH Zurich Science City, Switzerland, 2011.
58. Kapur P, Premakumar S, Jax SA, Buxbaum LJ, Dawson AM, Kuchenbecker KJ: Spatially Distributed Tactile Feedback for Kinesthetic Motion Guidance, EuroHaptics conference and Symposium on Haptic Interfaces for Virtual Environment 2009, 621 – 622.
59. Baram Y: Virtual sensory feedback for gait improvement in neurological patients. *Frontiers in Neurology* 2013, 4:138. doi: 10.3389/fneur.2013.00138.
60. Schultheis M, Rizzo A: The application of virtual reality technology in rehabilitation. *Rehabil Psychol* 2001, 46:296-311.
61. Moseley AM, Herbert RD, Sherrington C and Maher CG: Evidence for physiotherapy practice: a survey of the Physiotherapy Evidence Database (PEDro). *The Australian Journal of Physiotherapy* 2002, vol. 48, no. 1, 43–49.
62. Espay AJ, Baram Y, Kumar Dwivedi A, Shukla R, Gart-ner M, Gaines L, Duker AP, Revilla FJ: At-home training with closed-loop augmented-reality cueing device for improving gait in patients with Parkinson disease. *J Reha-bil Res Dev* 2010, 47(6):573–82. DOI:10.1682/JRRD.2009.10.0165
63. Griffin HJ, Greenlaw R, Limousin P, Bhatia K, Quinn NP, Jahanshahi M. The effect of real and virtual visual cues on walking in Parkinson's disease, *J Neurol* 2011, 258:991–1000.
64. Kaminsky TA, Dudgeon BJ, Billingsley FF, Mitchell PH, Weghorst SJ: Virtual cues and functional mobility of people with Parkinson's disease: A single-subject pilot study, *Journal of Rehabilitation Research & Development* 2007, Vol. 44, N. 3, 437–448.
65. Liebermann DG, Berman S, Weiss PL, and Levin MF: Kinematics of Reaching Movements in a 2-D Virtual Environment in Adults With and Without Stroke, *IEEE Transactions on Neural Systems and Rehabilitation Engineering* 2012 vol. 20, No. 6, 778-787.
66. Walker ML, Ringleb SI, Maihafer GC, Walker R, Crouch JR, Van Lunen B, Morrison S: Virtual reality-enhanced partial body weight-supported treadmill training poststroke: feasibility and effectiveness in 6 subjects. *Arch Phys Med Rehabil* 2010, 91:115-22.
67. Dvorkin AY, Ramaiya M, Larson EB, Zollman FS, Hsu N, Pacini S, Shah A and Patton JL: A "virtually minimal" visuo-haptic training of attention in severe traumatic brain injury, *Journal of NeuroEngineering and Rehabilitation* 2013, 10:92.
68. Fischer HC, Stubblefield K, Kline T, Luo X, Kenyon RV and Kamper DG: Hand Rehabilitation Following Stroke: A Pilot Study of Assisted Finger Extension Training in a Virtual Environment. *Top Stroke Rehabil* 2007, 14(1):1–12, Thomas Land Publishers, Inc.
69. Mirelman A, Bonato P and Deutsch JE: Effects of Training With a Robot-Virtual Reality System Compared With a Robot Alone on the Gait of Individuals After Stroke, *Stroke* 2009, 40:169-174.
70. Caudron S, Guerraz M, Eusebio A, Gros JP, Azulay JP, Vaugoyeau M: Evaluation of a visual biofeedback on the postural control in Parkinson's disease, *Neurophysiologie Clinique/Clinical Neurophysiology* 2014, 44, 77–86.
71. Baram Y, Aharon-Peretz J, Simionovici Y and Ron L: Walking on Virtual Tiles, *Neural Processing Letters* 2002, 16: 227–233.
72. Lewis GN, Byblow WD, Walt SE: Stride length regulation in Parkinson's disease: the use of extrinsic, visual cues. *Brain* 2000, 123:2077-2090.
73. Arias P, Cudeiro J: Effect of Rhythmic Auditory Stimulation on Gait in Parkinsonian Patients with and without Freezing of Gait. *PloS ONE* 2010, 5(3):e9675. doi:10.1371/journal.pone.0009675.
74. Bryant MS: An evaluation of self-administration of auditory cueing to improve gait in people with Parkinson's disease. *Disabil Rehabil Assist Technol* 2009, 4(5): 357– 363.

- 1 75. Van Wegen E, De Goede C, Lim I, Rietberg M, Nieuwboer A, Willems A, et al.: The effect
2 of rhythmic somatosensory cueing on gait in patients with parkinson's disease. *Journal of*
3 *the Neurological Sciences* 2006, 248:210–214.
- 4 76. Pongmala C, Suputtitada A, Sriyuthsak M: The Study of Cueing Devices by Using Visual,
5 Auditory and Somatosensory Stimuli for Improving Gait in Parkinson Patients,
6 *proceedings of Bioinformatics and Biomedical Technology (ICBBT)* 2010, 185-89.
- 7 77. Velik R, Hoffmann U, Zabaleta H, Marti Masso JF, Keller T: The Effect of Visual Cues on
8 the Number and Duration of Freezing Episodes in Parkinson's Patients, *34th Annual*
9 *International Conference of the IEEE, San Diego, California USA*, 2012, 4656 – 4659.
- 10 78. Yoshizawa et al: Development of Virtual Reality Systems for Tests and Rehabilitation of
11 Patients with Hemispatial Neglect, *IEEE/ICME International Conference on Complex*
12 *Medical Engineering* 2007, 1313-1316.
- 13 79. Martin JP: Locomotion and the basal ganglia. In: Martin JP, editor. *The basal ganglia and*
14 *posture*. London (UK): Pit-man Medical 1967, 20–35.
- 15 80. Morris ME, Iansek R, Matyas TA, Summers JJ: Stride length regulation in Parkinson's
16 disease. *Normalization strategies and underlying mechanisms*. *Brain* 1996, 119(Pt 2):
17 551–68.
- 18 81. Jiang Y, Norman KE: Effects of visual and auditory cues on gait initiation in people with
19 Parkinson's disease. *Clin Rehabil* 2006, 20(1):36–45.
- 20 82. Rochester L, Nieuwboer A, Baker K, Hetherington V, Willems AM, Chavret F, Kwakkel G,
21 Wegen E, Lim I, Jones D: The attentional cost of external rhythmical cues and their
22 impact on gait in Parkinson's disease: effect of cue modality and task complexity. *J Neural*
23 *Transm* 2007, 114:1243-1248.
- 24 83. Helmich RC, De Lange FP, Bloem BR, Toni I: Cerebral compensation during motor
25 imagery in Parkinson's disease. *Neuropsychologia* 2007, 45(10):2201–15.
- 26 84. Prothero JD: The treatment of akinesia using virtual images. M.Sc. Thesis, U. of
27 Washington, 1993.
- 28 85. Siegel KL and Metman LV: Effects of bilateral posteroventral pallidotomy on gait in
29 subjects with Parkinson's disease. *Arch Neurol* 2000, 57, 198.
- 30 86. Widrow B and Winter R: Neural Nets for Adaptive Filtering and Adaptive Pattern
31 Recognition. *Computer* 1988, 21, part 3, 25.
- 32 87. Deutsch JE, Merians AS, Adamovich S, Poizner H, Burdea GC: Development and
33 application of virtual reality technology to improve hand use and gait of individuals post-
34 stroke. *Restor Neurol Neurosci* 2004, 22:371–386.
- 35 88. Yang
36 89. Gregory RL: Perceptions as hypotheses *Phil Trans R Soc Lond B*, 290:181–197.
- 37 90. Azulay JP, Mesure S, Blin O: Influence of visual cues on gait in Parkinson's disease:
38 Contribution to attention or sensory dependence? *J Neurol Sci* 2006, 248:192—5.
- 39 91. Kate Laver K, Ratcliffe J, George S, Burgess L, and Crotty M: Is the Nintendo Wii Fit
40 really acceptable to older people? a discrete choice experiment. *BMC Geriatrics* 2011,
41 11:64.
- 42
- 43
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Figure 1

	All fields	Cueing [mh]
AND	All fields	Virtual cues [majr]
	All fields	Virtual motor cues
OR	All fields	Virtual motor cueing
	All fields	Virtual Rehabilitation
AND	All fields	Virtual cueing
	All fields	Virtual Rehabilitation [mh]
AND	All fields	Virtual cueing [majr]
	All fields	virtual motor cues/RH
OR	All fields	virtual motor cueing/RH
	All fields	Virtual Cueing [mh]
OR	All fields	Virtual cues [mh]
AND	All fields	Motor rehabilitation

Fig. 1. Sample search queries used for article retrieval from Medline.

Figure 2

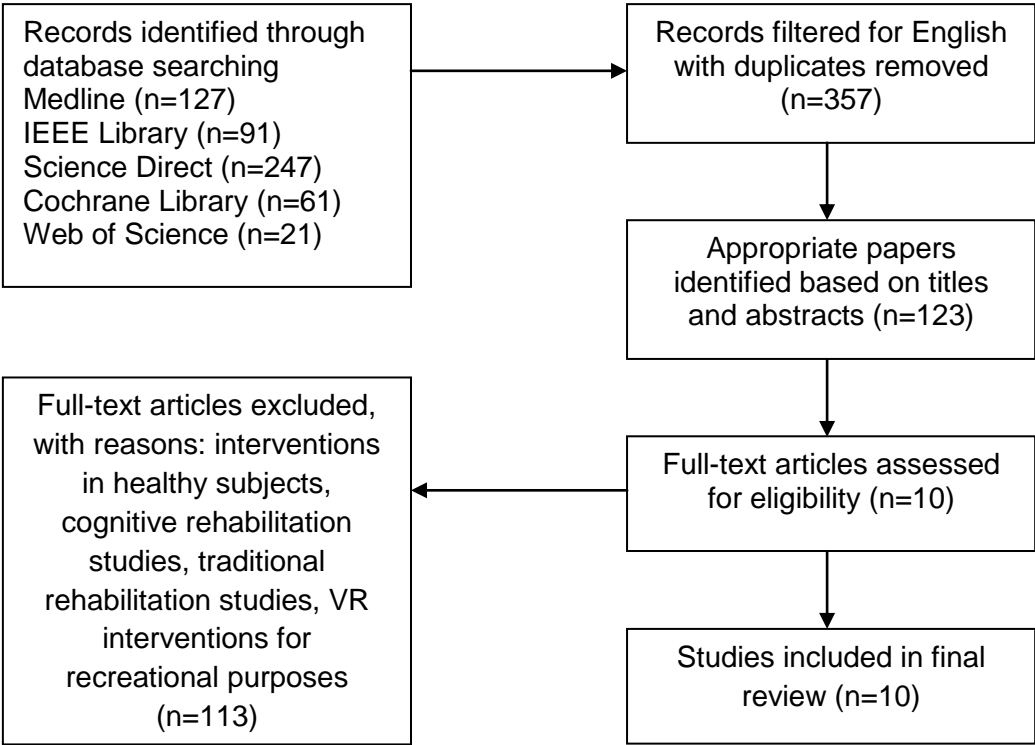


Fig. 2. Consort diagram of study selection.

Figure 1 TIF

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	All fields	Cueing [mh]
AND	All fields	Virtual cues [majr]
	All fields	Virtual motor cues
OR	All fields	Virtual motor cueing
	All fields	Virtual Rehabilitation
AND	All fields	Virtual cueing
	All fields	Virtual Rehabilitation [mh]
AND	All fields	Virtual cueing [majr]
	All fields	virtual motor cues/RH
OR	All fields	virtual motor cueing/RH
	All fields	Virtual Cueing [mh]
OR	All fields	Virtual cues [mh]
AND	All fields	Motor rehabilitation

Figure 2 TIF
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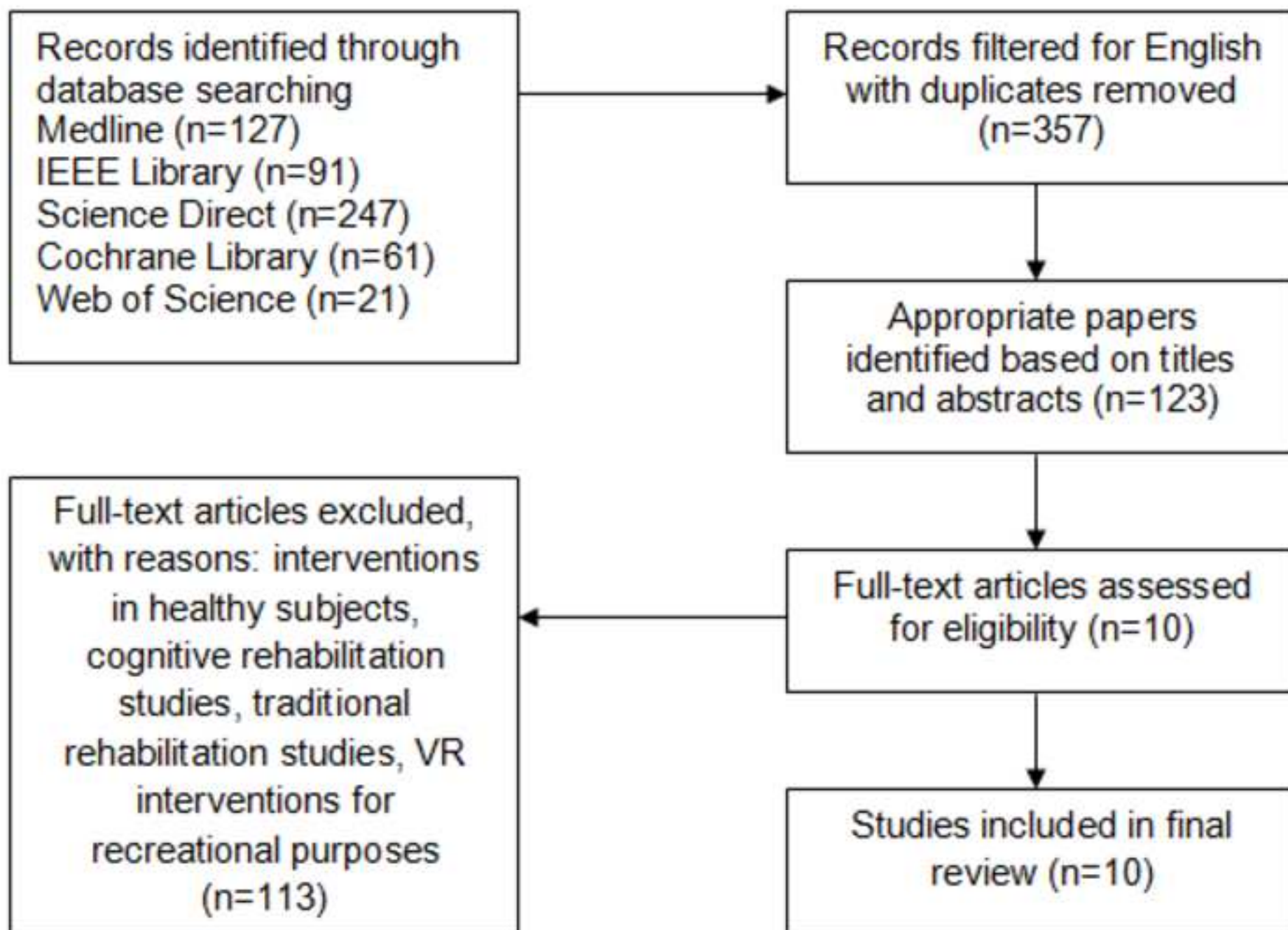


Table 1. Characteristics of the different studies.

Author(s) Year of publication	Pathology and sample size	Age Mean (SD) years	Gender (% male)	Design of Study	Type of cueing	Type of VR	VR Intervention	Outcome measures	Conclusions
Espay et al. (2010) [62]	PD/13	73.3 ± 11.7	6/15	Comparative study	AV	Immersive	At-home training exercises to improve gait using virtual augmented reality goggles and earphones operating in an adaptative closed-loop mode	Gait velocity, stride length, and cadence, FoGQ.	Effectiveness of interventions with devices using closed-loop sensory feedback. Improvement of gait in patients with PD while decreasing freezing.
Griffin et al. (2011) [63]	PD/26	64.3 (7.58)	22/26	Pre-post	V	immersive	VR walking exercises with VRG to improve gait and reduce FoG	Measures of gait (task completion time; velocity, cadence, stride length; FoG frequency) and self-rated FoF.	Visual-flow cues through the VRG can improve some aspects of walking without medication in mid-stage PD. No particular VRG stimulus emerged as effective in a majority of the patients
Kaminsky et al. (2007) [64]	Idiopathic PD/6	65.1±12.3	4/6	A single-subject pilot study	V	immersive	Activities of Daily Living (ADL) with VCS	Counts of LOBs and freezes, pre-/post intervention completion of the PDQ-39, observation of baseline and intervention gait, and an interview regarding user satisfaction with VCS.	VCS appeared to improve the functional mobility of all six participants in some way.
Liebermann et al. (2012) [65]	right-handed right-hemiparetic Stroke/16	65.2±9.8	13/16	Comparative study (VR versus non VR conditions)	V	Non-immersive	Seated subjects made 14 reaching movements towards each of three targets in two conditions, a physical environments and a 2-D Virtual environment, using the IREX video-capture system	Motor performance variables: endpoint peak speed, path length, path straightness, movement precision: 3-D absolute root mean square (rms) directional errors; motor pattern variables: final angles of elbow extension and shoulder flexion, sagittal trunk displacement.	Results describe a decrease in overall movement quality due to the Virtual environment in comparison with the physical environment.
Walker et al. (2010) [66]	Stroke/7	54,3	50%	Pre-post	VA	Non-immersive	Twelve treatment sessions of BWSTT with VR	FGA score, BBS score, and overground walking speed.	Participants made significant improvements in their ability to walk. Reasonable increase in FGA, BBS and overground scores.
Dvorkin et al. (2013) [67]	severe TBI/21	37.8 ± 17.9	17/21	Comparative study	VH	Immersive	Exercises to reach targets appearing randomly at various locations in the 3D space.	Spatial and temporal kinematic parameters (total trial time (s), from target appearance to trial completion, hand path, velocity (m/s), and distance from target (m).	The interactive visuo-haptic environments were well-tolerated, but they exhibited attention loss both before (prolonged initiation) and during (pauses during motion) a movement.

									Compared to no haptic feedback, patients benefitted from haptic nudge cues but not break-through forces.
Fischer et al. (2007) [68]	Stroke- Chronic upper extremity hemiparesis/15	60±14	9/15	Pre-post-follow up	VA	Immersive	Grasp-and-release training integrating virtual reality with mechatronic devices to assist hand opening.	Biomechanical assessments included grip strength, extension range of motion and velocity, spasticity, and isometric strength.	Participants demonstrated a decrease in time to perform some of the functional tasks, although the overall gains were slight.
Mirelman et al. (2009) [69]	chronic hemiparesis after stroke/18	Exp. Group: 61.8±9.94 Control Group: 61±8.32	15/18	A single-blind, randomized, control study	VA	Non-immersive	Movements of ankle into dorsiflexion, plantar flexion, inversion, eversion, and a combination of these movements on the Rutgers Ankle Rehabilitation System	Distance (km in 7 Days), number of Steps/Day, average Speed (m/sec), step length (m) and top speed (m/sec).	Walking speed and distance walked improved and were retained for 3 months in the experimental group, whereas improvements in the control group were modest and did not transfer significant functional changes.
Caudron et al. (2014) [70]	Idiopathic PD/17	61.9±8.2	10/17	Pilot study	VA	Semi-immersive	Patients were submitted to several sequences of pull tests. These tests were performed with eyes open, eyes closed and with visual biofeedback. Two verbal instructions were given	Postural reaction peak, final orientation, fall parameter, instability parameter.	Auditory cues did not modify postural responses. Stabilization and orientation improved with the visual cues.
Baram et al. (2002) [71]	PD/14	68.2±8.17	not specified	Pre-post	V	Immersive	Walking a straight track of 10 meters four times, displaying a virtual tiled floor in perpetual motion towards the observer.	The time to complete the track and the number of steps for each path, speed and stride length.	The best effect can be achieved using a closed-loop display, which responds to the patient's own motion and helps him regulate his gait. Performance was improved significantly.

PD: Parkinson's Disease, TBI: Traumatic Brain Injury, A: Auditory cue, V: Visual cue, T: Tactile cue, H: Haptic cue, VR: Virtual Reality, VRG: Virtual Reality Glasses, VCS: Virtual Cueing Spectacles, ADL: Activities of Daily Living, IADL: Instrumental ADL, BWSTT= body weight-supported treadmill training, FoG: Freezing of Gait, FoGQ: Freezing of Gait Questionnaire, FoF: Fear of falling, FGA: Functional Gait Assessment, LOB: Loss of Balance, BBS: Berg Balance Scale, PDQ-39: Parkinson's Disease Questionnaire.