VIRTUAL REALITY FOR SENSORIMOTOR REHABILITATION OF NEUROLOGICAL HEALTH CONDITIONS ACROSS THE LIFESPAN

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PUBLISHED IN: Frontiers in Neurology

frontiers Research Topics

ISSN 1664-8714
ISBN 978-2-88974-064-2
DOI 10.3389/978-2-88974-064-2

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VIRTUAL REALITY FOR SENSORIMOTOR REHABILITATION OF NEUROLOGICAL HEALTH CONDITIONS ACROSS THE LIFESPAN

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Citation: de Mello Monteiro, C. B., Dawes, H., Deutsch, J. E., eds. (2022). Virtual Reality for Sensorimotor Rehabilitation of Neurological Health Conditions Across the Lifespan. Lausanne: Frontiers Media SA. doi: 10.3389/978-2-88974-064-2

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frontiers in Neurology

EDITORIAL
published: 25 November 2021
doi: 10.3389/fneur.2021.766349

Editorial: Virtual Reality for Sensorimotor Rehabilitation of Neurological Health Conditions Across the Lifespan

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Keywords: sensorimotor rehabilitation, virtual reality, rehabilitation technology, exergames, development of technologies

Editorial on the Research Topic

Virtual Reality for Sensorimotor Rehabilitation of Neurological Health Conditions Across the Lifespan

The National Institutes of Health define, rehabilitation technology as tools that help people recover their function after injury or illness. In recent years, advances in rehabilitation technology have created exciting opportunities and generated significant improvements in the autonomy and quality of life of people with neurological health conditions. Virtual reality (VR) in particular, is a rehabilitation technology that has rapidly risen to prominence and is achieving promising results in improving the sensorimotor function for people with neurological disabilities (1–3). Virtual reality uses interactive simulations created with computer hardware and software to present users with opportunities to perform activities in virtual environments with life-like objects and events. Development of technologies for both the assessment and treatment of persons with neurological health conditions has the potential to either adapt to or target underlying sensorimotor dysfunction and improve body structure, activities, and participation (4).

Given the growing interest in the use of technology in neurological rehabilitation, studies are needed to justify the safe effective use of Virtual Reality in clinical practice. This special issue aimed to collect insightful and multi-disciplinary evidence of the development, testing and application of virtual reality innovations for sensorimotor rehabilitation of neurological health conditions across the lifespan.

Ten papers were published in this Research Topic with contributions to support practice. Espy et al. presents a conceptual framework to guide clinical-decision making for the selection, adaptation, modulation, and progression of virtual reality or gaming when used as a therapeutic exercise modality. The study of Oliveira et al. found benefits in using virtual reality-based exercise in spatial navigation of institutionalized older persons. Cheng et al. investigated performance variability over time during learning of standing postural control tasks in a non-immersive virtual environment in children with cerebral palsy. Benady et al. studied the contribution of vision to locomotion in a dynamic immersive environments to support rehabilitation strategies for neurological disorders associated with gait impairments.

Interestingly, six studies presented the development and use of custom games instead of using non-custom commercial games (Tong et al.; Finley et al.; Al-Sharman et al.; Lubetzky et al.; Da silva et al. and Fluet et al.). Although evidence suggesting that non-custom commercial games can be

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Specialty section:
This article was submitted to Neurorehabilitation, a section of the journal Frontiers in Neurology

Received: *29 August 2021*
Accepted: *07 October 2021*
Published: *25 November 2021*

Citation:
Monteiro CBM, Dawes H and Deutsch JE (2021) Editorial: Virtual Reality for Sensorimotor Rehabilitation of Neurological Health Conditions Across the Lifespan. Front. Neurol. 12:766349. doi: 10.3389/fneur.2021.766349

successfully used in clinical settings, they have limitations such as calibration of a game's difficulty for persons with different abilities, game scores or progress measurements being to generic, lacking specificity in tracking the progress of persons with different abilities, and many require movements that cannot be performed by people with disabilities (5).

Custom games were developed by, Tong et al. who created a ball-pushing task to be used in the HTC VIVE's. Individuals with Phantom limb pain "inhabit" a virtual body (avatar) and the movements of their intact limbs are mirrored in the avatar, providing participants with the illusion that their limbs respond as if they were both intact and functional. They found that repetitive exposure to VR intervention led to reduced pain and improvements in anxiety, depression, and a sense of embodiment of the virtual body.

Finley et al. presented a custom VR game where individuals with Parkinson's disease have to complete a puzzle that consisted of a word with missing letters in the virtual environment. The player had to determine which letters were necessary to complete the puzzle, collect the necessary virtual letters as they floated in 3D space, and then place the letters in the appropriate location. Al-Sharman et al. created a non-immersive VR task to be used with Microsoft Kinect sensor and found improvement in participants with Parkinson's disease when asked to steer a helicopter up and down to collect coins and to avoid specific number of obstacles by moving from sitting to standing and vice versa. Lubetzky et al. created two VR tasks (one using stars on the sky and the other a busy street) with Head Mounted Displays (Oculus Rift) and found significant differences in performance between environments evaluating Postural and Head Control in individuals with unilateral vestibular hypofunction and monaural hearing. Da silva et al. in a study protocol presented two non-immersive custom virtual reality games developed for individuals with disabilities (movehero and moveletrando), both can be used with computer webcam. Fluet et al., presented different studies using a home-based virtual rehabilitation system and a robot assisted virtual rehabilitation to improve paretic hand and arm of persons with chronic stroke. They suggested that persons with stroke may adapt to virtual rehabilitation of hand function differently based on their level of impairment and stage of recovery.

We believe that the studies published in this special issue present research on the benefits of using virtual reality in the rehabilitation for persons with neurological health conditions. It is noteworthy that many authors are integrating game mechanics into their virtual rehabilitation. The research will need to be ongoing to facilitate application to clinical practice.

AUTHOR CONTRIBUTIONS

All authors read and approved the final editorial.

FUNDING

HD was funded by the Elizabeth Casson Trust and the NIHR Oxford Health Biomedical Research Centre. CM was funded by Fundação de Amparo a Pesquisa do Estado de São Paulo (FAPESP)- Finance Code: 2017/24991-7 and Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq). JD was funded by NIH (1R15AG063348-01).

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Neurology

BRIEF RESEARCH REPORT
published: 25 August 2020
doi: 10.3389/fneur.2020.00876

"I Dreamed of My Hands and Arms Moving Again": A Case Series Investigating the Effect of Immersive Virtual Reality on Phantom Limb Pain Alleviation

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Phantom limb pain (PLP) is a type of chronic pain that follows limb amputation, brachial plexus avulsion injury, or spinal cord injury. Treating PLP is a well-known challenge. Currently, virtual reality (VR) interventions are attracting increasing attention because they show promising analgesic effects. However, most previous studies of VR interventions were conducted with a limited number of patients in a single trial. Few studies explored questions such as how multiple VR sessions might affect pain over time, or if a patient's ability to move their phantom limb may affect their PLP. Here we recruited five PLP patients to practice two motor tasks for multiple VR sessions over 6 weeks. In VR, patients "inhabit" a virtual body or avatar, and the movements of their intact limbs are mirrored in the avatar, providing them with the illusion that their limbs respond as if they were both intact and functional. We found that repetitive exposure to our VR intervention led to reduced pain and improvements in anxiety, depression, and a sense of embodiment of the virtual body. Importantly, we also found that their ability to move their phantom limbs improved as quantified by shortened motor imagery time with the impaired limb. Although the limited sample size prevents us from performing a correlational analysis, our findings suggest that providing PLP patients with sensorimotor experience for the impaired limb in VR appears to offer long-term benefits for patients and that these benefits may be related to changes in their control of the phantom limbs' movement.

Keywords: immersive virtual reality, phantom limb pain, motor execution, motor imagery, brachial plexus nerve injury, serious games

OPEN ACCESS

Edited by:
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This article was submitted to Neurorehabilitation, a section of the journal Frontiers in Neurology

Received: 26 April 2020
Accepted: 09 July 2020
Published: 25 August 2020

Citation:
Tong X, Wang X, Cai Y, Gromala D, Williamson O, Fan B and Wei K (2020) "I Dreamed of My Hands and Arms Moving Again": A Case Series Investigating the Effect of Immersive Virtual Reality on Phantom Limb Pain Alleviation. Front. Neurol. 11:876. doi: 10.3389/fneur.2020.00876

INTRODUCTION

Phantom limb pain (PLP) is a type of chronic pain caused by limb amputation (1). Besides amputation, brachial plexus avulsion (BPA) injury—the detachment of the nerves from the nerve roots of the spinal cord in the arm—also leads to partial or complete arm paralysis and chronic pain (2). Most patients with BPA develop sensations in their damaged arm such as tingling, electric shock, and burning pain; this is similar to the PLP experienced by amputees (3). Therefore, researchers believe that studying BPA has the potential to deepen our understanding of the roles that the peripheral and central nervous systems play in PLP (4). The neural mechanism of PLP is still under debate. Some researchers proposed that cortical reorganization of neural representations of the missing limb and its neighboring body parts causes PLP (5–7). Others hold that the functional representation of the missing limb is preserved (8, 9), and "peripheral" contributors—such as neuroma formation and ectopic firing in the residual nerves—are the major contributors of PLP (10–12). It has also been proposed that impaired sensorimotor circuitry leads to PLP because both central and peripheral factors play a role (13, 14).

Researchers postulated that behavioral interventions for PLP might owe their analgesic effects to restoring the sensorimotor circuitry (15). These interventions usually provide augmented sensorimotor experience of the affected limb, including tactile stimulation (6) and surrogated visual representation (16). For example, in mirror therapies (MTs), the movements of the intact limb are reflected in a mirror, giving patients a vivid experience of their affected limb as if it is in motion (16). While critical reviews of MT find its analgesic effects are limited (17, 18), some researchers believe that this limitation is because the limb movements are restricted to the mirror surface (14). Combining virtual reality (VR) with MT has provided a better sense of embodiment of the phantom limb, including a sense of ownership (SoO) and a sense of agency (SoA) (19, 20) over their virtual body. In this article, the VR environment refers to immersive environments (21), where users are completely isolated from their physical surroundings and experience the three-dimensional virtual worlds through a stereographic head-mounted display (HMD). The resulting analgesic effects are comparatively stronger than those from traditional MT (22). However, most researchers focused only on the short-term analgesic effect from one VR session (20, 23). In fact, longitudinal studies on PLP used representations of a virtual limb displayed on a computer monitor instead of in immersive VR *per se* (24–26). Thus, longitudinal studies involving VR are still lacking.

With impaired sensorimotor circuitry, PLP patients also show degraded movement performance of the phantom limb. As a phantom limb is usually paralyzed or perceived as fixed in one or more particular positions (13), it is difficult for patients to imagine moving their phantom limbs visually. Thus, the capacity of motor imagery (e.g., the time a patient takes to perform a task) might serve as a measurement of movement performance of the phantom limb, given that similar activations in the motor cortex during motor imagery and actual movements were observed in healthy individuals (27). Indeed, previous studies demonstrated a prolonged response time and a lack of activation in the sensorimotor cortex during motor imagery tasks in amputees with PLP when compared to those without and that their response times, as well as activation, were closely related to the magnitude of the PLP (28, 29).

Here we examined the long-term effects of VR-based MT interventions on alleviating PLP and the accompanying changes in the motor imagery capacity involving the phantom limb. We hypothesized that the VR-MT interventions could simultaneously alleviate the pain and improve the motor imagery capacity for the phantom limb across multiple sessions.

MATERIALS AND METHODS

Participants

We recruited five BPA and amputees' outpatients, all of whom were diagnosed with PLP (all male, age mean = 50.2, age SD = 7.73 years) from China-Japan Friendship Hospital in Beijing. All suffered from medium to severe levels of daily pain, and three of five have been taking the pain and/or antianxiety medicine. Detailed medical and demographic information is listed in **Supplementary Table 1**. For the inclusion criteria, we adopted similar standards as in a previous study (25): participants (1) need to be adults; (2) have been treated for PLP by at least one clinical approach; and (3) have not reported any pain changes for at least a year after the last session of prior treatments. Three patients exited the study before the planned 10 sessions because of their work and travel matters. They all signed the consent form and were informed that they could withdraw from the study without consequences. Each participant received monetary compensation. The Ethical Review Board of Peking University approved this study protocol (School of Psychological and Cognitive Sciences, #2018-06-02). Written informed consent was obtained from the participants for the publication of any potentially identifiable images or data included in this article.

Setting and Apparatus

The immersive room-scale VR system and HMD were from HTC VIVE (30) with 1,080 × 1,200 pixels resolution per eye and a field of view of 110 degrees. Unity3D (31) software was used to develop the VR environment. Final IK Unity3D assets provide inverse kinematics' solutions for the avatar's body rigging and movement mapping (32). Participants saw the environment from a first-person perspective of a gender-matched avatar and remained seated during the entire study. The VR controller, held by the intact hand, and can register hand motion and button click.

Instruments

We assessed the changes in pain ratings both before and after the VR intervention. Two pain ratings were used (1) Short-Form McGill Pain Questionnaire (SF-MPQ), which is the pain rating index (ratings from 0 to 75) formed by the summed contribution of 15 characteristics of pain (33); and (2) the visual analog scale (VAS) ratings from 0 to 10. Sense of embodiment (SoO and SoA) was rated once before the whole study and once after. Sense of ownership and SoA ratings were reported in an 11-point numerical rating scale (NRS) from 0 to 10, where 0 means "don't agree at all," and 10 means "strongly agrees." The SoO and SoA questions (**Supplementary Table 2**) were modified from related research (19). Further, the patients' depression and anxiety levels were measured using the Hospital Anxiety and Depression Scale (HADS) questionnaire (34) once before the entire study and once after.

Procedures

Each session lasted approximately 1 h with the following steps (**Supplementary Figure 1**):

(1) The patient filled out the questionnaires for self-reported anxiety and depression ratings before session 1, and SoO and SoA ratings after session 1.
(2) The researcher conducted semistructured interviews to collect the patients' subjective feedback before each session. The questions regarded (a) pain qualities and frequencies, (b) sleep quality, (c) medicine intake, (d) emotional changes, and (e) any other thoughts.
(3) The patient filled out the two pretest pain questionnaires before each session.
(4) The patient wore a VR HMD and held a controller in their intact hand, performing two motor tasks for 30 min (**Figure 1**).
(5) The patient carried out the motor imagery and motor execution tasks, once before the first session and once after the last session. Before the former, the researchers detailed the task instructions before a practice session when patients performed the two VR motor tasks by execution and by imagery, three times each. The ball-pushing task required the participant to push a ball off the table with extension of both virtual limbs whose motion was driven by the measured motion of the intact limb only. The ball-shoot task is to extend both limbs to shoot a basketball toward a basket. Again, the motion of two limbs was driven by the intact limb only; the ball release was initiated by clicking the trigger button on the controller. The order of these practice runs (execution vs. imagery, ball-pushing vs. ball-shooting) was pseudorandomized across patients, and they performed each for three times per session. In the subsequent former test, patients were asked to visually imagine performing the two VR tasks with either limb (not both limbs); each task and each limb was repeated three times. They were instructed not to perform motor imagery unless they were told to. Patients then executed each task with the intact hand for three times. For each trial, the patient clicked the trigger button of the controller once before the trial, and once after the trial to register the time needed for imagery and execution.
(6) The patient filled out the posttest VAS ratings after each session.
(7) The patient filled out the questionnaires for self-reported anxiety and depression ratings, and SoO and SoA ratings immediately after the last session.

RESULTS

Primary Outcomes—Pain Ratings

The pain ratings showed that all five patients had pain reduction, both before and after a session and across sessions (**Table 1** and **Figure 2**). Patients P01 and P04 withdrew from the study after the third session, P5 after the fourth session; P2 and P3 completed all 10 sessions as planned. Because of the limited sample size, we opted to perform a non-parametric test to compare the pain ratings between the first session and the third session to examine whether the pain reduction was significant. The average of five patients' MPQ ratings was 16.4 (SD = 5.14) in the first session and 10.4 (SD = 5.03) in the third session, respectively. A Wilcoxon signed-rank test showed a significant improvement of pain rating in the third session compared to the first session with a large effect size despite the small sample size ($Z = -2.02$, $p = 0.043$, $r = 0.9$). Notably, all patients showed continuous pain reduction over consecutive sessions. Overall, patients reported an average improvement of 56.96% (SD = 17.49%) on the SF-MPQ ratings when comparing the last session, they took part in with their first session. Specifically, 56% improvement (SD = 18.08%) was on the pain sensation categories (throbbing, shooting, stabbing, sharp, cramping, gnawing, hot-burning, aching, heavy, tender, and splitting) and 58.33% (SD = 30.5%) on the emotional categories (tiring-exhausting, sickening, fearful, and cruel-punishing). Notably, all patients showed more than 50% improvement (ranging from about 50%, e.g., P01, to 90.91%, P02), although their initial pain ratings differed substantially (**Figure 2B**). Scrutinizing 15 pain qualities (**Supplementary Figure 2**), we found that all patients initially experienced and subsequently improved on emotional categories in their SF-MPQ ratings. For the sensory intensity category, four of the five patients shared throbbing, sharp, and heavy experiences; the heavy sensation disappeared after the intervention.

Further, we also categorized the pain qualities into "kinesthesia-related pain characteristics" (splitting, exhausting, burning, aching, throbbing, stabbing, sharp, shooting) and "somatosensory-related pain characteristics" (gnawing, fearful, cramping), as a previous study found that VR mirror-movement therapy specifically improved the kinesthesia-related pain characteristics (20). However, we found that these two categories improved to a similar extent, with an average 50.47% (SD = 31.57%) and 56.67% (SD = 36.51%) improvement, respectively (**Figures 2D,E**).

The VAS ratings showed a similar but less drastic analgesic effect than the SF-MPQ ratings (**Figure 2B** and **Table 1**). The averages of the five patients' VAS ratings in the first three pretests were 7.6 (SD = 1.47), 7.19 (SD = 1.4), and 6.88 (SD = 1.56), whereas the posttests mean ratings were reduced to 5.71 (SD = 2.26), 5.07 (SD = 2.12), and 5.59 (SD = 1.91), respectively. The Wilcoxon signed-rank test showed that all three posttests had significantly reduced VAS ratings when compared to their corresponding pretests with a large effect size (for all three tests, $Z = -2.02$, $p = 0.043$, $r = 0.9$). Comparing VAS ratings across days, we found a marginally significant difference in pretest ratings between the first session and the third session ($Z = -1.75$, $p = 0.08$); however, the posttest ratings did not show a significant across-session difference ($Z = -0.41$, $p = 0.68$), possibly because the analgesic effect in each session masked the across-session differences. The average improvement of the VAS rating was 19.04% (SD = 13.47%). We found that each session induced an average improvement of 21.23% (SD = 15.95%) when comparing the pre-test VAS ratings with the posttest ones. All five participants showed this one-session improvement. Given the small sample size in this study, we would like to state the statistics should be viewed with caution.

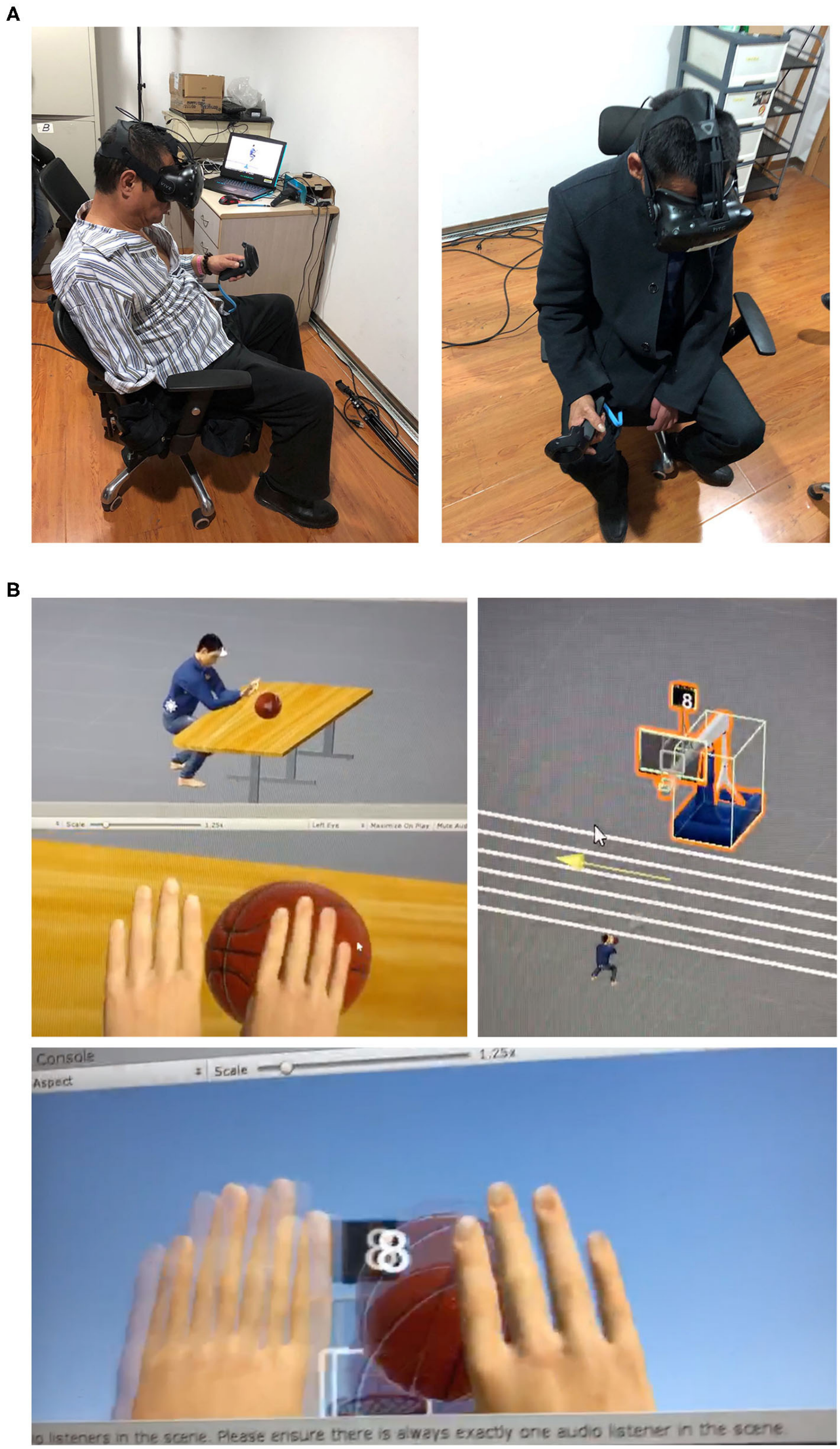

FIGURE 1 | (A) Patients performing the ball-pushing task with an HTC VIVE's controller held in the intact hands (left: P04; right: P03). **(B)** The VR environment as depicted during the two tasks (the ball-pushing task and the ball-shooting task from third-person and first-person perspectives). Participants only saw the VR environment from the first-person perspective.

TABLE 1 | Patients' pain reduction percentages between the first and last sessions of their participation of each individual and the group mean and standard deviation (SD) values.

	No. of sessions participated	SF-MPQ rating reduction (%) (across sessions)			VAS (%) (across sessions)	VAS (%) (mean value before and after each session)
		Pain sensation categories	Emotional categories	Total		
P01	3	42.86	66.67	49.21	25.36	20.6
P02	10	83.33	100	87.76	39.29	4.09
P03	10	38.46	66.67	45.98	9.89	28.79
P04	3	52.94	33.33	47.71	5.87	8.82
P05	4	64.71	25.00	54.12	14.79	43.86
Mean (SD)	6 (3.67)	56.48 (18.08)	58.33 (30.05)	56.96 (17.49)	19.04 (13.47)	21.23 (15.95)

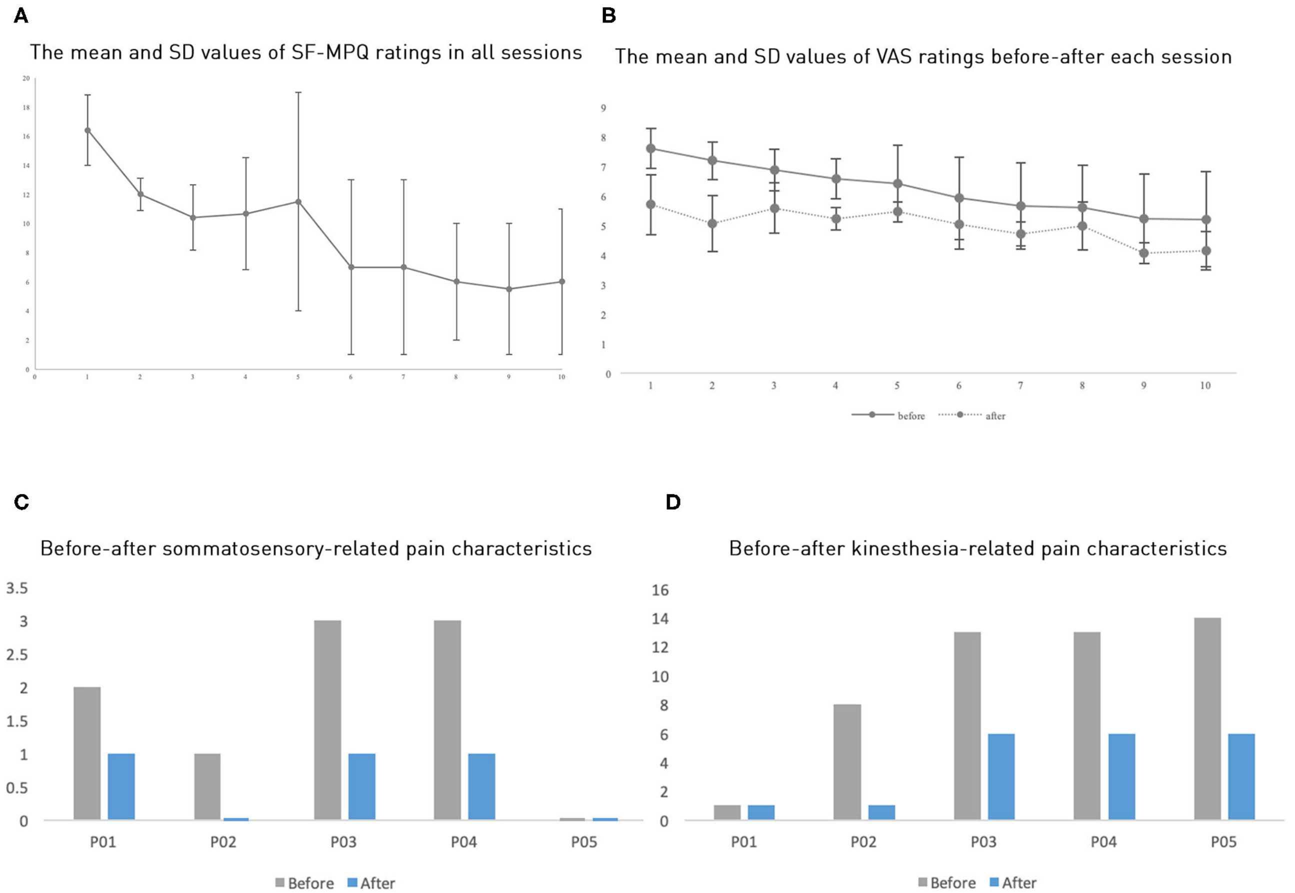

FIGURE 2 | (A) The average SF-MPQ ratings across all sessions. **(B)** The average VAS ratings across sessions. **(C,D)** Each participant's ratings of somatosensory-related pain characteristics and kinesthesia-related characteristics (where P02 and P05 do not have bars meaning zero value). Here, error bars denote standard errors.

Phantom Limb Movement: Motor Imagery and Motor Execution Movement Time

The performance of motor imagery and execution was quantified by their movement time (**Figures 3A,B**; individual data in **Supplementary Tables 3**, **4**). First, execution time and imagery time were similar for the intact limb, suggesting that participants followed our instruction. Both measures tended to decrease when measured again after the VR intervention, possibly due to a practice effect. As expected, we also observed that the impaired limb had substantially larger imagery time than the intact limb, with average of 12.83 ± 6.45 s and 17.23 ± 8.98 s for the ball-pushing and ball-shooting tasks, respectively. In

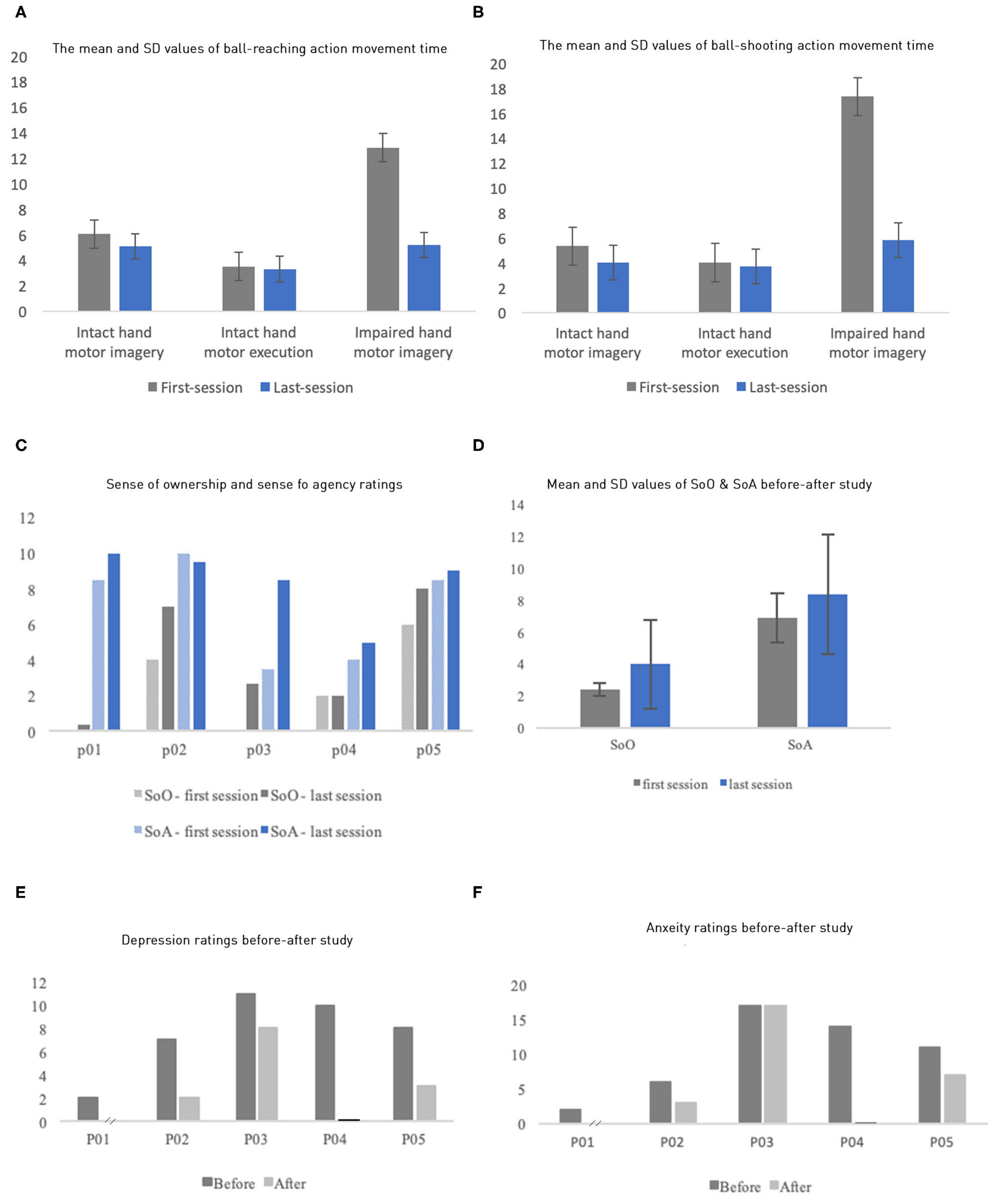

FIGURE 3 | (A,B) Mean and SD of motor imagery time and motor execution time for the *ball-reaching* task by both the intact limbs and the impaired limbs (*y* axis: in seconds). **(F)** Similar results as **(E)** but for the ball-shooting task. **(C)** Each participant's sense of ownership and sense of agency ratings of their virtual body. **(D)** The mean SoO and SoA ratings of the first and the last sessions. **(E,F)** Patients' anxiety and depression ratings before and after the study (P01's after study depression and anxiety data were missing; P04's after-study rating means zero value).

contrast, the intact limb had average imagery time of 6.05 ± 3.30 s and 5.35 ± 1.79 s for these two tasks, respectively. Critically, the imagery time of the impaired limb was reduced dramatically after VR intervention, averaging 5.19 ± 3.84 s and 5.80 ± 4.48 s for the two tasks, respectively. These reductions, averages of 60.59 and 66.53%, brought the imagery time to the level comparable to that of the intact limb, suggesting that the phantom limb movement was dramatically improved after the intervention.

Sense of Embodiment Ratings

The rating of SoO and SoA for the avatar in the VR increased in our experiment (**Figures 3C,D**). The ratings were measured twice through an 11-point NRS before and after all sessions, right after they took off the HMD. The questions for each category (**Supplementary Table 2**) were added up and averaged to one score per category. The SoO and SoA ratings increased, from the first to the last session, by 66.67 and 21.74%, respectively. Average SoA increased from 6.9 (first session, SD = 1.32) to 8.4 (last session, SD = 0.89); Correspondingly, average SoO increased from 2.4 (SD = 1.66) to 4.0 (SD = 1.48). However, P04's rating of SoO and P02's rating of SoA did not increase.

Anxiety and Depression Ratings

The patients' anxiety and depression levels were measured using HADS, once before the first session, and once after the last session (**Figures 3E,F**). We missed the posttest ratings from P01 and P04 because they withdrew. All the remaining three patients experienced an improvement in anxiety and/or depression with varying degrees. P02 and P05 experienced an improvement in both the anxiety and the depression levels, whereas P03 showed improvement only on depression levels.

Qualitative Interview Analysis

All patients reported one or a few positive changes after the intervention. Here, we report the qualitative results briefly. P01 said the VR intervention had provided him with an analgesic effect ranging from 2 h or longer until he went to bed at night. However, his anxiety from over 10 years of suffering hardly changed. P02 did not report a substantial change in pain before and after each intervention, but he did report a substantial decrease in pain ratings across the entire study. Furthermore, he reported multiple pain sensations in SF-MPQ initially, and only one at the study's conclusion. P03, before the study, reported over 30 times of "unbearable bursts of pain every day," which he rated as 9 or 10 in VAS and lasted for 1 to 5 min. After the study, P03 reported that the intensity of his pain bursts was "much more endurable now" and that they lasted half the time. Notably, P03's quality of sleep steadily improved. Before participation, he woke up 8–10 times because of the pain bursts; at the conclusion of the study, he only woke up two to three times per night. P05's reported similar improvement in sleep: before the study, he reported, "I have problems falling asleep and I need to take pills. But now I don't need to." Surprisingly, even though we did not ask, three out of five patients mentioned that they dreamt that their impaired limb moved again, the same way it had before their injury. According to P05, "I had a dream yesterday, and I saw my right hand and arm moving! It felt so good and so vivid that I can still remember." Thus, these semistructured interviews showed that all five patients' subjective experiences are consistent with the quantitative measures, including pain ratings and motor imagery time.

DISCUSSION

Our brief report with five PLP patients reveals that a long-term VR-MT intervention produced substantial analgesia, indexed by SF-MQP and VAS pain ratings, along with improved phantom limb movement, quantified by reduced motor imagery time. Short-Form MQP and VAS ratings showed different percentages of improvement, given that they measure different aspects of pain perception with different levels of responsiveness (35, 36). We also found an enhanced sense of embodiment with the VR avatar and improved ratings in anxiety and depression. We observed all of these changes in each patient, although with varying effect sizes.

These findings suggest that VR-MT interventions hold promise as effective analgesia for patients who suffer PLP, particularly considering that four out of five participants suffered severe PLP for more than 10 years, and were first treated with at least one of the traditional pain management methods. Therefore, it is unlikely that carryover effects from previous therapies can explain our findings. For the same reason, pain relief owing to natural regression to the mean effects is unlikely to explain the observed large effect. Furthermore, patients who were taking medication had already been on it for over 2 years without an increase in dosage during the study; this makes medications an unlikely explanation for our results.

In our study, five patients underwent the VR intervention for 4–6 weeks, ranging from 3 to 10 sessions (**Table 1**). Previous VR studies mostly had a limited number of participants in longitudinal tests. For instance, Murray et al. (37) conducted a case study with three patients over two to five sessions; Henriksen et al. (38) investigated the feasibility of their VR environment with three upper limb amputees over seven sessions, and Chau and colleagues' case study involved only one PLP patient who participated in five sessions (39). Other VR studies involved a single session with one or more patients (20, 40–43). One reason that prevents large sample sizes is that patients with PLP usually need the help of caregivers to travel, and most patients lived far from the research laboratory (not in the same province). We also found that patients we initially tried to recruit were too physically inactive, mentally impaired, or socially disengaged to participate in the study.

While the potential of using VR for relieving PLP has been demonstrated, why and how it works remain unclear. Some researchers believe that having a sense of ownership over a virtual body in VR might alleviate pain for healthy subjects and pain patients (19, 44). Others proposed that VR distracts acute pain patients' attention from their pain by the multisensory, immersive VR environment (45–47). Both explanations received respective support. In fact, a combination of modified embodiment and distraction—by pairing a VR intervention with mindfulness meditation in order to direct attention inward to awareness of and agency over a patient's body—was shown as an effective intervention for chronic pain management (48). Our longitudinal data cannot be accounted for by distraction as the accumulated effect is obvious. We indeed observed more SoO and SoA, but their effect is relatively small.

With the growing evidence that the level of the phantom limb's movement may be correlated with a cortical or subcortical reorganization, others have also suggested that improved phantom limb movement may be associated with pain reduction (49). However, in only one study was the phantom limb's movement actually measured quantitatively (20). Our data here also showed an improvement in movements of a phantom limb, quantified as a reduction in motor imagery time that was specific to the impaired limb. Given that the motor imagery was measured only twice, we believe that the practice effect alone could not explain the large and limb-specific effect. The observed 60.59 and 66.53% reduction in imagery time in the two motor tasks was remarkable because it dropped to levels comparable to that of the intact limb. The improvement suggests better control of the impaired limbs' movement. Osumi and colleagues used a bimanual coupling effect between the affected limb and the intact limb as an indirect measure of changes in phantom limb control. They found that bimanual coupling increased with VR interventions and, importantly, were correlated with the VR-induced analgesic effect. Our findings of improved motor imagery in the affected limb are in line with Osumi et al. (20) findings, suggesting that improved voluntary movement of the phantom limb might reflect the neuroplastic changes in PLP patients that are associated with VR's analgesic effects. However, we did not run a correlation analysis between the improvement in motor imagery and the analgesic effect due to the small sample size.

The first limitation of this study is the small sample size which prevents us from establishing the correlation between pain reduction and accompanied changes in the phantom limb movement and embodiment. In future studies, we plan to conduct a longitudinal controlled trial with more samples and methodological improvements. For example, a motor imagery test can be performed measuring electromyography in residual muscles. Sense of agency and SoO can be potentially quantified by more objective approaches, such as intentional binding. We could also compare VR interventions without or without a virtual body. The VR experience can be complemented with haptic feedback to enhance embodiment (50). Importantly, the improvement in the phantom limb movement, as revealed by motor imagery time, can be further investigated by electroencephalogram or functional magnetic resonance imaging scans to probe possible neural reorganization brought about by VR interventions.

DATA AVAILABILITY STATEMENT

All datasets generated for this study are included in the article/**Supplementary Material**.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethical Review Board of Peking University. The patients/participants provided their written informed consent to participate in this study.

CONSENT FOR PUBLICATION

Written informed consent was obtained from the participants for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

XT and KW designed the study and the VR environment. XT and XW conducted this research study. XT, KW, YC, DG, XW, and BF wrote and revised the paper. XW and BF recruited participants. OW gave suggestions to the VR environment design and revised the paper. All authors contributed to the article and approved the submitted version.

FUNDING

We thank National Natural Science Foundation of China (Nos. 31671168, 31622029, and 61533001) and the Natural Sciences and Engineering Research Council of Canada (No. 371783) for funding this study. The funding bodies themselves had no role in the design of the study or in the collection, analysis, and interpretation of the data or in writing the manuscript.

ACKNOWLEDGMENTS

We gave our special thanks to the patients and their families who participated in this study for their time and effort, despite their struggle with pain.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2020.00876/full#supplementary-material

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Neurology

STUDY PROTOCOL
published: 02 September 2020
doi: 10.3389/fneur.2020.00953

Effect of Combined Therapy of Virtual Reality and Transcranial Direct Current Stimulation in Children and Adolescents With Cerebral Palsy: A Study Protocol for a Triple-Blinded Randomized Controlled Crossover Trial

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OPEN ACCESS

Edited by:
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Reviewed by:
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Specialty section:
This article was submitted to Neurorehabilitation, a section of the journal Frontiers in Neurology

Received: 20 April 2020
Accepted: 23 July 2020
Published: 02 September 2020

Citation:
Silva TD, Fontes AMGG, Furlan BSO, Roque TT, Lima AII, Souza BMM, Alberissi CAO, Silveira AC, Moraes ÍAP, Collett J, Silva RP, Airoldi MJ, Ribeiro-Papa DC, Dawes H and Monteiro CBM (2020) Effect of Combined Therapy of Virtual Reality and Transcranial Direct Current Stimulation in Children and Adolescents With Cerebral Palsy: A Study Protocol for a Triple-Blinded Randomized Controlled Crossover Trial. Front. Neurol. 11:953. doi: 10.3389/fneur.2020.00953

Background: Transcranial direct current stimulation (tDCS) and therapy-based virtual reality (VR) have been investigated separately. They have shown promise as efficient and engaging new tools in the neurological rehabilitation of individuals with cerebral palsy (CP). However, the recent literature encourages investigation of the combination of therapy tools in order to potentiate clinic effects and its mechanisms.

Methods: A triple-blinded randomised sham-controlled crossover trial will be performed. Thirty-six individuals with gross motor function of levels I to IV (aged 4–14 years old) will be recruited. Individuals will be randomly assigned to Group A (active first) or S (sham first): Group A will start with ten sessions of active tDSC combined with VR tasks. After a 1-month washout, this group will be reallocated to another ten sessions with sham tDCS combined with VR tasks. In contrast, Group S will carry out the opposite protocol, starting with sham tDCS. For the active tDCS the protocol will use low frequency tDCS [intensity of 1 milliampere (mA)] over the primary cortex (M1) area on the dominant side of the brain. Clinical evaluations (reaction times and coincident timing through VR, functional scales: Abilhand-Kids, ACTIVLIM-CP, Paediatric Evaluation of Disability Inventory-PEDI- and heart rate variability-HRV) will be performed at baseline, during, and after active and sham tDCS.

Conclusion: tDCS has produced positive results in treating individuals with CP; thus, its combination with new technologies shows promise as a potential mechanism for improving neurological functioning. The results of this study may provide new insights into motor rehabilitation, thereby contributing to the better use of combined tDCS and VR in people with CP.

Trial Registration: ClinicalTrials.gov, NCT04044677. Registered on 05 August 2019.

Keywords: cerebral palsy, virtual reality exposure therapy, plasticity, motor rehabilitation, autonomic nervous system, non-invasive brain stimulation, transcranial direct current stimulation

INTRODUCTION

Cerebral palsy (CP) describes a group of permanent disorders of movement and posture that limit activity. It is attributed to non-progressive disturbances that occur in the developing foetal or infant brain (1). The difficulties that accompany individuals with CP lead to their registration in different and continuous rehabilitation programmes to promote the development of general motor skills, and some studies defend the importance of upper limb tasks to promote physical activity for people with CP. According to Pontén et al. (2) and Sarcher et al. (3), contractions in the upper limbs of individuals with CP start early and require adequate intervention and special attention to provide increases in (or maintenance of) range of movement, better performance and physical activity (especially for the ones with less global mobility), improving the performance of the functions of daily life, increasing independence, activities, and participation (4). Likewise, there is growing evidence of the higher prevalence of metabolic syndrome, cardiovascular disease risk factors, and autonomic nervous system (ANS) dysfunctions in adults with CP (5). According to Katz-Leurer and Amichai (6), because of the sedentary behaviour that results from their limited mobility (i.e., the more limited the mobility, the less activity), individuals with CP are more disposed to chronic disorders such as heart conditions and hypertension.

Thus, considering the presence of musculoskeletal and metabolic conditions in individuals with CP, professionals involved in their care need to consider all the impaired structures and functions and look for proposals for interventions based on scientific evidence that can effectively and comprehensively treat the limitations and restrictions caused by the brain injury (7). To do so, they rely on modern technologies to create new practices and interventions to stimulate different body structures and physiological responses, even for those with more severe conditions, to optimise the acquisition of mo(tor skills, which leads to a more active life (8, 9).

In addition to evidence for the benefits of different techniques for the treatment in rehabilitation of individuals with CP (8–10), recent studies encourage the combination of interventions and technologies as a promising approach for rehabilitation (11). Currently, few studies had investigated the effect of combined therapies in the rehabilitation of individuals with CP, though they presented some encouraging results (12–15). Muszkat et al. (11), suggested that the combination of therapeutic tools should be encouraged to enhance clinical effects and provide more effective and long-lasting results. In this sense, with the increasing accessibility and evolution of technology, virtual reality (VR) and transcranial direct current stimulation (tDCS) have the potential to advance the treatment of CP (10).

The use of VR in rehabilitation is a modern concept of treatment that is based on the use of games and tasks in virtual environments to stimulate physical and cognitive functions in individuals with different types of deficiencies (16, 17). In VR, the user interacts with a three-dimensional environment through remote input devices, such as a keyboard or a mouse (a non-immersive environment), or by more advanced devices (an immersive environment) such as a camera, glasses or special gloves (16). Some studies were carried out using VR in individuals with CP, and the effects were significantly positive concerning the balance and strength of lower limbs (18), learning of general motor skills (19), day-to-day activities (19), and improvement of general learning processes with increased attention in the task (20).

Transcranial direct current stimulation is a non-invasive neuromodulatory technique that produces benefits in the sensorimotor and physiological functions of individuals with different neurological deficits (21), including individuals with CP [see the review by (22)]. The tDCS uses low electrical current (1–2 mA) to modulate the resting potential of neurons below the stimulated site (23). The action mechanism of tDCS is related to the changes in the rates of spontaneous neuronal firing and synaptic and non-synaptic plasticity, whichh influences changes in the resting polarisation of the neurons, and promotes neuroplasticity in cortical areas critically involved in the performance of tasks and in promoting functional benefits (24).

The benefits of tDCS include the flexibility to use it for different activities and exercises (as it presents a mobile characteristic) and the possibility of combining it with other interventions. Spampinato et al. (25) showed that the combination of tDCS with a task using reward characteristics produced neurophysiological modulation of inhibitory networks, and it resulted in enhanced retention of the learned task. Thus, it can be used during fine motor tasks [to reinforce learning of coordinative tasks; (26)], global movements [to increase range of movement; (22)] and physical activities [in order to facilitate motor activities; (12)], and to improve heart and autonomic conditions (27).

Abbreviations: tDCS, transcranial direct current stimulation; VR, virtual reality; CP, cerebral palsy; mA, milliampere; HRV, heart rate variability; GMFCS, gross motor function classification system; MACS, manual ability classification system; PEDI, pediatric evaluation of disability inventory; WISC, wechsler intelligence scale for children; TRT, total reaction time.

Some studies have produced positive results when combining VR and tDCS therapies in stimulating the lower limbs for gait improvement (12) and balance (28, 29). However, no studies have investigated VR and tDCS interventions using an upper limb motor task, which might benefit different clinical conditions of individuals with CP. We organised a triple-blinded, randomised, and controlled crossover trial to investigate the upper limb motor function of individuals with CP with the aims of (1) investigating the effectiveness of the use of tDCS while performing a non-immersive VR task on upper limb motor function and (2) to analysing the influence of a combined VR and tDCS in upper limb motor function through different functional assessment scales, reaction times, and coincident timing analysis, as well as physiological analyses such as heart rate variability.

We hypothesise that all individuals with CP will show an improvement in performance after practising a non-immersive virtual reality task, with benefits in upper limb functional scales, reaction times and, coincident timing analysis underpinned by an adaptation of autonomic neural physiological control after the protocol, and retention of these variables at the 30-day follow-up. However, such improvement and benefits will be more evident after the application of active tDCS than the sham (placebo) tDCS group. If this hypothesis is confirmed, the results of this study will be relevant to the treatment of individuals with CP.

METHODS/DESIGN

We registered this trial on ClinicalTrials.gov (NCT04044677). This paper has been reported in accordance with the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) (30) (**Figure 1** and **Table 1**).

Overview of the Study Design

A triple-blinded randomised controlled crossover trial with a 1:1 allocation ratio will be conducted, and all participants will undertake non-immersive VR tasks and active or sham tDCS. Groups A–S will start with 10 daily sessions of tDCS-active combined with VR tasks for 20 min. After a 1 month washout, this group will be reallocated to another 10 daily sessions of 20 min with sham tDCS combined with VR tasks. Meanwhile, groups S–A will carry out the opposite protocol (participants will start an allocated 10 sessions of sham tDCS combined with VR tasks, and after a 1 month washout period will be reallocated to 10 sessions of active tDCS combined with VR tasks). The 1 month washout period has been used and was shown to be sufficient to reset the effects of the first 10 sessions in Biabani et al. (31). **Figure 2** summarises the planned experimental design. This research protocol follows the SPIRIT recommendations.

Thirty-six participants will be recruited through referral by the coordinators of three clinics in Brazil: *Intensiva, Intertherapy*, and *Therapies,* located in São Paulo state. Those interested in participating will undergo a detailed screening using the eligibility criteria for enrolment in the study.

The sample size was calculated using statistical software (GPower 3.1.5) on the main outcome measure (i.e., the motor score). This calculation was based on data from one study with a group of individuals with CP who received tDCS (32). The power was 0.80; the alpha was 0.05; and the effect size was 0.65 (Cohen's d). The sample estimation indicated that 28 participants would be necessary (i.e., 14 per group). With an adjustment to allow for a withdrawal rate (20%), we will recruit 36 participants.

Inclusion Criteria

Participants will be included if they have: the agreement to participate in the research from themselves [by signing assent form (33)] and their legal guardians (by signing a consent form); a clinical diagnosis of CP will be carried out by a neuropaediatric clinician; with GMFCS levels I to IV and MACS I to IV; age ranging from 4 to 14 years.

Exclusion Criteria

Participants will be excluded if they (1) do not understand the tasks—the understanding of the task will be evaluated through five attempts at each task in VR, because even with a low intelligence quotient (IQ) a large number of the children and adolescents can understand virtual tasks and interact with improved performance; (2) motor difficulties that impede the completing of the virtual tasks; (3) cardiac diseases that impede the assessment of HRV; (4) surgery or use of an upper limb spasticity inhibitor during the last 6 months; and (5) a metal prosthesis in the head.

Withdrawal Criteria

Participants will be withdrawn from the study if they are not willing to continue, cannot be present on the day of the experiment, or miss two treatment sessions out of 10 (four in total).

Randomisation

Participants will be randomly allocated to either group A-S (active tDCS and VR tasks) or group S-A (sham tDCS and VR tasks) with a 1:1 allocation defined by a website (randomization.com). As we will have the participant's characteristics, immediately after the randomisation the age and motor function (GMFCS/MACS) will be compared between groups; if the groups are not homogeneous, a new randomisation will be carried out. This protocol will be repeated until there is no difference between age and GMFCS amongst groups (in a maximum of first three attempts at randomisation, we always have homogeneous groups). Randomisation will be under the control of a blinded investigator who will be the only person allowed to manage the electronic security file of the randomisation to locate the individuals. (More details about this can be found in the section that follows). The investigator will be blind to the group to which the participant is allocated.

Blinding

The participants, the researchers delivering the intervention, those performing the assessments, and the statistician will be blind to group allocation until after the data analysis. To ensure proper blinding, participants will receive codes and will be separated from the allocation process by a different investigator. The researchers responsible for applying the intervention and the outcome assessors will not know the allocation of the participants. In addition, for the blinding of the experimenter, the

	STUDY PERIOD										
	Enrolment	Allocation	Post-allocation								Close-out
TIMEPOINT*	$-t_1$	0	t_1	t_2	t_3	t_4	t_5	t_6	t_7	t_8	t_9
			1 day	6 days	10 days	25 days	40 days	46 days	50 days	65 days	80 days
ENROLMENT:											
Eligibility screen	X										
Informed consent	X										
Assessment scales and tasks	X										
Allocation		X									
INTERVENTIONS:											
Group 1			←	—	→		←	—	→		
Group 2			←	—	→		←	—	→		
ASSESSMENTS:											
Coincident timing task			x	x	x	x	x	x	x	x	x
Reaction Time			x	x	x	x	x	x	x	x	x
Heart Rate Variability			x	x	x	x	x	x	x	x	x
Timed up and Go			x	x	x	x	x	x	x	x	x
GMFM			x	x	x	x	x	x	x	x	x
PEDI			x	x	x	x	x	x	x	x	x
Abilhand-Kids			x	x	x	x	x	x	x	x	x
Visual assessments			x	x	x	x	x	x	x	x	x
Cognitive assessments			x	x	x	x	x	x	x	x	x

FIGURE 1 | SPIRIT: Description of the study protocol, schedule of enrolment, interventions, and assessments. *List of specific timepoints in this row.

device to be used has a "study" mode, in which a code is inserted for each participant, so the device (DS-Stimulator Mobile, neuroConn®, Ilmenau, Germany) recognises and programmes the settings (active or sham). Further details about settings used in both active and sham interventions are presented in section tDCS Intervention.

Assessment Scales and Tasks

We will use two classification systems to characterise both groups, five assessments to characterise participants and to measure improvement, and one physiological assessment; and one enjoyment scale, four visual assessments, one cognitive assessment, and two VR tasks (reaction time and coincident timing) for motor performance.

Classification Systems for Group Characterisation

Manual Ability Classification System (MACS) for Children With CP

The MACS describes how children with CP use their hands to manipulate objects in daily activities, and is used for children and adolescents aged 4 to 18 years (34, 35).

The MACS has five levels. They are based on a child's ability to initiate the manipulation of age-appropriate objects alone and on the need for assistance or adaptation to perform manual activities in daily life. Levels are determined by a parent or caregiver who regularly observes the child's day-to-day functions in collaboration with a healthcare professional.

Children who are able to manipulate objects easily with maximum limitations to perform manual tasks that require speed and accuracy are classified regardless of their age as level I, and those who handle objects of lower quality and speed are classified as level II. Children at level III manipulate objects with difficulty and need help or an adapted activity, and those at level IV require continuous support and assistance and/or adapted equipment adapted to partially perform the activity. Finally, children at level V are severely compromised in manual skills and need full assistance. Given the difficulties associated with this level, it will be an excluded item in our study.

Gross Motor Function Classification System (GMFCS)

GMFCS is a reliable and valid standard classification system for measuring the functional abilities of children with CP (36). It describes self-initiated movement and the use of assistive devices (walkers, crutches, canes, wheelchairs and so on) for mobility during an individual's daily activities.

It uses locomotion as a key assessment and analyses the individual at five levels of locomotor performance, separated by age range from 0 to 18 years (37, 38). Thus, an individual classified as GMFCS I is able to walk without limitations. A child classified as level II may walk with limitations, where a GMFCS II operation may result in the use of wheeled mobility over long distances. A GMFCS III-graded child can usually walk with a portable mobility device indoors, but uses wheeled mobility in the community over longer distances. A GMFCS IV-rated individual may sit supported, but their own mobility is limited and they are often carried in a manual wheelchair or use motorised mobility. Children classified as GMFCS V have more severe limitations with head and trunk control, and self-mobility is only possible with an electric wheelchair (37). Considering the

TABLE 1 | Trial characteristics based on WHO Trial Registration Data Set.

Data category	Trial information
Primary registry and trial identifying number	ClinicalTrials.gov, ID: NCT04044677
Date of registration in primary registry	05 August 2019
Secondary identifying numbers	Ethical Committee of the University of São Paulo, under the number CAAE: 99577318.0.0000.5390
Source(s) of monetary or material support	Coordenação de Aperfeiçoamento de Pessoal de Nível Superior–Brasil (CAPES)
Primary sponsor	University of São Paulo–USP
Secondary sponsor(s)	NA
Contact for public queries	TDS, CBMM
Contact for scientific queries	TDS, CBMM
Public title	Virtual reality therapy and transcranial direct current stimulation in cerebral palsy
Scientific title	Effect of combined virtual reality therapy and transcranial direct current stimulation on children and adolescents with cerebral palsy
Country of recruitment	Brazil
Health condition(s) or problem(s) studied	Cerebral palsy
Interventions	Group 1 will start with 10 sessions of active tDSC combined with VR tasks. After a 1 month washout, this group will be reallocated to another 10 sessions with sham tDCS combined with VR tasks. Meanwhile, group 2 will carry out the opposite protocol (i.e., participants will start an allocated 10 sessions of sham TDCS combined with VR tasks, and after a 1 month washout period will be reallocated to 10 sessions of active tDCS combined with VR tasks).
Key inclusion and exclusion criteria	Inclusion criteria: the agreement to participate in the research from themselves and their legal guardians; a clinical diagnosis of CP will be performed by a neuropaediatric clinician; with Gross Motor Function Classification System (GMFCS) levels I to IV; and Manual Ability Classification System (MACS) I to IV; age range 4–14 years. Exclusion criteria: do not understand the tasks; motor difficulties that impede the completing of the virtual tasks; cardiac diseases that impede the assessment of heart rate variability (HRV) and surgery; use of an upper limb spasticity inhibitor during the previous 6 months; metal prosthesis on the head. Withdrawal criteria: participants will be withdrawn from the study if they are not willing to continue cannot be present on the day of the experiment, or miss two treatment sessions.
Study type interventional allocation	Randomised
Masking	Triple-blinded
Assignment	Crossover
Primary purpose	Treatment
Date of first enrolment	March 2019
Target sample size	35
Recruitment status	Recruiting
Primary outcome(s)	Motor skills improvement
Key secondary outcome(s)	HRV improvement

difficulties that are associated with level V, it will be an excluded item for our study.

Assessments to Characterise Participants and Measure Improvement

Pediatric Evaluation of Disability Inventory (PEDI)

The PEDI is a standardised instrument consisting of a structured interview with the caregiver, capable of documenting the functional performance of children between 6 months and 7 years old in their daily life activities (39, 40).

This test covers three domains: self-care, mobility, and social function. The self-care scale covers food, personal hygiene, toilet use, clothing, and toilet control. The functional items of mobility provide information about transfers, walking indoors and outdoors, and use of stairs. The social function dimension reflects issues related to communication, problem solving, interaction with colleagues, amongst others.

Total scores are calculated for each scale in each domain, where each item receives a score of 0 (the child is unable to perform the activity) or 1 (the activity is part of the child's repertoire), and the sum of the items generates the score for each domain. Studies have shown that the PEDI test is valid and sufficiently reliable to be applied to children with CP in Brazil (40, 41).

ABILHAND-Kids

ABILHAND-Kids is a questionnaire about manual ability in self-care activities in children with upper limb involvement based on their parents' perception (42, 43).

The scale consists of 21 mainly bimanual items classified by parents as impossible, difficult, easy to complete, or unknown, defining a one-dimensional measure of manual skill in children with CP.

Scores are significantly related to school education, CP type, and gross motor function, but not to age, sex, or laterality (42, 44).

Finally, ABILHAND-Kids measures are significantly related to GMFCS levels; a higher manual skill is related to a higher gross motor function. A similar relationship between bimanual fine motor function and GMFCS levels has been found previously (45).

ACTIVLIM-CP

The ACTIVLIM-CP is a questionnaire for parents that measures the performance of global activity in daily activities. It has been validated for children with CP (46–48).

It includes 43 items of activities of daily living related to self-care, mobility, and domestic life, and represents a valid and reliable measure of the performance of global activity. In addition, the ACTIVLIM-CP was built based on parents' perception. They are asked to estimate the ease or difficulty their children have in performing each activity, by rating this on a three-level scale: impossible (the child is unable to perform the activity without using any other help), difficult (the child is able to perform the activity without any help, but experiences some difficulty), or easy (the child is able to perform the activity without any help and experiences no difficulty).

Physiological Assessment (HRV)

We will use HRV to analyse autonomic nervous systems before, during, and after the intervention recovery. The analysis will follow the guidelines of the Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology (49). The strap (for data collection) will be positioned on the participant's chest, and the Polar V800 (Polar Electro, Finland) heart rate receiver will be positioned next to it. HRV will be recorded after the initial assessments at rest for 10 min and during VR combined with tDCS training for 20 min. For analysis of HRV data at rest 1,000 consecutive resting rate (RR) intervals will be used, and during the tasks 256 consecutive RR intervals will be used.

Heart rate will be recorded beat by beat throughout the protocol by the Polar V800 heart rate receiver and RR intervals recorded by the monitor will be transferred to the Polar ProTrainer program, which allows HR visualisation and cardiac period extraction in the "txt." file format.

Moderate digital filtering will be performed in the program itself, complemented with manual filtering performed in Excel software to eliminate premature ectopic beats and artefacts, and only series with more than 95% sinus beats will be included in the study (50).

HRV analysis will be performed using linear (time and frequency domain) and non-linear methods that will be analysed using Kubios HRV® software (Kubios HRV v.1.1 for Windows, Biomedical Signal Analysis Group, Department of Applied Physics, University of Kuopio, Finland).

Enjoyment Scale

An enjoyment scale using smiley faces (0 is "not fun at all;" 1 is "boring;" 2 is "a bit of fun;" 3 is "fun;" and 4 is "great fun") will be applied after the end of the game sequences, since the motivation may be related to the motor proficiency level.

This scale was developed by Jelsma et al. (51) to evaluate how children feel when interacting with proposed non-immersive VR games. It was used in other studies using different games (52, 53).

In this study, the scale will be applied in the first and last days of the protocol to verify the children's level of satisfaction with the games presented.

Visual Assessments

For visual evaluation the following tests will be used: the Ishirara Test and the Titmus Test.

Ishihara Test

The Ishihara Test (chromatic vision—Ishirara pseudoisochromatic slides) is the best known and most widely used in the world for green and red colour perception or colour blindness. It was originally created to diagnose congenital colour vision deficiencies, but it has also been shown to be effective in identifying acquired colour deficiencies (54, 55). Its application is based on the analysis of planks formed by coloured circles, with two or three shades and different sizes on a background of similar colour and structure, in which a number or maze appears in a certain colour, which should be identified by the possible bearer of the disability (56).

The boards can be classified into: demonstration boards—visible to all observers in which the figure is presented with a significant contrast brightness against the background, making chromatic sensitivity not necessary for a correct answer; and masking boards—only individuals with normal vision can see the picture in which the object is close in colour to the background (54, 56).

Titmus Test

The Titmus Test is a test used to assess stereoscopic vision or depth perception (the "3D view") that is given by both eyes together and based on the principle of polarisation. It is composed of a two-sided book, and on each side are arranged figures that are projected in duplicate and horizontally disparate from each other (57).

With the use of polarised glasses, and the book positioned between 30 and 40 cm from the eyes, the participant is instructed to indicate the figures they perceive in "relief" (three-dimensional). This perception of three-dimensionality is image disparity, and is measured in arc seconds (57–59).

Quantitatively the steroscopic acuity in this test ranges from 3,000 to 40 seconds of arc, and the level of image disparity decreases as the participant is able to identify them. Therefore, the lower the numerical value in arc seconds, the greater the stereoscopic acuity (57, 59).

Cognitive Assessment

The Wechsler Intelligence Scale for Children (WISC-IV) was developed to assess intelligence in children and adolescents. Because it assesses different intellectual aspects, WISC-IV can be used in different situations, such as psychoeducational, clinical and neuropsychological assessment, diagnosis of neurodevelopmental disorders, and psychiatric disorders (60, 61), and is indicated for the evaluation of subjects between 6 and 16 years old (62, 63).

The WISC-IV is composed of 15 subtests divided into four indices: verbal comprehension, perceptual organisation, working memory, and processing speed (61). The Intelligence Quotient is considered a global cognitive functioning index and traditionally used as a crucial measure in case-control studies in neurodevelopmental disorders (64).

VR Task for Assessment

We will use two VR tasks to assess the participants' capacity and improvement with intervention. The tasks will be used as assessment at three points: initial assessment (D0); assessment after 5 sessions (D5); and final assessment (D11).

The assessment tasks are presented below:

Coincident Timing

Coincident timing is defined as the perceptual motor ability to perform a motor response in synchrony with the arrival of an external object at a given point (65, 66). This task will use non-immersive virtual coincident timing software, which displays on the computer screen (of a 15' computer) 10 (3D) spheres that light up (in red) in sequence until the last sphere—the target—is reached. The participant must rest his/her hand next to the

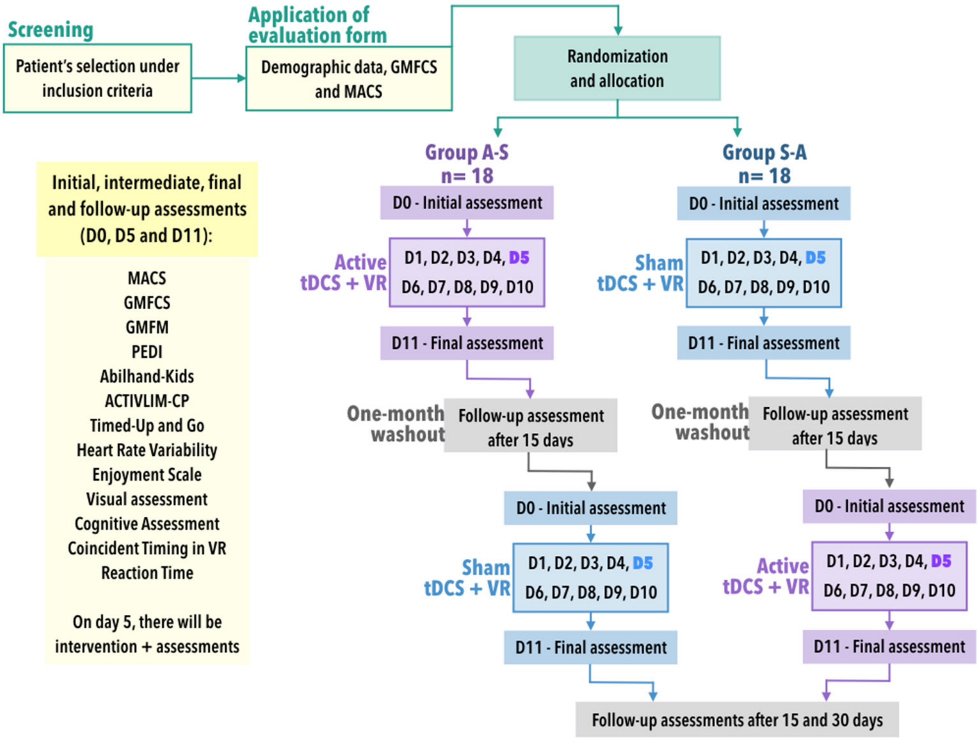

FIGURE 2 | Study design. MACS, Manual Ability Classification System; GMFCS, Gross Motor Function Classification System; PEDI, Pediatric Evaluation of Disability Inventory; VR, virtual reality; n: sample size; tDCS, transcranial direct current stimulation; D0-D11, days of interventions in which D0 is the baseline, D1 to D10 are the days of interventions and the D11 is the day of the final assessments. Participants and sampling.

keyboard of the computer and then press the space key at exactly the moment when the last (target) sphere lights up. The software provides immediate feedback on the success or otherwise of the task by means of different previously demonstrated sounds and colours [for more details, see (8, 17, 67, 68)]. If the participant anticipates or delays the timing of the stimulus, a red light will appear around the feedback; if he/she hits the target, a green light will appear (**Figure 3**).

The magnitude and direction of error of each participant in anticipating or delaying the arrival of the light is recorded by the software in milliseconds. The object is to evaluate the time difference between the participant's response and the arrival of the object at the target location (accuracy) and his/her global temporal precision and therefore his/her coincidence–anticipation ability (8, 17, 67, 69, 70).

The software is programmed to provide a unique username for each participant and the following data are stored: participant name, date of birth, sex, and the researcher's name.

FIGURE 3 | Representative design of the accomplishment of the coincident timing task. **(A)** Demonstration of error performed by the participant on each attempt (red light–unsuccessful). **(B)** Demonstration of hit performed by the participant on each attempt (green light–successful). **(C)** Demonstration of the movement on the space bar on keyboard to perform the task. Main image is about an example of the initial position of the participant.

Reaction Time

To analyse the reaction time, the software TRT_S2012 will be used [constructed and validated by (71)]. The software proposes a simple total reaction time (TRT) test, which consists of the appearance of a yellow square (parameterisable) in the centre of the monitor at predefined time intervals (ranging from 1.5 to 6.5 ms) and, when it is presented, the participant should react as quickly as possible by pressing the spacebar of the computer keyboard (**Figure 4**).

FIGURE 4 | Reaction time task.

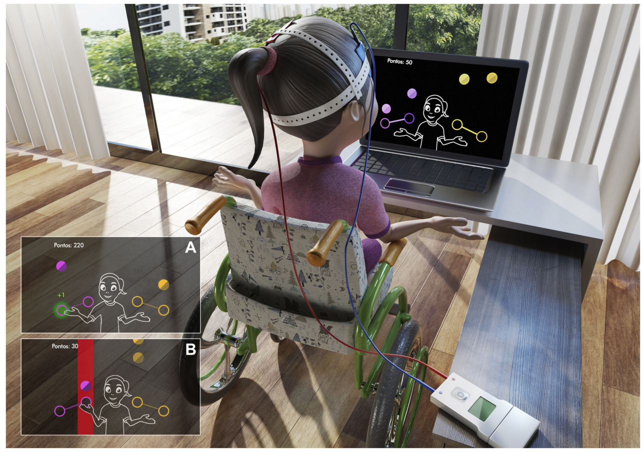

FIGURE 5 | Representative design of the *MoveHero* software performed during tDCS intervention. **(A)** Demonstration of hit performed by the participant (green light). **(B)** Error performed by the participant (red bar).

ASSESSMENT PROTOCOL

The assessment protocol will have the following sequence: the assessment scales will be undertaken with the participants' parents in a separate room (PEDI, Abilhand-Kids, and *ACTIVLIM-CP*), and GMFCS and MACS will be carried out by observacional analysis of their abilities. Also, cognitive (WISC-IV) and visual assessments (*Titmus Test and Ishihara Test)* will be made by a psychologist and a psychometrist, respectively.

Then, for the VR assessment, the coincident timing task will be carried out with a short-term motor learning protocol as used by Monteiro et al. (17), with 20 repetitions for acquisition. After 15 min of no contact with the task, the participants will perform five repetitions of the same task (for retention analysis), and five more repetitions with a speed increase (for transfer of performance analysis).

The reaction time task will be carried out with two attempts of adaptation and 10 attempts for analysis, as used by Crocetta et al. (71).

The HRV will be assessed by 20 min of rest seated in a comfortable chair or their own wheelchair, as used by Alvarez et al. (72).

The assessment part of the protocol will take around 1 h and 30 min in total (inferential analysis method follows in the item "Data analysis").

INTERVENTION

All participants will attend the assigned tDCS and VR intervention as follows: there will be 20 sessions over 4 weeks with tDCS and non-immersive VR tasks, 10 of which will involve active tDCS combined with VR tasks and 10 will involve sham tDCS combined with VR tasks, separated by a 1 month washout period. The sessions will be administered consecutively and once a day (except for weekends). The investigators will have certification to apply the tDCS in children and adolescents with CP and will have experience of the VR tasks.

VR Intervention

During application of the active or sham tDCS, in all sessions the participants will perform tasks in a non-immersive VR environment to stimulate and verify improvement of motor performance. Thus, we will use the *Bridge Games* software tasks [for details and publication, see (68, 71)]. The software that will be used was developed by the Research Group and Technological Applications in Rehabilitation (Grupo de Pesquisa e Aplicação Tecnológica em Reabilitação–PATER) group from the School of Arts, Sciences, and Humanities of the University of São Paulo (EACH-USP) (12).

The two tasks that will be used are presented below.

MoveHero

MoveHero, as presented by Martins et al. (68), is a game that displays falling spheres in four imaginary columns on the computer screen, with a musical rhythm selected by the researcher. This is also considered a coincident timing task; the action is to react (using the upper limbs) and not let the balls pass from the fixed targets. The spheres should only be intercepted when they reach the targets allocated in parallel (at two height levels), two on the left (left position targets A and B) and two on the right of the participant (right position targets C and D), as shown in **Figure 5**. The virtual contact is performed by the avatar of the individual, i.e., a representation of the individual appears on the computer screen. The individual moves their arms and trunk (only if they can move the trunk) in front of the webcam to coincide with the moment the ball touches the target. The individual is positioned at a distance of 1.5 m metres from the computer monitor and waits for the balls (which fall randomly on each target) to drop. The avatar's hand should reach the target sphere along with the arrival of the ball, and the game offers feedback on correctness and error by means of changing the spheres' colour (green for correct and a red line for error).

FIGURE 6 | Representative design of the *Moviletrando* software performed during tDCS intervention.

Moviletrando

The computer game *MoviLetrando* was developed at the Laboratory for Research on Visual Applications in the State University of Santa Catarina, Brazil (73, 74). It has been used in different studies [see (75, 76)]. The game uses the concept of projection-based VR with a webcam and creates a mirror images so that participants can see themselves on the screen (**Figure 6**).

As presented by Guarnieri et al. (75), *MoviLetrando* is a face-to-face learning computer program that involves interaction with virtual symbols projected on the screen: letters of the alphabet (vowels and/or consonants) and numbers (1 to 10). The software allows the therapist or education professional to control different phases that are identifiable as alphabet phases (AP) and numbers phases (NP). In each phase, the software offers various levels of difficulty (generating symbols on the left side, on the right side, or both sides; an increase/decrease in the number of symbols; an increase/decrease the size of the symbols; and an increase/decrease in the time of the exposure to symbols). For this study we chose two phases (one alphabet and one number). The game shows a symbol (an alphabet or number according to the phase) in the top middle of the screen, and the participant has to reach the same symbol, moving his/her hands in the virtual environment. The score obtained is based on whether or not participants reach a symbol, whether it is correct, and the elapsed time taken to carry out each task.

tDCS Intervention

Active tDCS

The anodal active tDCS will be performed over 10 consecutive sessions per weekday (i.e., one session daily, no stimulation during the weekend) during the practice of VR games. The active tDCS will be performed with a current of 1 mA and 20 min of duration (and 30 s of ramp-up and ramp-down). The stimulation target will be the M1 area and aimed at the elbow, shoulder, and trunk of the Penfield homunculus (i.e., 10% instead of 20% laterally to CZ), choosing the more functional side of the participant (C1 or C2 areas of the International 10–20 System for EEG).

Sham tDCS

The sham tDCS will be performed over 10 consecutive sessions per weekday (i.e., one session daily, no stimulation during the weekend). However, the electrodes will be positioned at the same sites of the active tDCS and the device will be switched on for 30 s (ramp-up), giving the children the initial sensation of the 1 mA current, but with no stimulation administered the rest of the time (32). The current will be interrupted after 30 seconds. This sham protocol is already programmed in the device prior to data collection.

PROCEDURE

During the tDCS combined with VR protocol, participants will be seated comfortably in an ordinary chair or their own wheelchair, with their hands arranged over their legs and their feet resting on the floor (or on the wheelchair support). The demarcation and application of the active TDCS will then be performed in the cortical area corresponding to the C1 and C2 primary motor cortex according to the International 10–20 System for EEG (area M1), in order to reach the elbow, shoulders, and trunk.

Therefore, anodal tDCS with electrodes with 25 cm^2, intensity of 1 mA and a density of up to 0.057 mA/cm^2 for a period of 20 min will be used. The same active procedure setting will be used for the sham (placebo) procedure; however, the current will be interrupted after 30 s (32). This configuration will ensure that the electrical stimulus is interrupted before generating considerable stimuli, while the other characteristics of the intervention will be maintained. After each session the participants will be questioned about the presence of any adverse effects. The device used will be the DS-Stimulator Mobile from NeuroConn, which allows blindness of the subjects of the research and the experimenters.

After 5 min of stimulation, the individuals will perform the VR training. The protocol will count on the execution of the following sequence of games: *MoveHero* for 5 min and *Moviletrando* for another 5 min. The participants will have the rest of the time (5 min) with tDCS (sham or active) only. The training time will take 20 min in total. This kind of protocol was used by previous authors who used tDCS (22). The method of inferential analysis follows is described in the “Analysis of the data” section of this paper.

PRIMARY OUTCOME

To evaluate the effect of the combined therapy of virtual reality and tDCS in the upper-limb and trunk motor area on M1 (C1 or C2) of individuals with CP, and to check the possibility of generating motor gains in individuals with CP, we will observe the change from baseline motor values provided by different scales and VR tasks.

Assessments for Primary Outcome

The VR task will be used to assess the participants' motor abilities (accuracy, precision, and trend of anticipation or delay in movement) during each intervention. Also, we will use coincident timing and reaction time tasks, ABILHAND-Kids, ACTIVLIM-CP, and visual and cognitive assessments to characterise the group and to find influences on motor improvement by using correlation tests. These tests will be carried out at three stages: initial assessment (D0); assessment after five interventions (D5) and final assessment (D11) (**Figure 1**).

SECONDARY OUTCOME

We will observe changes in the ANS after active and sham tDCS combined with VR tasks in children and adolescents with CP.

Assessments for Secondary Outcome

In addition to the motor tests, the HRV analysis will be verified throughout the intervention. Some studies point to ANS alteration, with a reduction in HRV in individuals with CP (77, 78). HRV represents the autonomic function, and short-term HRV measurement has been used to evaluate sympathetic and parasympathetic heart rate modulation. Therefore, because of the ease of evaluation (non-invasively, through a chest strip) and because of its high clinical relevance, it is important to evaluate HRV before and during the intervention with tDCS and VR, since some studies indicate improvement of the autonomic balance after VR tasks in individuals with Duchenne muscular dystrophy (72) and post-stroke (79). In the case of CP, some studies had identified low HRV in foetuses that would later be given a CP diagnosis (80), at rest and during postural change (81), and submaximal tests (78). Low HRV is often an indicator of abnormal and insufficient ANS adaptation, which may indicate the presence of physiological malfunction in the individual (50) and is associated with an increased risk of cardiac events (6).

STATISTICAL ANALYSIS

For the coincident timing task for the inferential analysis of the initial tasks (transversal) and the longitudinal protocol with tDCS and HRV as dependent variables, the error measures (constant, absolute, and variable errors) will be considered (time in milliseconds). If the data meet the assumptions for the use of parametric analysis, ANOVA will be performed to identify intra and inter-group differences. These, if any, will be detected by the *post hoc* Tukey-HSD test. If the normality assumptions are not met, non-parametric analyses will be undertaken to identify and locate the differences: a Friedman and *post hoc* Wilcoxon test (for within groups) and a Kruskal–Wallis and *post hoc* Mann–Whitney *U*-test (between groups). For the between-groups analysis of HRV indices, MANOVA will be used, with repeated measures for within groups analyses (for evaluations and follow-up) or Mann–Whitney for intergroup analyses and Friedman for intragroup analyses. A significance level of 0.05 (5%) will be defined; all intervals constructed throughout the work will be 95% statistical confidence. The statistical program used will be SPSS (Statistical Package for Social Sciences), version 26.0.

DISCUSSION

Although treatment with tDCS is feasible and effective, further studies with individuals with CP are essential for a better understanding of the motor and autonomic effects of treatment with VR associated with tDCS for clinical practice. Therefore, we organised this study to analyse the influence of combined therapy of VR and tDCS for children and adolescents with CP, with VR tasks for upper limb and trunk movements. As outcome measures, we chose different upper limb functional assessment scales, computer tasks for the analysis of reaction time and anticipatory timing, as well as physiological analyses such as heart rate variability (HRV). Considering our hypothesis, supported by previous studies using similar tasks (8, 68, 70, 71), we speculate that all individuals with CP will show an improvement in performance during therapy sections and will maintain this improvement in follow-up assessments (15 and 30 days). We also hypothesise that the individuals using active tDCS with present better results.

The results from this study can positively influence the rehabilitation programs and provide answers to four important topics:

1. Safety. The tDCS and VR are safe non-invasive techniques according to current knowledge (24, 82). Two systematic reviews of tDCS in children with CP (83) and paediatric motor disorders (22) found that a large number of individuals have been involved in studies with tDCS since 2014 and noted a small number of adverse effects such as erythematous rash, mild skin burn, redness, and tingling of the skin. The use of Virtual reality presented some adverse symptomatology (especially with immersive VR and commercial games) such as nausea, dizziness, disorientation, frustration for the failure of the interface to detect movement or actions, and difficulty with hand-held interfaces, mainly in positioning users with movement and postural impairments (84). Thus, to avoid adverse effects and risks to the individual, the tDCS parameters used in the present trial will be within the safety limits described in the methods, and to prevent the adverse VR effects, we will use a game developed especially for individuals with disabilities with the use of non-immersive VR task.
2. Use of non-commercial games. Despite promising studies in the literature using commercial games (85), an important question is the potential and future use of customised serious games–defined as a game developed for a specific target (84). Commercial games are designed for entertainment rather than rehabilitation and require high cognitive and motor performance, which makes them unsuitable for patients with restrictions on mobility. In contrast, studies using games specifically developed for rehabilitation have presented interesting results (71). Thus, for the present study, we selected a serious game that provided an engaging task, specially designed and created to effectively capture the performance

of individuals with disabilities and provide a report of their performance (68).

3. Combined intervention for different levels of motor impairment. There is a significant gap in knowledge about the benefits of combining different technologies for the rehabilitation of upper limbs, in order to increase accuracy of movement, reaction time, coincident timing and physical activity for children and adolescents with CP with different levels of gross motor function. Thus, we hope to contribute knowledge for clinical practice by examining the effects of a combined intervention on gross motor functions in individuals classified as GMFCS I-IV.
4. Autonomic nervous system. In addition, there is another gap in knowledge concerning the adaptation of the autonomic nervous system (assessed through heart rate variability–HRV) to a combined therapy of VR and tDCS, by measuring HRV before, during, and after this intervention. Heart Rate Variability is a well-known risk marker for chronic disorders and reflects the control of autonomic nervous system in the sinus node in different health conditions, physical activity levels and exercise (70, 72, 86). HRV is impaired in individuals with CP, with a sympathetic predominance, which leads to less adaptation to physical demands (78). It characterises a cardiovascular neural profile that can lead to negative clinical results (87), such as increased cardiac arrhythmias and cardiovascular mortality (88), in addition to the risk of sudden death (86, 89), and there is evidence that maintained exercise is a feasible option to decrease cardiovascular risk in persons with sympathetic compromise (90).

Thus, we believe that the results of this study will provide scientific support for the use of combined tDCS and VR therapy in individuals with CP to improve motor skills, functionality, and the autonomic nervous system.

TRIALS STATUS

Participant recruitment started in December 2019 and is expected to end in July 2020. Study completion is estimated by October 2020.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethical Committee of the University of São Paulo, under the number CAAE: 99577318.0.0000.5390. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

TS designed the study, drafted the article, collected the patient data, is going to perform the statistical analyses, and interpret the data. AF collected patient data and drafted the article. TR, AL, BS, CA, AS, ÍM, and DR-P collected the patient data and revised the manuscript. BO-F, RS, and MA provided assistance on patient data collection and revised the manuscript. JC and HD revised the manuscript critically for intellectual content. CM coordinated the study, drafted the article, and revised the manuscript critically for intellectual content. All authors read and approved the final manuscript.

FUNDING

TS was supported by the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior–Brasil (CAPES)–Finance Code 001 and Fundação de Amparo a Pesquisa do Estado de São Paulo (FAPESP)–Finance Code: 2016/08358-0. CM was supported by the Fundação de Amparo a Pesquisa do Estado de São Paulo (FAPESP)–Finance Codes: 2011/07277-2, 2013/00175-5 and 2017/24991-7, and by the Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq)–Finance Code 442456/2016-6. Professor HD is supported by the Elizabeth Casson Trust and the NIHR Oxford Health Biomedical Research Centre.

The views expressed are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health.

ACKNOWLEDGMENTS

We would like to acknowledge Dr. Tania Brusque Crocetta and Laboratório de Realidade Virtual Aplicada da Universidade do Estado de Santa Catarina (LARVA UDESC) for their assistance with the database and development of Movilétrando and TRT_S2012 games. To Murillo Vinícius Brandão da Costa, Dr. Luciano Vieira de Araújo and Grupo de Pesquisa e Aplicação Tecnológica em Reabilitação da Universidade de São Paulo (PATER USP) for the development of the MoveHero game.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Neurology

ORIGINAL RESEARCH
published: 15 January 2021
doi: 10.3389/fneur.2020.577713

Design and Development of a Virtual Reality-Based Mobility Training Game for People With Parkinson's Disease

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OPEN ACCESS

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Specialty section:
This article was submitted to Neurorehabilitation, a section of the journal Frontiers in Neurology

Received: 29 June 2020
Accepted: 20 November 2020
Published: 15 January 2021

Citation:
Finley JM, Gotsis M, Lympouridis V, Jain S, Kim A and Fisher BE (2021) Design and Development of a Virtual Reality-Based Mobility Training Game for People With Parkinson's Disease. Front. Neurol. 11:577713. doi: 10.3389/fneur.2020.577713

People with Parkinson's disease (PD) commonly have gait impairments that reduce their ability to walk safely in the community. These impairments are characterized, in part, by a compromised ability to turn and negotiate both predictable and unpredictable environments. Here, we describe the development and usability assessment of a virtual reality training application, *Wordplay VR*, that allows people with PD to practice skills such as turning, obstacle avoidance, and problem-solving during over-ground walking in a game-based setting. Nine people with PD completed three sessions with *Wordplay VR*, and each session was directed by their personal physical therapist. Our outcome measures included perceived sense of presence measured using the International Test Commission–Sense of Presence Inventory (ITC-SOPI), levels of motivation using the Intrinsic Motivation Inventory (IMI), overall system usability using the System Usability Scale (SUS), and setup time by the physical therapists. Both the people with PD and the physical therapists rated their sense of presence in the training system positively. The system received high ratings on the interest and value subscales of the IMI, and the system was also rated highly on usability, from the perspective of both the patient during gameplay and the therapist while controlling the experience. These preliminary results suggest that the application and task design yielded an experience that was motivating and user-friendly for both groups. Lastly, with repeated practice over multiple sessions, therapists were able to reduce the time required to help their patients don the headset and sensors and begin the training experience.

Keywords: virtual reality, walking, Parkinson's disease, cognition, user-centered design

INTRODUCTION

Parkinson's disease (PD) is a chronic, progressive neurodegenerative disorder that diminishes motor ability and quality of life in over 1.5 million people in the USA and 7 to 10 million people worldwide (1). In addition to difficulties with straight walking, turning and negotiating both predictable and unpredictable environments associated with community accessibility are significant problems for people with PD and greatly impact participation in societal roles (2–4). Importantly, gait disorders respond poorly to dopaminergic replacement therapy (5–7).

Physical activity has consistently been identified as an effective, non-pharmacological intervention for improving motor performance in PD (8). As a result, clinicians and researchers are actively searching for means to increase lifelong participation in physical activity for people with PD. Virtual reality (VR)-based mobility training is a promising tool to provide an enjoyable, engaging, and enriched setting for forms of physical therapy capable of improving functional mobility in older adults, people post-stroke, and individuals with PD (9–11).

Two specific aspects of VR make it an ideal platform within which people with PD can practice complex gait skills. First, the emergence of consumer-level, "roomscale" VR systems has widened the feasibility of using VR during the performance of a broad range of locomotor activities. Room-scale VR applications allow the user to physically move around a given space and practice both straight walking and turning. Secondly, virtual environments allow for the natural and seamless integration of motor learning practice variables known to optimize long-term retention of learned skills. Environmental context (12, 13), motivation (14), and external attentional focus (15) are three specific practice variables that have recently emerged as being particularly influential in PD and highly amenable to control within virtual environments.

Despite the aforementioned benefits of incorporating VR in skill training for people with PD, previous studies have demonstrated inconsistent results when VR-based interventions are compared to conventional approaches for improving gait and balance (11, 16, 16–21). Many studies have used non-immersive off-the-shelf (17, 20, 22, 23) or custom games (16) that focus primarily on balance training as their VR-based intervention. Other studies have used bespoke games created for mobility training. Although these games allow participants to negotiate virtual obstacles and select different virtual paths, participants are unable to practice turning because they are constrained to walk on a treadmill (18, 19). To date, there have been no VR-based mobility training applications that allow users to practice skills such as turning and obstacle negotiation with simultaneous problem-solving while walking over-ground. A fundamental assumption of the use of VR for motor skill training is that the skills learned in the virtual environment will transfer to the real world. However, the degree of transfer is known to depend on the similarity between the training environment and the real-world context in which the learned skill is to be performed (24–26). By incorporating skills such as turning and obstacle negotiation in combination with problem-solving in a fully immersive, over-ground training system, it may be possible to enhance the transfer of locomotor skills for people with PD beyond what has been observed in non-immersive systems that focus on balance or treadmill-based walking.

Evaluations of VR-based interventions typically focus on determining efficacy relative to the current standard of care. Still, even efficacious VR interventions may have limited clinical translation because the needs of the stakeholders have not been considered throughout the design and evaluation process. There are many known barriers and facilitators to clinical translation of VR-based training interventions including "the degree of match between the system and the client's goals/needs, the ability to grade the degree of training, transfer of training to real life, (...) knowledge about how to operate and to apply the technology clinically, therapist self-efficacy and perceived ease of use, perceived utility (...) technical and treatment space issues, access, time to learn/practice and use the technology, support for setup/takedown and administering treatment, client and therapist motivation (27, 28)." Each of these barriers and facilitators necessitates a user-centered design approach with a wide range of stakeholders who need to be involved during formative research of VR interventions and not just the recipients of care (the patients).

In this paper, we describe the design and development of a VR-based mobility training application for people with PD. We first describe our iterative, user-centered needs assessment, where we consulted with people with PD and physical therapists to determine the design specifications for our system. We then describe the development and usability assessment of our mobility training application, where people with PD completed a set of three progressive, 30-min sessions under the direction of their current physical therapist. We paired our PD participants with their therapist because they were already working together on common goals, and their therapist would be best able to match the parameters of the training application to their client's needs. Together, the outcomes of this process provide solutions to the challenges mentioned above that have limited both the real-world transfer of skills learned in VR and the integration of VR-based interventions into clinical practice. In trying to address the barriers and facilitators of clinical translation, this study went beyond the evaluation of system usability to measure "entertainment efficacy," which, for VR-based health games, includes intrinsic motivation and presence.

METHODS

Participants

We recruited 17 total participants for the study (**Table 1**), including nine people with PD (64 $\pm$ 12 years) and eight physical therapists (PT, 36 $\pm$ 10 years). Physical therapists were recruited by contacting known neurological clinical specialists who worked with people with PD in the greater Los Angeles area. Physical therapist participants selected an eligible person with PD among their patients. We selected our sample size to be larger than the accepted sample size of five users per software iteration for usability testing (8, 29, 30). Moreover, our statistical analyses focused on within-subject differences, consistent with the repeated-measures design of our assessments.

Potential participants with PD were eligible for our study if they were diagnosed with idiopathic PD with no motor fluctuations, had Hoehn and Yahr scores between 1 and 3 (mild to moderate PD), were greater than or equal to 18 years of age, and were walking independently. Participants were also required to be stable with their pharmacological treatment without differing in

Abbreviations: IMI, intrinsic motivation inventory; ITC-SOPI, independent television commission sense of presence inventory; MDS-UPDRS, movement disorder society–unified Parkinson's disease rating scale; SSQ, simulator sickness questionnaire; SUS, system usability scale; VR, virtual reality.

TABLE 1 | Participant characteristics.

Group	Age range	Years since diagnosis	MDS-UPDRS (III)	H&Y	Mini-BEST
PT	35–39	NA	NA	NA	NA
PT	30–34	NA	NA	NA	NA
PT	25–29	NA	NA	NA	NA
PT	40–44	NA	NA	NA	NA
PT	30–34	NA	NA	NA	NA
PT	55–59	NA	NA	NA	NA
PT	25–29	NA	NA	NA	NA
PT	35–39	NA	NA	NA	NA
PD	70–74	11	7	2	18
PD	45–49	2	24	1	27
PD	65–69	9	29	1	28
PD	45–49	12	28	3	23
PD	70–74	6	47	3	16
PD	60–64	2	15	1	26
PD	65–69	19	26	3	17
PD	75–79	1	29	2	23
PD	65–69	11	26	2	22

H & Y, hoehn and yahr stage; MDS-UPDRS: Mini-BEST: Mini Balance Evaluation Systems Test; MDS-UPDRS, movement disorders society–unified Parkinson's disease rating scale; PD, participants with Parkinson's disease; PT, physical therapists.

Hoehn and Yahr staging between medication-off and medication-on conditions. Potential participants were excluded if they showed side effects such as uncontrolled, involuntary movements (dyskinesia), if they had musculoskeletal injuries, or if they had pain that limited their movement. Participants were always tested while they were on their routine PD medication. Physical therapists were eligible to participate in our study if they had expertise in the treatment of people with PD and were currently treating an eligible participant with PD.

Participants were informed that they would place a VR headset onto their head, hold a controller in each hand, and have a set of sensors attached to their waist and on top of each foot. During the session, participants viewed the virtual environment through the headset, heard different sounds when completing tasks, and felt slight vibrations from the hand controllers. They were told that they would be asked to perform tasks within the virtual environment, such as reaching out to virtually grasp objects, stepping over or around obstacles, and turning. Lastly, participants were informed that they would be asked to complete a set of computer-based questionnaires regarding their experience after the end of the VR session. The Institutional Review Board at the University of Southern California approved the study protocol, and all participants provided informed consent before participating. All aspects of the study conformed to the principles described in the Declaration of Helsinki.

Application Design

The software used in this study was developed by the authors through a user-centered, participatory design process that incorporated feedback from people with PD and physical therapists throughout the development phase. The *Wordplay* game used as the intervention in this study was the result of a multi-year process of formative research. This process helped identify barriers to community mobility in people with PD, such as environments with people or things that move in irregular patterns (e.g., crowds, road crossings), externally imposed time pressure, performing simultaneous cognitive tasks, and increased anxiety (17). In addition, the fact that people with PD have difficulty turning (17, 18) and are more likely to fall from tripping over obstacles than age-matched controls (19) informed the design brief describing the types of tasks that were to be elicited from players in the virtual environment. We also identified and subsequently incorporated into the design key principles known to modulate the efficacy of motor skill learning (14). These included practicing skills in multiple environmental contexts, enhancing motivation for practice, and focusing attention on the outcomes of one's movements.

The specifications in the design brief aimed to (1) address specific functional limitations of people with PD, (2) integrate gameplay features that provide a low barrier to use, (3) motivate the patient, (4) stimulate a desire for replaying, and (5) incorporate principles of motor skill learning. In the second stage, we selected, created, and combined key hardware and software assets to produce a unique system with a corresponding set of mobility training tasks. This system allows people with PD to practice tasks such as walking, reaching, turning, obstacle negotiation, and problem-solving in a fully immersive, 3D virtual environment.

The objective of *Wordplay VR* was for users to complete a puzzle that consisted of a word with missing letters located at eye level in the virtual environment. The player had to determine which letters were necessary to complete the puzzle, collect the necessary virtual letters as they floated in 3D space, and then place the letters in the appropriate location. This training application was specifically designed to encourage people with PD to practice walking, reaching, turning, obstacle negotiation, and dual-tasking in a fully immersive, 3D virtual environment. The level of challenge and the required speed of movement were customized on an individual basis by varying word difficulty, the number of missing letters, the time allotted to complete the task, the spatial distribution of solution letters, whether the solution letters disappeared and reappeared, and whether participants had to negotiate virtual obstacles simultaneously.

Hardware

We used the HTC Vive (HTC Corporation, USA) to allow participants to interact with the Wordplay VR experience (**Figure 1A**). The HTC Vive is a head-mounted display (HMD) with a 100° field of view, a resolution of 1,080 × 1,200 pixels per eye, and a frame rate of 90 Hz. The HTC Vive was equipped with a wireless adapter that allowed participants to walk in the virtual environment without being tethered to a computer. Additionally, the system used two HTC controllers, two Vive trackers on the feet, and one Vive tracker on the trunk to control an avatar (**Figures 1B,C**) and interact with the virtual environment. The HMD and trackers were tracked by two lighthouse cameras that were placed in opposite corners of the 3 × 3 m play area.

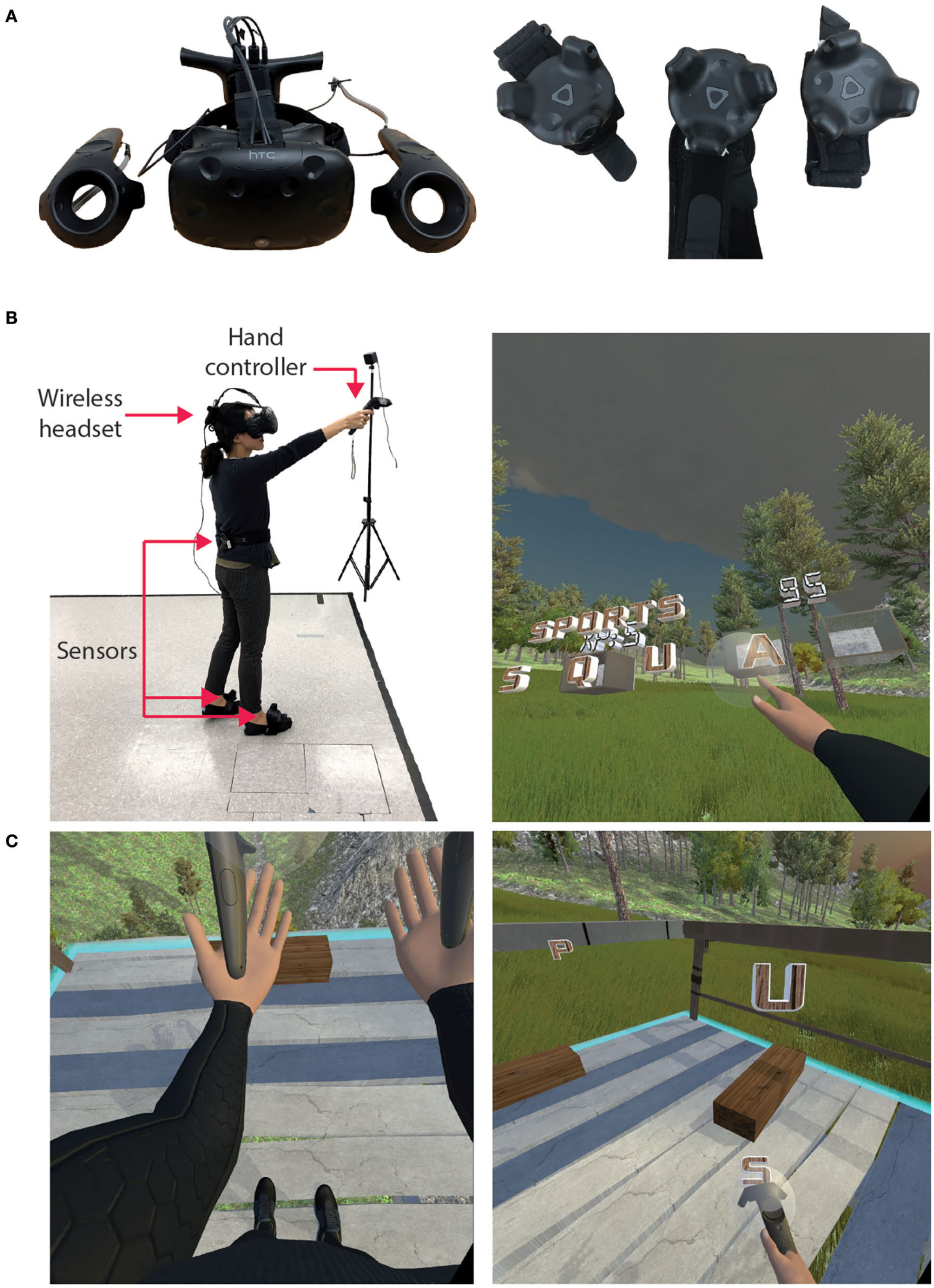

FIGURE 1 | VR hardware and in-game views. **(A)** HTC Vive headset, hand controllers, and sensors. **(B)** A third-person outside view and first-person inside view of Wordplay VR. An individual donned the wireless headset and held a controller in each hand. HTC Vive trackers were worn on the feet and the lower back. Participants' movement was tracked in real time and presented in VR using an avatar. **(C)** In-game views of the avatar, virtual obstacles, and solution letters during gameplay.

TABLE 2 | Testing protocol.

	Day 1			Day 2		Day 3	
	Pre-test	**Post-tutorial**	**Post-play**	**Pre-play**	**Post-play**	**Pre-play**	**Post-play**
Unified Parkinson's disease rating scale	PD						
mini-BESTest	PD						
Safety							
Simulator sickness questionnaire	PD, PT	PT	PD	PD	PD	PD	PD
User experience							
System usability scale (play)		PT	PD		PD		PD
System usability scale (control)			PT		PT		PT
Intrinsic motivation inventory (play)		PT	PD		PD		PD
Intrinsic motivation inventory (control)			PT		PT		PT
ITC sense of presence inventory		PT	PD		PD		PD

The application was programmed in Unity, and the avatar was rendered and controlled via the IKINEMA Orion plugin.

Protocol

All data collection sessions were completed at the University of Southern California Locomotor Control Lab in Los Angeles, California. Participants completed each of the following self-assessments by completing questionnaires through the web-based Research Electronic Data Capture (REDCap) application.

Patient–therapist pairs completed three training sessions using our system over 1 week (**Table 2**). During the first session, we assessed the therapists' baseline levels of symptoms of simulator sickness (31), and then they completed 10 min of gameplay. After completing the 10-min session, they completed a post-test assessment of simulator sickness and the System Usability Scale (SUS) (32) to quantify potential adverse effects and perceived usability. They also completed the Interest and Value subscales of the Intrinsic Motivation Inventory (IMI) (33) from the perspective of a player within the game. Next, they completed a tutorial to learn how to navigate the tablet-based user interface (**Figure 2**) and select training parameters for their patients.

While the therapist completed their baseline assessments, we assessed the level of motor dysfunction in our participants with PD using the Movement Disorder Society-Unified Parkinson Disease Rating Scale (MDS-UPDRS) part III (34). Then, we performed baseline measures of their dynamic gait and balance using the Mini-Balance Evaluation Systems Test (Mini-BESTest) (35). After the clinical exams were complete, we performed a baseline assessment of simulator sickness in our participants with PD to capture any baseline symptoms of discomfort associated with the disease. They then completed 15 min of training in the virtual environment after their therapist selected the appropriate training parameters through the tablet-based interface.

After the training session, participants with PD completed a Simulator Sickness Questionnaire, the ITC Sense of Presence Inventory (36), the IMI, and the SUS (32) to evaluate adverse effects, sense of presence, levels of motivation, and overall system usability, respectively. Our PT participants also completed the IMI and the SUS from the perspective of their role in controlling the training session. During the second and third visits, patients completed 20 min of training, and then both the patients and PT participants completed the same set of questionnaires as the first session. We also recorded the time required for the therapists to set up the system so that we could evaluate how the use of the system in a therapeutic setting might impact the time available for therapy.

Outcome Measures

The Independent Television Commission Sense of Presence Inventory (ITC-SOPI) (36) is a 44-item survey used to assess three domains of "being there": physical space (spatial presence), engagement, and ecological validity/naturalness. The Spatial Presence subscale evaluates the extent to which the player felt as if they were actually in the virtual space. The Engagement subscale evaluates how psychologically involved the player was in the game and how much they enjoyed it. The Ecological Validity subscale assesses whether the user perceived the virtual environment to be like real life. Each response was provided on a five-point Likert scale (1 = strongly disagree; 5 = strongly agree). We computed the total score for each subscale by calculating the mean value of all questions for the respective subscale.

We assessed participants' subjective experience with the virtual environment using the interest/enjoyment and value/usefulness subscales of the IMI (33). Each subscale was scored on a seven-point Likert scale. For data analysis, negative items were reverse-scored, and subscale scores were calculated by averaging across all items on each subscale. A higher score indicates a greater contribution from the concept described in the subscale name. We customized three items on the value/usefulness subscale to make them specific to our training environment. These items were customized as follows: "I think that doing this activity is useful for [increasing mobility]," "I think this is important to do because it can [increase mobility]," and "I think doing this activity could help me [increase mobility]." An overall IMI score was generated by calculating the mean score of all subscales. Based on previous experience with this instrument and prototypes of interactive entertainment, we set benchmarks of 75% of participants rating the game higher than

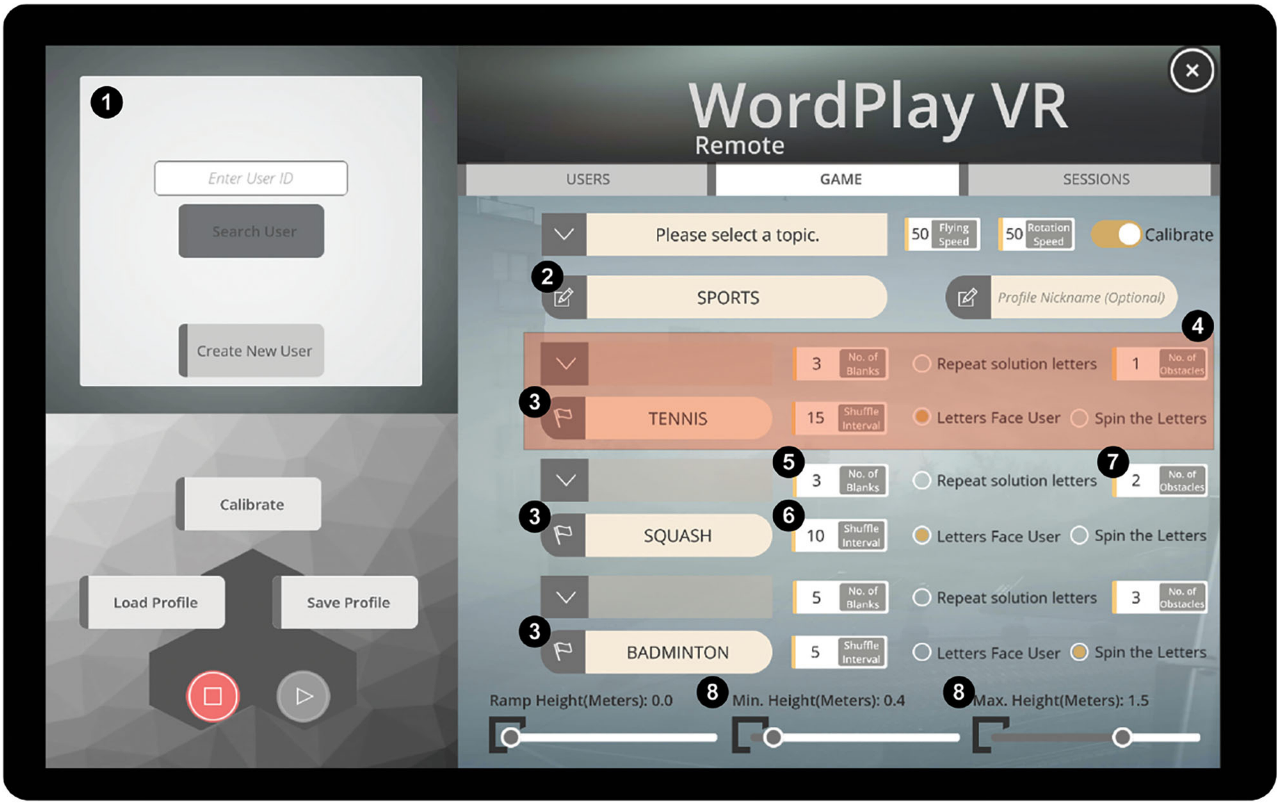

FIGURE 2 | Tablet-based user interface. (1) User profile menu, (2) category for the current session, (3) puzzle words for each of three rounds, (4) settings for a single round, (5) number of missing letters in the puzzle, (6) time interval between letter movements, (7) number of virtual obstacles, and (8) range of heights at which the solution letters could be placed.

the scale midpoint for the interest/enjoyment subscale and 50% of participants rating the game higher than the midpoint for the value/usefulness subscale.

The SUS was used to measure overall system usability (32). The SUS is a 10-item questionnaire with five response options ranging from "Strongly agree" to "Strongly disagree." Based on data from ∼500 studies using the SUS, we used a score of 68 to denote the threshold for above-average overall usability (37, 38).

We measured the time required for therapists to help their patients don the VR headset and trackers, specify the gameplay parameters in the user interface, and begin gameplay.

Levels of symptoms associated with simulator sickness were measured using the Simulator Sickness Questionnaire (SSQ) (31). The SSQ includes 16 questions related to symptoms of simulator sickness, and we used the questionnaire to detect changes in symptoms of nausea, oculomotor discomfort, or disorientation due to exposure to the virtual environment. Participants answered each of the 16 questions based on the severity of symptoms they experienced at the moment using a four-point scale from "none" to "severe" (0–3). A cutoff score of 20 was used to determine if participants experienced significant simulator sickness after exposure (39).

Statistical Analysis

We performed a Wilcoxon signed-rank test to determine if our PT participants increased their SSQ scores after exposure to the virtual environment on Day 1. Similarly, we performed Friedman's test to determine if there was a significant increase in SSQ scores in our patients with PD after exposure to the virtual environment or across days. We also performed a non-parametric Friedman's test to determine if there were statistically significant changes in measures of simulator sickness from baseline to after the gameplay period. We performed a non-parametric Friedman's test on the measures of setup time to determine if our PTs improved their proficiency using the system following repeated sessions. For the ITC-SOPI, IMI, and SUS, we report median values and interquartile ranges for each day and each user group. We do not perform formal statistical analyses of these metrics as we were primarily interested in using the scores for a qualitative evaluation of our system.

RESULTS

Simulator Sickness and Safety

Simulator-related sickness symptoms measured by the SSQ overall did not change after WordplayVR sessions or across days in patients with PD (**Figure 3**). There was no significant

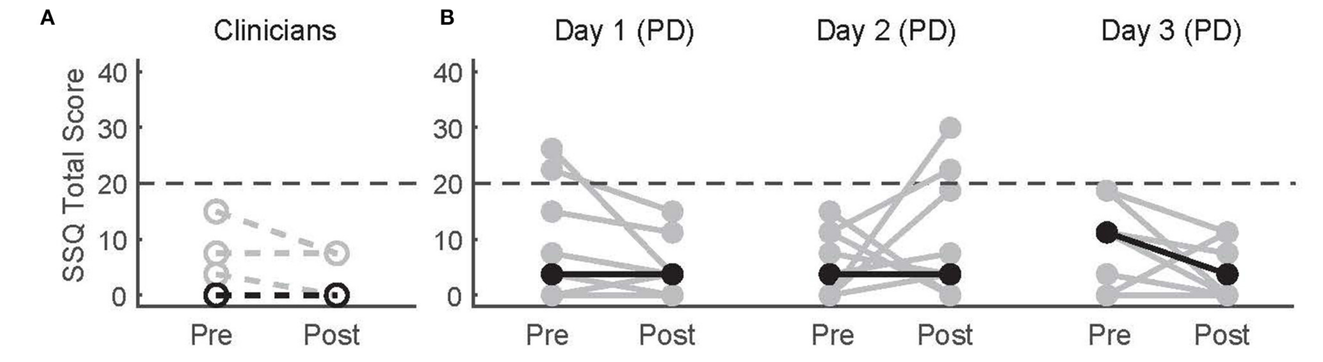

FIGURE 3 | Pre-test and post-test SSQ scores for **(A)** physical therapists and **(B)** patients with PD across three sessions. Gray data points correspond to different participants. Black points correspond to median scores across participants for each time point. Lines connect the pre- and post-scores for each participant. The horizontal dashed line indicates the threshold for significant adverse symptoms of simulator sickness.

difference in the SSQ total scores between pre- and post-WordplayVR on Day 1 in PTs ($p = 0.5$). Moreover, there was no significant effect of time point (pre vs post, $p = 0.62$) or day ($p = 0.86$), nor was there a significant interaction between time point and day ($p = 0.16$) on the SSQ scores in patients with PD. Only two patients with PD increased their SSQ scores after playing WordplayVR above the threshold of 20, which is the benchmark score for having symptoms of simulator sickness, and this occurred on Day 2. These increases resulted from an increase in nausea-related symptoms. We did not observe any falls or other adverse effects in any of our study participants.

Sense of Presence

We found overall agreement with the statements relating to Spatial Presence, Engagement, and Ecological Validity, as seen in the ITC-SOPI responses from both the PTs and the patients with PD (**Figure 4**). Participants from both groups generally agreed with the statements comprising the Spatial Presence subscale, which was indicated by group medians >3 [PTs = 3.68 (IQR = 3.47–3.74), PD day 1 = 3.58 (3.26–4.10), day 2 = 3.63 (3.58–3.84), day 3 = 3.63 (3.42–3.79)]. The responses for the Engagement subscale followed a similar trend, with both groups generally agreeing with the related statements [PTs = 3.92 (3.77–4), PD day 1 = 4.08 (3.69–4.15), day 2 = 3.77 (3.46–4.31), day 3 = 4.08 (3.69–4.54)]. Participants from both groups also generally agreed with the statements related to the Ecological Validity subscale as the median scores were all >3 [PTs = 3.6 (2.8–4), PD day 1 = 3.8 (3.6–4), day 2 = 3.6 (3.4–3.8), day 3 = 3.8 (3.4–4.2)]. Median scores across all subscales for the PD group were similar across the three sessions, suggesting that neither their experience of the virtual space, their engagement, or their perceptions of ecological validity changed with repeated exposure.

Intrinsic Motivation While Playing Wordplay VR

We used the IMI to assess the participants' subjective sense of interest and value of the gameplay experience (**Figure 5**). Both PTs and people with PD responded positively to their experience during the play sessions, with the median scores for both groups being above the neutral point of four. This was observed for both the Interest [PTs = 6.29 (6.11–6.89), PD day 1 = 6.57 (5.25–6.86), PD day 2 = 5.57 (4.54–6.86), PD day 3 = 5.86 (5.43–6.75)] and Value [PTs = 6.29 (5.46–6.54), PD day 1 = 6.57 (4.71–6.79), PD day 2 = 6.14 (4.14–7), PD day 3 = 6.71 (5.68–7)] subscales. Additionally, the scores of the PD group for both scales remained stable over the 3 days, suggesting that intrinsic motivation remained high across all play sessions.

We also administered the IMI to the PTs at the end of each day to assess their intrinsic motivation from the perspective of the director of the training session (**Figure 6**). All the PTs provided high scores, all above the neutral point of four, on all 3 days. This was observed for both the Interest [Day 1 = 6.14 (5.57–6.79), Day 2 = 6.14 (5.50–6.64), Day 3 = 6.14 (5.57–6.54)] and the Value [Day 1 = 6.14 (5.43–6.86), Day 2 = 6.29 (5.21–6.75), Day 3 = 6.57 (5.54–7)] subscales. The responses were consistent across the 3 days, which indicates that the PTs did not lose interest in directing the gameplay session and did not perceive the value of the game to diminish with repeated sessions.

System Usability

We evaluated the usability of WordplayVR by measuring responses to the SUS from three user perspectives. These perspectives included (1) usability within the game as a player (**Figure 7**), (2) usability of the user interface by PTs (**Figure 8A**), and (3) usability for physical therapy practice (**Figure 8B**). From the perspective of playing the game, participants rated the system's usability highly throughout the play sessions [PTs = 82.5 (76.87–85.62), PD (Day 1) = 80 (80–90), PD (Day 2) = 85 (71.25–93.75), PD (Day 3) = 85 (76.25–92.50)].

Concerning the user interface, the median scores provided by the PTs across the 3 days were close to 68, which is generally considered to be an average overall usability score [Day 1 = 67.5 (56.87–76.25), Day 2 = 65 (62.50–83.75), Day 3 = 70 (61.25–81.87)]. The therapy usability scores also fluctuated around 68 for each of the 3 days [Day 1 = 75 (59.37–85.62), Day 2 = 72.5 (61.25–78.75), Day 3 = 65 (51.87–83.75)]. Individual scores indicated that all PTs perceived Wordplay VR

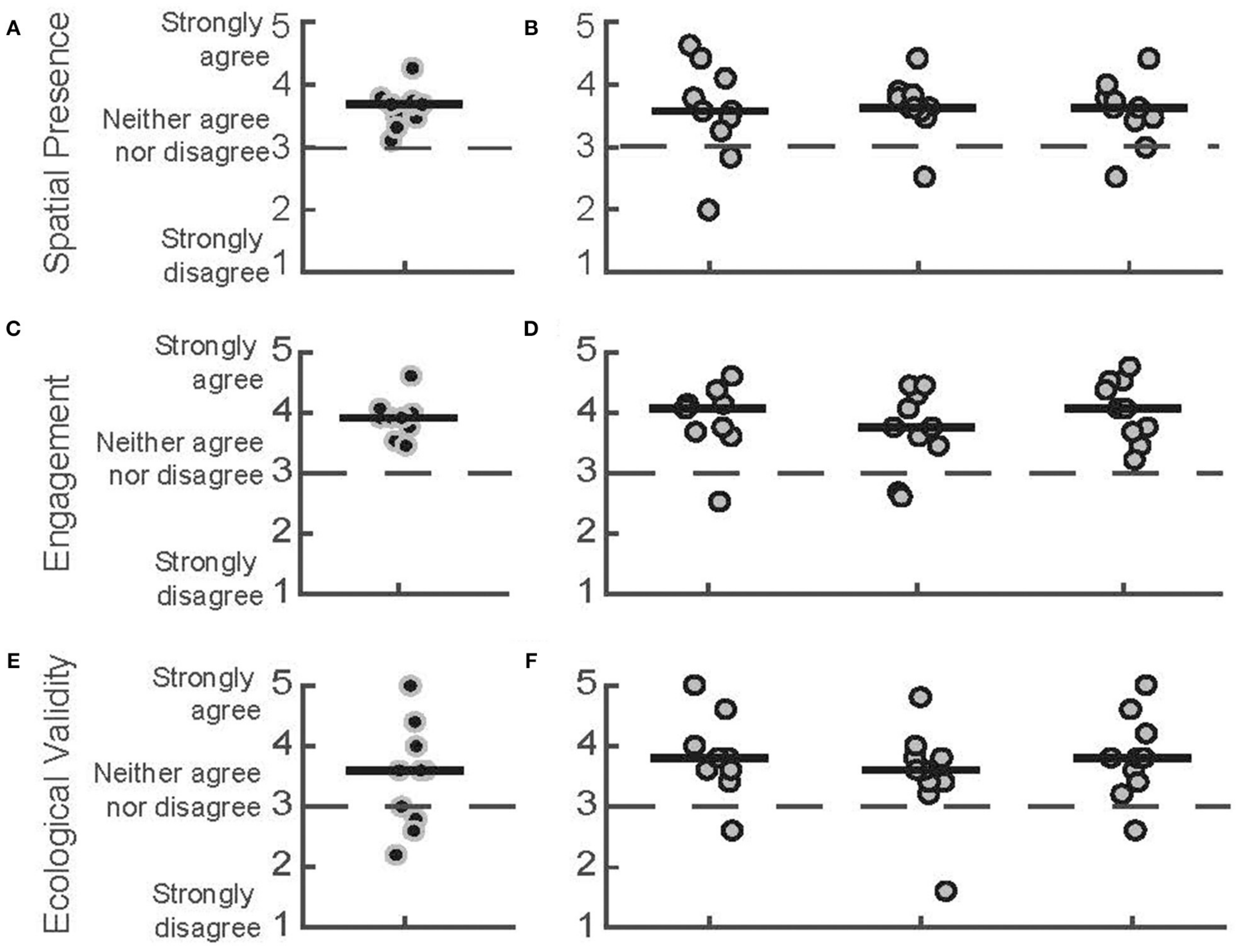

FIGURE 4 | ITC-SOPI subscale scores. Spatial presence scores for **(A)** PTs during the first day of play and **(B)** patients with PD for 3 days of play, respectively. Engagement scores for **(C)** PTs and **(D)** patients with PD. Ecological Validity scores for **(E)** PTs and **(F)** patients with PD. Each data point corresponds to a different participant. Black points correspond to PTs, and gray data points correspond to participants with PD. Median scores for each day are indicated by solid horizontal lines. The score corresponding to a neutral response is indicated by the horizontal dashed line.

as being acceptable or marginally acceptable for use in a therapy setting (40).

Setup Time

All PTs reduced the time required to set up the system across the three sessions (**Figure 9**). There was a trend toward a reduction in setup time across days [$F(2, 12) = 3.87, p = 0.05$]. The time taken for setup decreased by over 25% from the first to the third session [Day 1 = 6.09 min (5.63–8.01), Day 2 = 4.43 min (4.16–7.20), Day 3 = 4.40 min (3.46–6.13)].

DISCUSSION

We developed and evaluated a custom, VR-based mobility training application for people with PD. Our application provided a game-based environment in which people with PD could practice skills such as turning, obstacle avoidance, and navigating unpredictable environments while walking overground. The gameplay parameters were easily modifiable by the therapist, and this allowed them to create personalized levels of challenge for their patients. Our primary objective was to evaluate the usability of our system from the perspective of our two primary populations of end users: people with PD and their physical therapists. We found that both groups of participants provided high ratings on the interest and value subscales of the IMI and provided assessments of the system's usability that were equal to or above the average score for many types of products across a wide range of development stages (38). We also found no evidence of adverse effects following exposure to the virtual environment, and this suggests that our application is unlikely to produce adverse effects in people with similar characteristics to our study sample. Our design and evaluation framework addressed several previously acknowledged barriers and facilitators to clinical translations of VR-based training applications. As a result, this framework could also be applied in

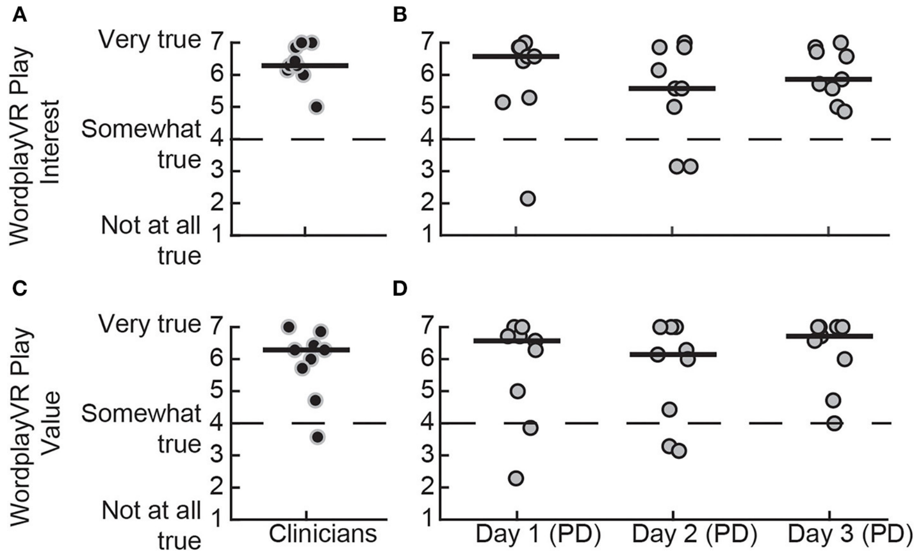

FIGURE 5 | IMI subscale scores for playing WordplayVR by PTs and patients with PD. Interest subscale score for **(A)** PTs during the first day of play and **(B)** patients with PD for the 3 days, respectively. Value subscale score for **(C)** PTs and **(D)** patients with PD. Black data points correspond to PTs, and gray data points correspond to participants with PD. Median scores for each day are indicated by solid horizontal lines. The score corresponding to a neutral response is indicated by the horizontal dashed line.

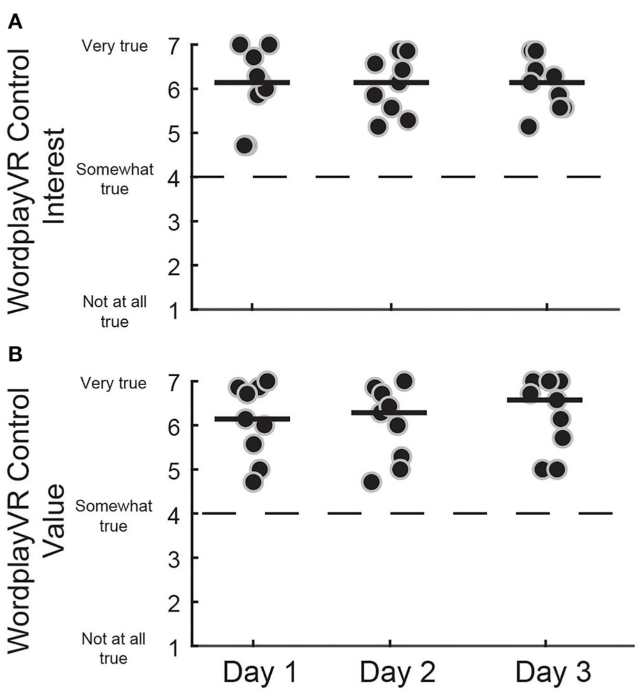

FIGURE 6 | IMI subscale scores for controlling WordplayVR software by PTs. **(A)** Interest subscale for three consecutive days of WordplayVR experience. **(B)** Value subscale. Black data points correspond to individual PTs. Median scores for each day are indicated by solid horizontal lines. The score corresponding to a neutral response is indicated by the horizontal dashed line.

future studies to integrate potential end users in the development pipeline and improve the likelihood that newly developed VR interventions will be clinically viable.

ITC-SOPI

We administered the ITC-SOPI to our participants for an evaluation of their experience with the game. This scale is used to evaluate the overall sense of presence, which is a subjective measure of the extent to which users feel that they are inside the virtual space even though they are physically elsewhere (41). We assessed three subscales of this questionnaire—Sense of Physical Space (Spatial Presence), Engagement, and Ecological Validity. We found general agreement with the statements relating to Spatial Presence, Engagement, and Ecological Validity, as seen in the responses by the physical therapists and the people with PD. The agreement was indicated by scores greater than the scale's neutral midpoint of three. The scores of both groups tended to be similar, and no large differences between them were observed. Additionally, the responses of the PD group were similar across all 3 days, suggesting that repeated exposure did not diminish their experience while playing the game. A recent study that compared users' sense of presence while playing a game with a head-mounted VR device vs. a traditional computer screen found greater presence in the VR group, with the group mean presence score being 3.44 (42). This is comparable to our group median score for presence.

Interest and Value of Wordplay VR

We evaluated the Interest and Value subscales of the IMI to assess participants' motivation levels while playing the game and the therapists' motivation levels while controlling the game sessions. We found high levels of motivation for both groups while playing the game, indicated by their responses on both subscales, which were greater than the midpoint of four. Additionally, the PTs also indicated high levels of motivation while controlling the game sessions. The responses of both groups were consistent

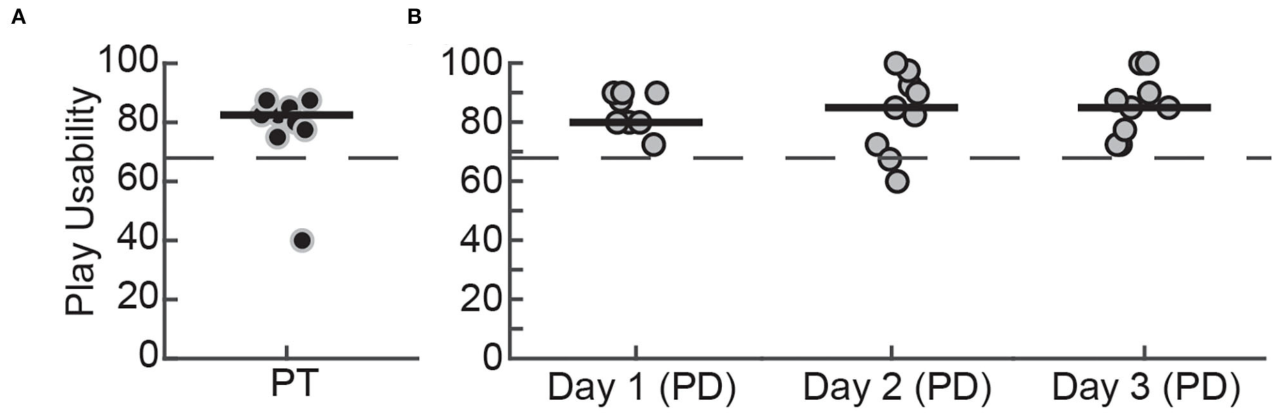

FIGURE 7 | SUS scores for playing WordplayVR by **(A)** PTs on the first day of play and **(B)** patients with PD for 3 days. Black data points correspond to PTs, and gray data points correspond to participants with PD. Median scores for each day are indicated by solid horizontal lines. The horizontal dashed line indicates the threshold of 68, which constitutes an average level of overall usability.

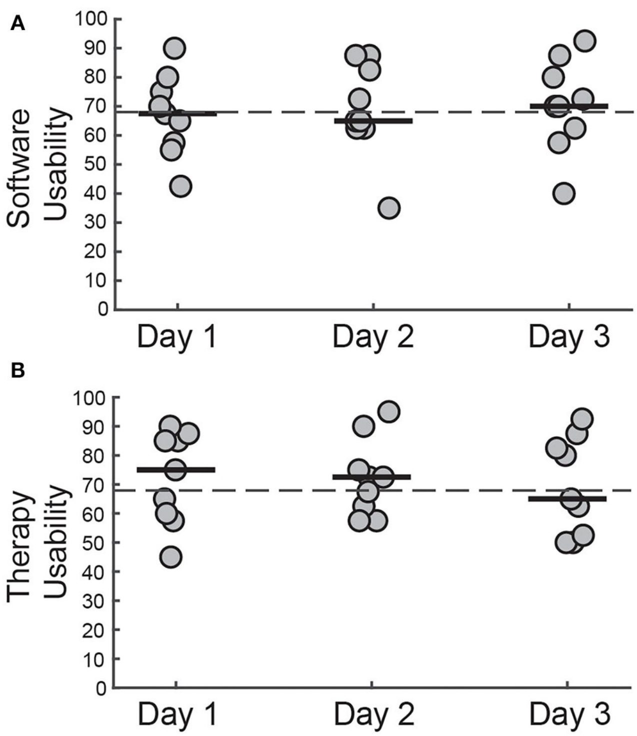

FIGURE 8 | SUS scores for **(A)** controlling WordplayVR software and **(B)** using WordplayVR in physical therapy practice by PT for 3 days. Each data point corresponds to a different PT. Median scores for each day are indicated by solid horizontal lines. The horizontal dashed line indicates the threshold of 68, which constitutes an average level of overall usability.

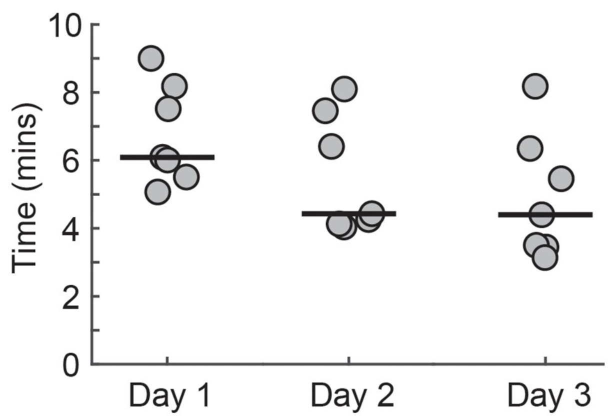

FIGURE 9 | The time required for the PTs to set up Wordplay. Each data point corresponds to a different PT. Median scores for each day are indicated by solid horizontal lines.

across the 3 days, suggesting no reduction in motivation. Lloréns et al. (43) assessed a VR-based telerehabilitation system for people post-stroke and found mean Interest and Value scores to be 6.16 and 6.12, respectively. A similar study in people post-stroke evaluated VR-based intervention reported scores of 5.46 and 5.66, respectively (44). Both of these sets of scores were comparable to our study as we observed Interest and Value scores on Day 3 for people with PD of 5.86 and 6.71, respectively. One of the unique features of our study is that we also evaluated interest and value from the point of view of the therapists who controlled the game. This has not been previously reported, but it is critical as therapists must perceive that the system has value for clinical practice for the system to be used in a therapeutic setting.

Usability of Wordplay VR From the Perspective of Patient and Therapist

Despite considerable interest in VR-based interventions, VR applications for physical rehabilitation are often not tested for usability. Usability evaluation should consider not only ease of use, but also utility for therapeutic purposes (40). Therefore, we investigated system usability in the context of playing Wordplay VR as well as usability from the perspective of how physical therapists would use the application in a therapeutic setting. Both people with PD and physical therapists rated our application as having acceptable levels of usability while playing Wordplay VR, and these perceptions were consistent across multiple days. These findings are consistent with a recent systematic review on usability issues of VR applications, which found that older adults perceived training applications in immersive VR acceptable or marginally acceptable (40). Moreover, physical therapists perceived that applying Wordplay VR in a therapeutic setting to be at least marginally acceptable, and the result held across multiple days. Novel rehabilitation techniques do not necessarily have good usability by default. For example, a previous study testing the acceptability of a biofeedback device by physical therapists found that several testers rated the device to have poor acceptability (45). The poor acceptability was primarily due to the excessive complexity of the device. During the development of our application, we intentionally designed the interface to be easy to use, and this was reflected in the therapists' usability assessment. However, the lab-based setting in which we assessed usability differs markedly from conventional practice environments.

By addressing the previously described issues that have led to minimal carryover between VR research and real life, we have developed a system that provides several potential solutions to achieving a seamless transition between lab-based VR systems and the use of these systems in clinical practice. For one, the design of our system is based almost entirely on input from the stakeholders, both physical therapists and individuals with PD, creating a match between the system and the client's goals/needs. Secondly, our system is scalable through customizable levels of challenge, thus providing the ability to tailor and grade the degree of training for each client regardless of disease severity. Likewise, motivation is enhanced by the ability of the system to capture an individual's progress in managing increasingly greater levels of challenge over practice. Third, our effort was not only the development of the VR system but in training the physical therapists in how to operate and to apply the technology. Designing intuitive user interfaces and training clinicians to use interactive technologies for rehabilitation has long been recognized as an ongoing challenge in this field (46, 47). Over the three intervention sessions, therapists were given the time to learn/practice and use the technology, including setup and takedown. Therapists were motivated by their improved skill and efficiency, which they developed through practice setting up the system. This is promising for any clinical setting where physical therapists may be hesitant to implement technologies in practice due to excessive setup time costing precious patient care time.

LIMITATIONS

As an early-stage, development, and proof-of-concept study, there are several features of the study's design that limit the extent to which our results can be used to inform the use of VR-based interventions for improving mobility in people with PD. First, our system was evaluated by a small set of clinicians and people with PD, and as a result, it remains to be seen if our results will generalize to a larger, more diverse sample. For example, since we did not include a cognitive assessment of our PD participants, it remains to be seen if the perspectives provided by our participants would be shared by individuals with cognitive impairment. This is important because mild cognitive impairment may be present in ∼25% of people with PD (48) and this can often progress into dementia (49). Since our training platform requires problem-solving, working memory, and visual search, it is possible that individuals with cognitive impairment could find the task to be overly challenging. However, this possibility could be mitigated in part through careful specification of the training variables by the physical therapist. Second, the assessment tools that we used, including the IMI, SUS, and ITC-SOPI, have not been validated in people with PD. As a result, the interpretation of the scores on these assessments relative to reported cutoff values could be inaccurate if our participants exhibited any systematic biases or inconsistencies in how they responded to these questionnaires. However, the observed day-to-day consistency of these outcome measures suggests that, at the very least, the evaluations that people with PD provided are reliable. Lastly, our training dose was not designed to be large enough to evaluate potential benefits of training with our system on gait and balance.

FUTURE DIRECTIONS

Despite the promising usability results we observed in the laboratory, the true test of implementation for such systems would be within a clinical environment and through pragmatic trials (50), or n-of-1 trials (51), which are more suitable for the highly personalized nature of intervention that is needed for the individuals with PD. Each of these trial types is designed to determine the effectiveness of an intervention, with pragmatic trials focusing on effectiveness in the context of routine clinical practice (50) while n-of-1 trials seek to evaluate the effectiveness of an intervention that is personalized to individual patients (51). Either of these trial types or a more conventional randomized trial is a feasible next step that we could perform at scale due to the following three facilitators: (a) our system hardware is consumer-grade and relatively affordable; (b) we have designed the application to have several features that can be individualized to the patient such as the word difficulty, time allotted to solve the puzzle, and the height and spacing of solution letters; and (c) allocating space that ideally allows for leaving the tracking cameras in place and demarcating the walkable volume on the floor with tape or paint is likely feasible in physical therapy clinics. Subsequent tests of effectiveness would require a systematic process to determine how best to structure features of the training environment, the necessary duration and frequency of training to achieve a clinically meaningful outcome, and the characteristics of patients who would best benefit from the intervention. Clinics would need to train therapists to use the system, which is not very difficult, and to determine the target population and adapt accordingly. For example, using it with patients at risk for falling would require the use of a safety harness, and using it with seated patients would require some tailoring of the features available within our game. Conducting a pragmatic trial would require that participants be willing to participate in the research study beyond their usual allocated PT time. However, the current game could replace up to 2 weeks of usual PT sessions. Greater use would require adding more depth to the current game, or new games that satisfy other PT needs. Ultimately, we will also need to consider the path to market and long-term viability of our application and the hardware on which it is used. The two paths to market include either commercialization by an entity who would sell the software and provide support to end users or provision of the software for free in an open-source format that is freely available and can be modified by the community (52). Regardless of the chosen path to market, the long-term success of interactive applications for health requires that we develop software that can be adapted to and implemented on both currently available and future devices for virtual and augmented reality.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by The Institutional Review Board at the University of Southern California. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

JF, MG, VL, AK, and BF contributed to conception and design of the study. JF, SJ, and AK collected the data. JF, MG, SJ, AK, and BF contributed to the analysis and data visualization. JF, MG, SJ, AK, and BF wrote the first draft of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

FUNDING

The research reported in this publication was supported by the Eunice Kennedy Shriver National Institute of Child Health & Human Development of the National Institutes of Health under Award Number R21HD088342, the USC Bridge Art & Science Alliance, the USC Undergraduate Research Associates Program, the USC Neuroplasticity and Repair in Degenerative Disorders Collaboration Fund Group, and a voucher from the Southern California Clinical and Translational Sciences Institute.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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CLINICAL TRIAL
published: 18 January 2021
doi: 10.3389/fneur.2020.609988

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2D Virtual Reality-Based Exercise Improves Spatial Navigation in Institutionalized Non-robust Older Persons: A Preliminary Data Report of a Single-Blind, Randomized, and Controlled Study

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Edited by:
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Specialty section:
This article was submitted to
Neurorehabilitation,
a section of the journal
Frontiers in Neurology

Received: 24 September 2020
Accepted: 15 December 2020
Published: 18 January 2021

Citation:
Oliveira LM, Evangelista e Souza EH, Alves MR, Carneiro LSF, Fagundes DF, de Paula AMB, Engedal K, Nascimento OJM and Monteiro-Junior RS (2021) 2D Virtual Reality-Based Exercise Improves Spatial Navigation in Institutionalized Non-robust Older Persons: A Preliminary Data Report of a Single-Blind, Randomized, and Controlled Study. Front. Neurol. 11:609988. doi: 10.3389/fneur.2020.609988

Background: Spatial navigation is a prodromal dementia marker. Exercise used alongside virtual reality improves many cognitive functions, but effects on spatial navigation are still unclear.

Objective: To investigate the effect of virtual reality-based physical exercise with 2D exergames on spatial navigation in institutionalized non-robust older persons.

Method: A total of 14 older persons (aged $\geqq$ 60) were randomly allocated to the exergame (EG) and active control (ACG) groups. EG performed exercises with 2D exergames, while the ACG used the same movements as the EG, but without the use of virtual reality. Spatial navigation was assessed through the Floor Maze Test, where the immediate maze time (IMT) and delayed maze time (DMT) were recorded.

Results: Spatial navigation was enhanced in EG participants compared to ACG individuals. A significant ($p = 0.01$) IMT reduction between groups was observed, while DMT time without prior planning was significantly different at the significance threshold ($p = 0.07$).

Conclusions: Virtual reality-based exercise improves the spatial navigation of institutionalized non-robust older persons. This study should be replicated to confirm the findings reported herein.

Clinical Trial Registration: This study was registered in the Brazilian Registry of Clinical Trials (Protocol RBR-8dv3kg - https://ensaiosclinicos.gov.br/rg/RBR-8dv3kg).

Keywords: dementia, spatial orientation, frailty, physical activity, video games

INTRODUCTION

The development of chronic diseases in older persons is common, harming their functional capacity and resulting in loss of autonomy (1). Independence reduction is the main reason why older persons dwell in long-term care institutions (LTCIs) (2).

In Brazil, over half of institutionalized older persons have dementia (3), which may occur after institutionalization (4). Spatial navigation is among the cognitive functions that deteriorate in dementia cases and compromises the older person's ability of locomotion (5), which in turn is associated with prodromal dementia (6). Spatial navigation is defined as the ability to integrate cognitive processes and sensorial systems, especially the visual system, into environment data processing and body positioning during spatial displacement (5).

An interesting method used to stimulate spatial navigation ability is immersive virtual reality-based navigation training (VR) (7), which involves the activation of brain zones associated with cognitive processes, such as the hippocampus, caudate nucleus, and frontal cortex (8). However, the use of VR immersive systems is complex and expensive, and difficult to apply in older persons living in LTCIs. Previous studies have indicated that active video games associating two-dimensional virtual environment digital games with physical exercise (2D exergames) improve short-term memory, executive functions, sensorimotor integration, and mobility in older individuals (9, 10). To date, however, no robust evidence that 2D exergames might alter spatial navigation in older individuals is available. In this context, this study aimed to analyze the effect of 2D exergame training on the spatial navigation in institutionalized non-robust older individuals.

METHODS

Trial Design

This trial comprised a controlled pilot study with blind randomization of two parallel groups. Consolidated Standards of Reporting Trials (CONSORT) were met. The study protocol was registered in the Brazilian Registration of Clinical Trials (ReBEC), under alphanumeric code number RBR-8dv3kg (https://ensaiosclinicos.gov.br/rg/RBR-8dv3kg).

Participants

The sample was comprised of older persons inhabiting four LTCIs in the Brazilian cities of Montes Claros/MG and Rio de Janeiro/RJ. Both men and women were recruited, aged 60+, totaling 186 eligible participants. The inclusion criteria were as follows: (a) Preserved capacity to communicate with others. (b) absence of medical diagnosis of neurodegenerative diseases or any other disease that may hinder exercise performance; (c) capacity to perform exercise, according to each LTCI physician; (d) no record of severe cardiopathy; (e) absence of acute musculoskeletal injuries that may hamper exercise performance; and (f) no severe sequels of cerebrovascular accident. Participant demographic data was analyzed, and the Brazilian version of the Mini-Mental State Examination (MMSE) was applied (11). NO MMSE cut-off point was applied to exclude participants.

Frailty syndrome was assessed by five objectively measured components, namely non-intentional weight loss, self-reported exhaustion, low physical activity levels, slow walking, and grip strength, leading to classifications of frail, pre-frail, and robust (12).

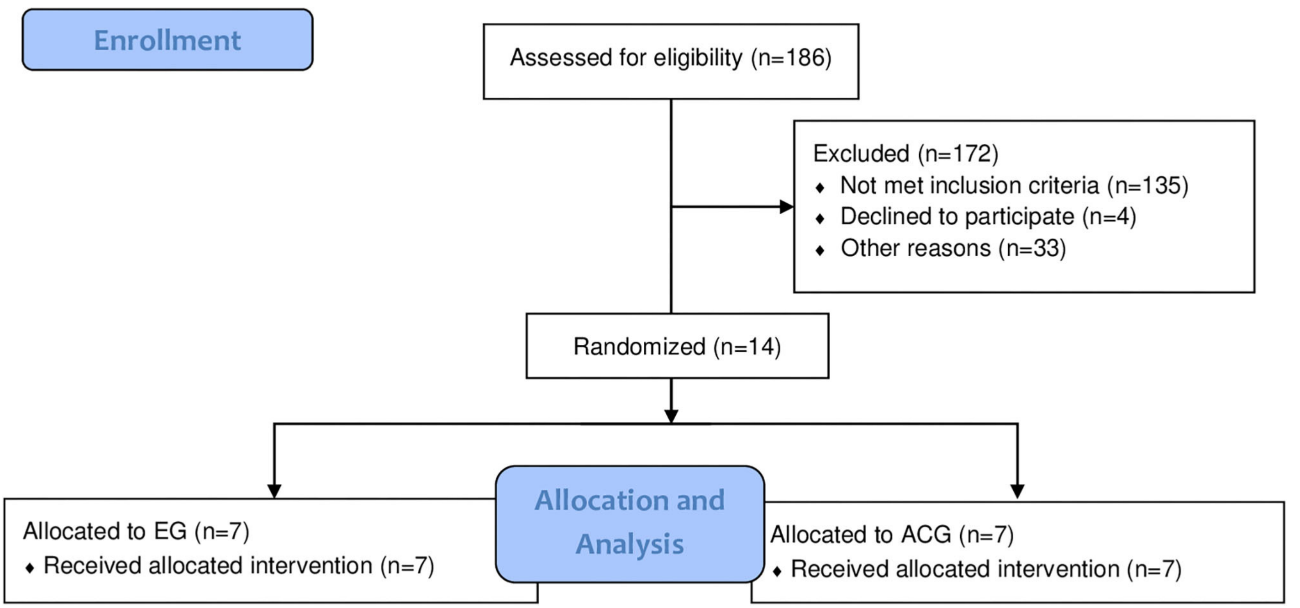

FIGURE 1 | Flowchart indicating the recruitment procedure.

Participant Randomization and Allocation

Randomization was applied with the division of parallel groups according to similar age. An independent researcher performed the procedure and used an Excel sequence of random numbers, with no participant identification. The codes of each older person's group allocation were sent to the data collection chief researcher to determine the intervention groups.

Interventions

Interventions were performed twice a week, totaling 16 sessions across approximately 2 months. Each session lasted 30–45 min. Participants were randomly allocated to the exergames and active control groups (EG and ACG, respectively). The EG performed exercises with 2D exergames, while the ACG used the same movements as EG without virtual reality. Both intervention programs have been previously published and detailed by our laboratory (13, 14). The frequency, number of sessions, and duration were the same for both groups.

TABLE 1 | Demographic, global cognition, and spatial navigation data.

Variable	EG (n = 7)		ACG (n = 7)		t/U	df	p-value
	Mean	SD	Mean	SD			
Age_{years}	81.28	9.74	85.14	6.98	0.85*	12	0.41
$Weight_{kg}$	57.58	17.68	68.35	15.19	1.22*	12	0.24
$Height_{m}$	1.55	1.10	1.53	0.09	0.38*	12	0.70
$MMSE_{score}$	20.8	6.6	24.0	4.8	−1.0*	12	0.33
$IMT_{seconds}$	384	385	146	104	14.00#	–	0.20
$DMT_{seconds}$	354	329	101	59	18.00#	–	0.45
	$Frequency^{EG}$		$Frequency^{ACG}$		χ^2	df	p-value
$Gender_{M/F}$	1/6		2/5		2.91	1	0.08

*Mini-Mental State Examination (MMSE) Status Examination. EG, exergame group; ACG, active control group; M, male; F, female. *Independent t Test; #Mann-Whitney U Test.*

Outcomes

Spatial Navigation Assessment

The Floor Maze Test - FMT (15) was used to assess spatial navigation. This test evaluates planning, allocentric spatial navigation, and episodic memory. FMT consists of a bidimensional white maze drawn in a dark blue carpet (6 m^2). Participants must find the exit of the maze as quickly as possible. Course planning time (PT), immediate course performance maze time (IMT), and maze course repetition time without previous planning (Delayed Maze Time - DMT) were assessed. To perform the DMT, the individual remained in a room for 10 min without visual contact with the maze. IMT and DMT trajectory errors were recorded.

Statistical Procedures

The Shapiro-Wilk and Levene tests were used to verify data normality and homoscedasticity, respectively. Descriptive analyses (mean, standard-deviation, median, and 95% confidence interval) were used for sample characterization and result presentation. Differences between post- and pre-intervention data (Δ) were estimated using the spatial navigation results. The independent *T* test and Kruskal-Wallis were used, when suitable, to compare independent group data (EG Δ vs. ACG Δ). Analyses considered $\alpha \leq 0.05$ and $\beta = 0.20$ parameters and were performed using the Statistics Package for Social Sciences (SPSS) 24.0. As the multiple comparisons inflate the alpha value, we did not perform paired analyses (within groups), to avoid Type I Errors [See (16)].

Ethical Procedure

This research was approved by the Research Ethics Committee of the State University of Montes Claros under n. 2.398.863/2017. Brazilian Ministry of Health rules were met, according to law n. 466/2012.

RESULTS

From the 186 eligible older persons, 14 were selected for the interventions, as all remained in the study until the end

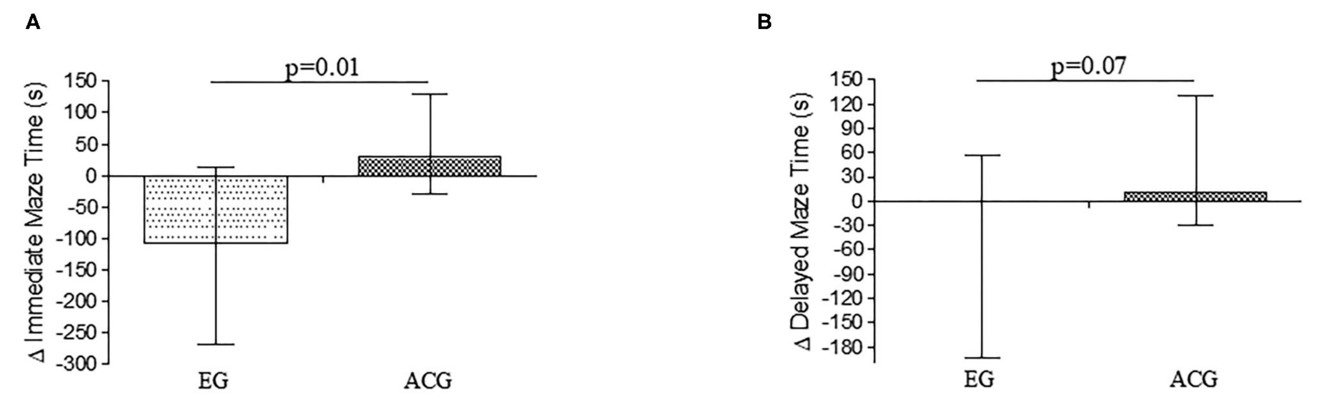

FIGURE 2 | (A) Δ time to finish the immediate Maze Test. **(B)** Δ time to finish the Delayed Maze Test. EG: 2D Exergame Group. ACG, Active Control Group. EG $IMT_{baseline}$: 388 ± 385 s; $IMT_{post-intervention}$: 165 ± 147 s; EG $DMT_{baseline}$: 354 ± 329 s; $DMT_{post-intervention}$: 117 ± 129 s; ACG $IMT_{baseline}$: 146 ± 104 s; $IMT_{post-intervention}$: 200 ± 170 s; $DMT_{baseline}$: 101 ± 59 s; $DMT_{post-intervention}$: 150 ± 117 s.

(**Figure 1**). Groups presented homogeneity regarding age, body weight, height, and global cognition (**Table 1**). All older persons exhibited frailty criteria, with 12 classified as frailty and two as prefrail.

Spatial navigation improved in EG participants compared to ACG individuals. A significant reduction in IMT performance time was observed between groups (**Figure 2A**), while the time to perform DMT was significantly different at the significance threshold (**Figure 2B**).

DISCUSSION

This study indicates that exercise with 2D virtual reality reduces immediate FMT performance time and improves spatial navigation in institutionalized non-robust older persons. These are promising findings regarding spatial navigation decline and speed reduction, which is a predictor of cognitive decline due to dementia disorders (6).

Spatial navigation is considered among the scientific community as a strong predictor of both cognitive impairment and Alzheimer's disease (6, 17, 18). Immediate FMT performance time is associated with executive functions and involves, mainly, planning, mental flexibility, and processing speed (14), functions which might be harmed in dementia cases and are paramount to maintaining independence and postponing institutionalization (4, 17, 19).

The main physical exercise benefits on cognition are associated with neuroplasticity, spatial learning, memory, and executive control (20–23). These benefits justify the improvement of spatial navigation ability found in the present study. Moreover, exercise with virtual reality distinguishes itself as a more attractive strategy for physical exercise practices in older individuals (24).

Other studies corroborating our findings are available, highlighting that the use of training with virtual reality improves the cognitive capacity of institutionalized older persons (10, 12, 13, 24–26). Interactions with virtual environments increase the activation of the frontoparietal cortex network, which contributes to explaining the findings reported herein, as this region is directly connected to spatial navigation (27). Furthermore, a lack of investigation on longitudinal intervention strategies on humans focusing on spatial navigation, as the one conducted in this study, is noted, as most assessments consider only acute effects.

Some studies conducted with animals have highlighted that aerobic and resistance physical exercise may result in positive interferences on brain structures associated with spatial navigation, such as the hippocampus, through the enhancement of trophic factor secretion, brain derived neurotrophic factor (BDNF), and growth factor similar to insulin type 1 (IGF-1), which promote neurogenesis (22, 28).

The most important and main limitation of this study is the sample size. Although *p*-value and statistical power were statistically significant, this finding should be interpreted with caution, as a replication of the experiment applied herein is required.

CONCLUSIONS

Exercise with 2D virtual reality improves the spatial navigation ability of institutionalized, non-robust, older persons. The results reported herein may aid in developing strategies to improve spatial navigation capacity in institutionalized older persons and, therefore, prevent or slow down the development of prodromal dementia in this population.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Comitê de Ética em Pesquisa da Universidade Estadual de Montes Claros. Protocol number: no. 2.398.863/2017. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

LO wrote the manuscript and collected the data. EE wrote the manuscript. MA participated in the data collection. LC partially wrote, revised the content, and translated the manuscript. DF participated in the data collection. AdP revised the manuscript content and performed the analyses. KE revised the manuscript, the analyses, and the English language. RM-J established the study objective, participated in the data collection, wrote the manuscript, and analyzed the data. ON revised the manuscript, language and analyses. All authors contributed to the article and approved the submitted version.

FUNDING

The authors acknowledge funding support from the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES) and Fundação de Amparo à Pesquisa do Estado de Minas Gerais (FAPEMIG).

ACKNOWLEDGMENTS

The authors thank the participants of the study and the following long-term care institutions: Asilo São Vicente de Paula, Lar Sérgio Falcão, and Lar da Amizade.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Neurology

PERSPECTIVE
published: 28 January 2021
doi: 10.3389/fneur.2021.623261

Virtual Rehabilitation of the Paretic Hand and Arm in Persons With Stroke: Translation From Laboratory to Rehabilitation Centers and the Patient's Home

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OPEN ACCESS

Edited by:
Carlos Bandeira de Mello Monteiro, University of São Paulo, Brazil

Reviewed by:
Anna Danielsson, University of Gothenburg, Sweden
Iris Charlotte Brunner, Aarhus University, Denmark

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Specialty section:
This article was submitted to Neurorehabilitation, a section of the journal Frontiers in Neurology

Received: *29 October 2020*
Accepted: *04 January 2021*
Published: *28 January 2021*

Citation:
Fluet G, Qiu Q, Patel J, Mont A, Cronce A, Yarossi M, Merians A and Adamovich S (2021) Virtual Rehabilitation of the Paretic Hand and Arm in Persons With Stroke: Translation From Laboratory to Rehabilitation Centers and the Patient's Home. Front. Neurol. 12:623261. doi: 10.3389/fneur.2021.623261

The anatomical and physiological heterogeneity of strokes and persons with stroke, along with the complexity of normal upper extremity movement make the possibility that any single treatment approach will become the definitive solution for all persons with upper extremity hemiparesis due to stroke unlikely. This situation and the non-inferiority level outcomes identified by many studies of virtual rehabilitation are considered by some to indicate that it is time to consider other treatment modalities. Our group, among others, has endeavored to build on the initial positive outcomes in studies of virtual rehabilitation by identifying patient populations, treatment settings and training schedules that will best leverage virtual rehabilitation's strengths. We feel that data generated by our lab and others suggest that (1) persons with stroke may adapt to virtual rehabilitation of hand function differently based on their level of impairment and stage of recovery and (2) that less expensive, more accessible home based equipment seems to be an effective alternative to clinic based treatment that justifies continued optimism and study.

Keywords: virtual reality, rehabilitation, stroke, hand, arm

INTRODUCTION

Virtual reality (VR) is an approach to human computer interface that utilizes multisensory feedback designed to foster a sense of immersion or agency in a simulated task or activity. Virtual environments, designed for the purposes of upper extremity rehabilitation in persons with stroke have been studied for more than 15 years. Unique aspects related to the control of sensory information make it an ideal method for presenting tasks in a manner consistent with the principles of use dependent neuroplasticity, affording scientists an opportunity to gain insight into the tenets of neuroplasticity and apply them to develop more effective rehabilitation interventions (1). Precise control of sensory presentations and task parameters as well as partial independence from the physics governing the real world make VR an efficient tool that is ideal for high volume practice, targeting motor skill development, in an enriched sensory environment. Animal and human studies have shown that the quantity, duration and intensity of training sessions are key variables in the design of interventions targeting structural changes at the synaptic level (2). Virtual rehabilitation is associated with substantially higher training volumes than traditional rehabilitation techniques in persons with stroke (3). The dynamic development of motor skills is a second requisite for adaptive changes in neural architecture (4). Virtual environments allow for an exquisite level of control over task parameters such as speed, accuracy demands and movement amplitude demands, which provide endless opportunities for incremental changes in task difficulty allowing therapists the ability to operantly shape progressively more normal motor skills (5).

Use of virtual environments to distort the relationship between actual participant movement and simulated movement can be leveraged in different ways to drive neuroplasticity in sensorimotor circuits at any impairment level. In severely impaired individuals with trace or absent hand movement, VR can be used to provide a modified form of mirror visual feedback training in which the unaffected limb is used to control a virtual avatar, visually representing movement of the affected limb. Mirror visual feedback training has been shown to enhance excitability in the ipsilateral (ipsilesional) hemisphere to moving hand via facilitation of compensoatory parieto-frontal networks (6–8). Virtual environments can also distort the relationship between actual participant movement and simulated movement. Trace movement of a body part can be scaled to produce meaningful avatar movement in a virtual environment that can accomplish meaningful tasks. For example, one or two degrees of finger flexion can move a virtual finger enough to strike a virtual piano key, producing a collision with the key that can be felt and movement of the key that can be seen in addition to the expected sound. This multimodal feedback of a scaled movement adds salience to small motor behaviors in profoundly impaired persons, and provides a reward signal for successful actions. Salience of sensory feedback about self-initiated actions is cited as a key requirement for neuroplasticity at any stage of recovery from stroke (9), and may play a crucial role early in the recovery period, when the levels of stroke-induced neuroplasticity are high (10), but the magnitude of upper extremity and particularly hand motor actions are often quite low (11). Furthermore, scaling the movement to provide a meaningful reward for sucessdful practice may help reinforce neural activity in motor and premotor areas of the practiced action. For less impaired individuals visuo-proprioceptive discordance can be created via hypometric or hypermetric feedback in order to promote sensorimotor learning. Sensorimotor motor learning using discordant feedback has been associated with increased excitability of the lesioned hemisphere that may induce a temporary enhancement of the neuroplastic effects of motor training (12, 13).

While the theoretical advantages of virtually simulated rehabilitation are many, the adoption of this technology in clinical settings has been slow. Initially, the cost of custom-made virtual rehabilitation systems was the most important initial barrier to adoption of this approach in clinical settings. This barrier hasbeen overcome by leveraging advancements made by the consumer electronics industries into lower cost rehabilitation technology. The other major hurdle that has been effectively overcome by technology advances is cyber-sickness which was experienced by early users of virtual environments. With these barriers addressed more domain specific limitations are being addressed. For example, the major technological limitation slowing development of the virtual rehabilitation of dexterity in persons with stroke (the focus of this paper) is the fidelity of lower cost motion capture systems (14).

VIRTUAL REHABILITATION OF THE HEMIPARETIC UPPER EXTREMITY

Rehabilitation of the hemiparetic hand caused by stroke has been one of the challenges that VR rehabilitation research has endeavored to overcome for a substantial portion of the field's existence. Early studies examined the ability of persons with chronic stroke to train safely and productively using this approach and comparisons between this approach, traditional interventions and repetitive task practice were conducted. Similar to the other labs in the growing field (5, 15), our group found that virtual rehabilitation interventions elicited clinically significant improvements in hand and arm motor function (16–21) that compared favorably to task–based interventions when measured using common clinical tests in persons with chronic stroke (22, 23). In addition, it was clear that our approach could modify specific aspects of motor function including finger fractionation, reaching trajectory length and smoothness, as well as arm stability during hand activity with virtually simulated motor training (18, 24). These changes have carried over to kinematic measures of transfer tasks utilizing real world objects (22) and improvements in activity level motor function (25) measured using standardized activity batteries such as the Wolf Motor Function Test and the Action Research Arm Test. Many labs including ours are working toward better measurement of participation level including 24 h activity monitoring and qualitative analysis of return to pre morbid roles in an attempt to overcome the varied success of identifying transfer to this level of function cited in the technology based rehabilitation literature (26, 27).

The early work in this area was followed by extensive work across the field. Large systematic reviews and meta-analyses support our assertion that virtual interventions elicit upper extremity function gains as measured by clinical test batteries that are comparable to, or better than traditionally presented interventions in persons with chronic stroke (26, 28). Demonstrating relative equivalence to in-person, physically presented rehabilitation is an important milestone for the field of virtual rehabilitation and a cause for heighteed focus in future studies. Many studies of virtual rehabilitation in persons with stroke are characterized by heterogenous subject pools and vaguely described interventions (29) which could lead to watered down effects and a poor understanding of the active ingredients of virtual interventions (30). Our group has endeavored to build on this initial success by attempting to identify patient populations, treatment settings and training schedules that will leverage virtual rehabilitation's unique strengths.

REHABILITATION EARLY AFTER STROKE

It is important to note that while consistent, measurable and statistically significant, the effect size of the gains demonstrated in studies of any rehabilitation intervention, virtual or otherwise were small and tended not to result in returns to full, pre cerebrovascular accident (CVA) levels of function or participation (31–33). The modest gains achieved by chronic stage upper extremity training and the identification of a critical period of heightened neuroplasticity (10) related to early recovery following a CVA, spurred many groups, including ours, to transition into the study of virtual rehabilitation during the acute and first few weeks of the early subacute stage (34) of recovery from stroke (11, 23, 35–37). Our group, successfully piloted an intervention in a small rehabilitation hospital. This study compared the outcomes of a group of subjects who recieved an in-patient rehabilitation program that started as few as five and as many as 15 days after stroke, with a second group receiving a similar rehabilitation program, supplemented with 8 h of VR based intervention, starting in the first few days after stroke, and a third group, that started the additional VR training between 30 and 90 days after their strokes (38). The safety and feasibility of this intensive training performed during an in-patient rehabilitation hospital stay was readily apparent. There were no adverse events associated with the training and no subjects missed regularly scheduled rehabilitation sessions due to their participation in our study. We found that the subjects performing additional VR based training of the hand in the early subacute phase after stroke demonstrated larger increases in motor performance when this change was normalized for overall recovery (average 6 month improvement in Normalized Box and Blocks Test score of 0.51 SD = 0.32) than subjects that only performed standard rehabilitation (0.43 SD = 0.32) or subjects that performed additional VR based training in the later subacute phase (0.13 SD = 0.10) (35). These findings differed from those summarized in the 2017 meta-analysis by Laver, but it is importatnt to note that Laver analyzed all studies in subjects <6 months post-stroke. This said, the two studies from this metanalysis that focused on the acute and first few weeks of the recovery stage both found non-significant trends favoring VR based interventions (23, 39). Our group has initiated a large scale clinicial trial addressing this topic as well as comparisons with a dose–matched program of traditional rehabilitation and a delayed onset program of virtual rehabilitation (40).

IMPACT OF VR TRAINING ON CORTICAL EXCITATABILITY

In an effort to gain insight into functional/electrophyisological changes made by the recovering brain and the impact of early, hand focused rehabilitation on these changes, we have employed transcranial magnetic stimulation (TMS) mapping in subsets of subjects participating in the pilot study we describe above. The first study compared 7 moderately impaired individuals who received an additional 8 h of VR/robotic intervention within 1 month post-stroke, to 6 similarily impaired individuals who did not receive additional hand focused rehabilitation (41). In both groups, there was an increase in ipsilesional first dorsal interosseous (FDI) map size from pre to post-training, and again from immediately post training to 1 month post-training suggesting that additional VR based hand rehabilitation might have had no impact on this aspect of the recovery process. This said, there was a stronger association between ipsilesional pre to 1 month FDI cortical map representation and long term (pre to 6 months post) improvements in Wolf Motor Function Test (WMFT) scores for the VR group (VR group r $= -0.81$, $p = 0.049$, UC group $r = -0.31$, $p = 0.61$). This may be due to the fact that the VR group, which received additional hand focused therapy in the very early recovery period, may have integrated expansion of the FDI motor map into better hand function. A companion study of 17 individuals who all received an additional 8 h hand focused VR/robotic training initiated within 3 months post lesion demonstrated a similar expansion of FDI area, and similar correlations between expansions in ipsilesional FDI map area and improvements in WMFT score ($r = -0.75$, $p = 0.017$) (42).

This correlation between lesioned hemisphere motor map expansion and hand function improvements following intensive hand training, but not usual care during the early recovery period, has been identified in studies by other labs (43, 44). Two groups using slightly different methods found no training related changes in map area (45, 46). These differing outcomes identified across our clinical, kinematic and neurophysiological studies examining the rehabilitation of persons with chronic stroke and those of our pilot studies of earlier virtual rehabilitation, have led us to initiate a larger study, adding a fourth group of subjects that perform an additional 10 h of traditional rehabilitation in an attempt to control for the timing of hand focused intervention, the dose of rehabilitation intervention, and the additive value of VR virtual reality-based rehabilitation (40).

IDENTIFYING PERSONS LIKELY TO BENEFIT FROM VIRTUAL REHABILITATION

An additional issue related to the early rehabilitation of persons with CVA is the accurate identification of persons that might benefit from the additional hand focused rehabilitation. Rehabilitation prognoses for persons with stroke based on early motor mobility (ability to extend fingers, shoulder abduction) or presence of attention or neglect still fail to predict accurate motor recovery in a high percent of stroke survivors (47, 48). Rohafza et al. identified a multivariate model of four kinematic measures of movement collected in two virtual environments. This model predicted 56% of the variance ($p = 0.042$) in Jebsen Test of Hand Function change as the result of a 2 week training intervention (49). Rohafza et al. developed a similar multivariate model of measures of reach to grasp and object transport trajectory smoothness, hand opening, and trunk movement during a real object interaction test collected at baseline testing. This model predicted change scores in the 12 item Wolf Motor Function Test battery in a group of persons completing a 2 week virtual rehabilitation intervention ($r^2 = 0.74$, $p < 0.05$) (50). The limited motor ability available to people earlier in the recovery process has led us to pursue other means of identifying patients that might benefit (42, 51). TMS-based measures of M1 excitability and electroencephalogram (EEG)-based cortical connectivity measures have shown to be promising biomarkers of recovery after stroke (52). Therefore, our current clinical trial aims to model recovery based on longitudinal measures of cortical excitability, cortical connectivity, and cortico-muscular connectivity (CMC) starting from the acute stage of stroke. Cortical excitability, connectivity, and CMC will be evaluated using measures of (1) motor evoked potential (MEP) – elicited by transcranial magnetic stimulation of the primary motor cortex and recording the response from target muscles, (2) cortical connectivity where EEG signals will be acquired during resting and active finger movement task, and (3) CMC where EEG and electromyographic (EMG) signals are acquired during active finger movement task. The only study we found that looked into changes in EEG activations from acute to chronic phases of stroke and their correlation with functional recovery was in ischemic rats (53). While MEP and cortical connectivity has been explored by other research groups as potential biomarkers of motor recovery (54), CMC during movement is a potential novel biomarker in a clinical setting, and has been explored by Kamp et al. as a marker of aging (55). Measures will be acquired: within 30 days post-stroke, before and after training,1 month post training and 4 and 6 months post-stroke. Data will be modeled to predict the extent of recovery and to understand if training early post stroke improves the prognosis of recovery.

REHABILITATION OF PERSONS WITH SEVERE IMPAIRMENTS

One adavantage afforded by virtual environments is the opportunity to manipulate sensory information (1). These manipuations can be utilized to enhance cortical excitability just prior to or during an activity (12) or to enhance the salience of training activities, maximizing long term neuroplasticity (2). A recent pilot study of ours tested a VR based intervention protocol for persons with severe hemiparesis leveraging some of these opportunities in an attempt to address the needs of this underserved population (56). There have been three studies examining virtual interventions in persons that are slightly less impaired during the chronic stage (Prange, Reinkensmeyer, Housman) Only the study by Housman suggests that virtual interventions might be more effective than traditional interventions. All three of these studies integrated robotic assistance into their interventions, but none utilized mirror priming activities. Our group's intervention included two priming activities. The first was a mirror activity designed to harness action observation networks. We attempted to strengthen the stimuli by allowing the subject to control the virtual image of their paretic hand by moving their non-paretic hand. This paired the image of their moving hand to a conscious intent to move. The second priming activity was movement based. This activity was designed to increase motor cortex excitability by moving the paretic hand passively with a cable actuated exoskeleton in an attempt to harness the impact of kinesthetic information on the lesioned motor cortex. Again we attempted to strengthen this stimuli by pairing it with a virtual image of the moving paretic hand, along with a haptically rendered collision with a ball at the end of the movement. An additional sensor-based pinching activity was also performed. This simulation allowed participants to utilize minimal active movement to perform a meaningful task, enhancing the salience of the intervention which optimized it as a stimuli for long term neuroplasticity. All but 1 of the nine subjects that enrolled in this study were able to control a cursor using a pinch grip measured with a sensitive force transducer. This active rehabilitation exercise was performed well before traditionally presented rehabilitation activities could be performed by these subjects. The group averaged a 30 point increase in Upper Extremity Fugl Meyer (UEFMA) score at 6 months (SD = 12). In addition, three of the seven subjects from this pilot demonstrated a >70% improvement in UEFMA score recovery at 6 months, exceeding the recovery predicted by prognostic algorithms (57, 58).

TMS mapping of a sub-set of patients from this more impaired group showed a different pattern of adaptation than the pattern identified in our less impaired subjects. In the more impaired subjects, extensive damage along the lesioned corticospinal tract made it impossible to elicit lesioned hemisphere motor evoked potentials at the impaired FDI, causing us to focus attention on the relationship between the contralesional motor cortex and the impaired UE. This sub-study showed an increase in the contralesional FDI map representation from pre to post training followed by a decrease from post to 1 month. The increase from pre to post intervention motor map area was associated with pre to 6 month increases in the UEFMA and maximum pinch force scores (56). We identified a similar pattern of increased cortical activation in the contralesional hemisphere during impaired finger movement in more impaired subjects, utilizing functional magnetic resonance imaging (fMRI) measures of cortical activation (51). These results are in line with several published articles highlighting that activity in the contralesional hemisphere is more pronounced in persons with larger lesions and more severe deficits - allowing for recovery in affected upper limb function via uncrossed corticospinal and reticulospinal tracts (59, 60) but diverge from another set of studies that do not demonstrate a relationship between contralesional changes and recovery in severely impaired subjects (61–63). It is important to note that this literature does not consider the impact of rehabilitation on this aspect of the recovery process. In a current clinical trial we are collecting cortical maps of both hemispheres at five points in the recovery process in persons with all levels of impairment (severe, moderate, and mild), that perform a standard rehab program as well as a standard rehab program plus added intensive hand training. We hope that this line of inquiry might help clarify the differing effects of rehabilitation across a wide variety of impairment levels, as this new study will include subjects with more extensive motor impairments than a majority of the major published upper extremity rehabilitation trials (40).

HOME BASED REHABILITATION

We are currently focusing on incorporating our experience with haptics, virtual reality and gaming simulations to create a portable, self-manageable, home-based system, that allows patients to continue their hand and arm rehabilitation by integrating repetitive practice into their daily lives within their home environment. The camera-based system collects finger and arm position at a fidelity and speed that allows HoVRS to utilize real time algorithms to shape desired movement patterns. This high quality data also allows the system to provide kinematic data to therapists on or offline, allowing them to monitor and modify 'patients' rehabilitation programs remotely (64). Recent pilot study subjects demonstrated statistically and clinically significant improvements in hand motor performance as measured by clinical tests [mean UEMA improvement = 4.53 (SD = 2.3), Repeated Measures ANOVA ($p < 0.001$)] (65). They also made statistically significant error reductions during sine wave tracing tasks controlled by hand opening, wrist extension and forearm pronation measured by the home rehabilitation system (64). These outcomes are comparable with other studies of technology supported home based rehabilitation (66–70). Direct (albeit remote) supervision of subjects in these trials varied between very minimal (Standen) to extensive (Holden, Dakodian). We feel that clinically important gains demonstrated by our subjects are an important initial finding, when considering that this group of subjects did not incur transportation costs, required minimal supervision and used equipment that cost a small fraction of the cost of our lab-based system.

OUR TEAM; ONGOING STUDIES

Over the years our group has been a collaboration between biomedical engineers, physical therapists and neuroscientists, all sharing an interest in motor learning and neuroplasticity. Our approach is unique in the participation of all of these disciplines in the earliest stages of intervention technology design. Our main lab, which is housed in an engineering building, is equipped with lab grade kinematic measurement equipment, EEG and TMS equipment, several 3-D printers and a fittings shop. More recently, we have added satellite labs on the campuses of two rehabilitation hospitals. The balance of this paper will present unpublished and synthesized findings from previously published and unpublished studies that all examined virtual rehabilitation simulations in an attempt to present three contrasts: (1) adaptations made by persons with severe impairments Upper Extremity Fugyl Meyer Assessment (UEFMA) <20 and those with moderate to mild impairments (UEFMA 21–60) (2) long term adaptations made by subjects in the early subacute phase of recovery; and finally; (3) adaptations made by patients performing directly supervised interventions using costly facility based equipment with those of subjects using inexpensive equipment, in their homes, independently. Synthesis of these findings provide an overview of the progression of technological interventions for the hemiplegic hand and arm post stroke based on non-immersive virtual rehabilitation and, importantly, may provide a window into the most promising future pathways.

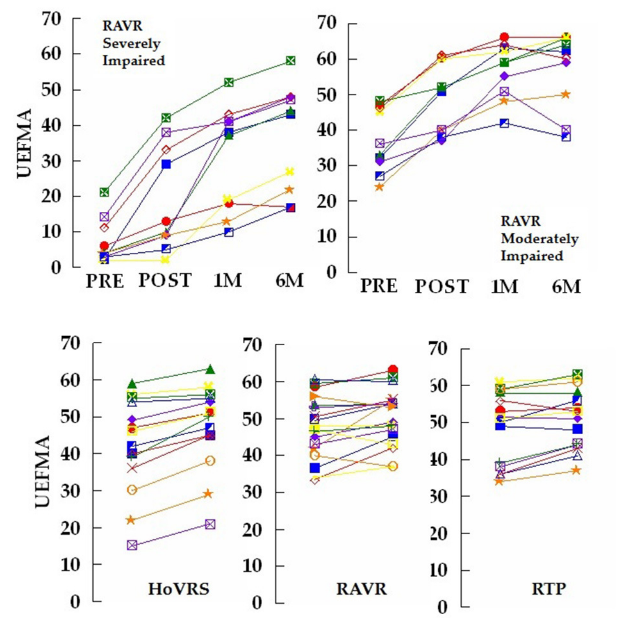

FIGURE 1 | Top left panel: Total UEFMA score for 10 subjects that participated in a 2 week robot assisted virtual rehabilitation (RAVR) training protocol. Measurements taken pre – training and post-training as well as 1, 4, and 6 months post-stroke. These subjects all initiated training <30 days post-stroke and scored <20 on the UEFMA pre-training. Four of the subjects demonstrated an increase from pre to post-test, that exceeds the minimum clinically important difference (MCID) for persons with acute/early subacute stroke of 10 (71). Note the two distinct patterns of response to training and non-response to training at 1 month post-stroke. **Top right panel:** Total UEFMA score for 10 subjects that participated in the same RAVR training protocol. Measurements taken pre – training and post-training as well as 1, 4, and 6 months post-stroke. These subjects all initiated training <30 days post-stroke and scored more than 20 on the UEFMA pre-training. Seven of the subjects demonstrated an increase from pre to post-test, that exceeds the MCID. **Bottom Panel:** Total UEFMA score for 14 subjects that participated in a 12 week home virtual rehabilitation system (HoVRS) training protocol, 10 subjects that participated in a 2 week robot assisted virtual rehabilitation (RAVR) training protocol and 11 subjects that participated in a 2 week repetitive task practice (RTP) protocol. All subjects demonstrated residual impairments from stroke at least 6 months post-stroke and were tested immediately before and after training. Nine of the 14 HoVRS subjects demonstrated improvements that exceeded the MCID of 4.25 (72). Six of 17 RAVR subjects and five of 15 RTP subjects exceeded the MCID. Note the more homogenous improvements demonstrated by the subjects performing HoVRS training. RAVR and RTP subjects were described in detail in Ref. (22).

COMPARING REHABILITATION OF PERSONS WITH SEVERE IMPAIRMENTS AND THOSE WITH MILDER IMPAIRMENTS

Our group has continued its examination of early rehabilitation in more impaired persons. Three additional subjects from our new study of early hand rehabilitation have completed the study through the 6 month data collection point and we have collected a total of 10 subjects with 6 month follow up that were less impaired as well. **Figure 1** depicts the two recovery patterns for each group (unpublished data). Interestingly, the less impaired group shows a relatively consistent pattern of improvement with some ceiling effects and a bit of regression, while the more impaired group demonstrates two patterns. One subgroup makes improvements that exceed 40 points at follow up resulting in recoveries that exceeed overall recovery experienced by less impaired subjects. A second subgroup of more impaired subjects demonstrates more moderate improvement. It is important to note that the initial level of impairment in the more impaired group did not seem to determine which pattern the subjects would follow. Our initial impressions of these new data continue to suggest that some persons with fairly profound hand impairments may have rehabilitation potential that has not been leveraged in protocols examining early technology and traditionally presented UE rehabilitation. We argue that continued study of this population should be a major focus of the study of technology supported rehabilitation. Going forward we plan to explore the use of neuromodulatory techniques in this population. Most recently, our group has explored paired associative stimulation (PAS) which combines simultaneous central (via TMS) and peripheral (via neuromuscular electrical stimulation) stimulation on changes in cortical excitability during virtual mirror activities of the hand (73).

EXAMINING REHABILITATION DURING THE EARLY SUBACUTE PHASES OF RECOVERY

Longitudinal data collected from our pilot subjects in studies of hand-focused, early virtual rehabilitation after stroke suggest that the relative benefits of early intensive rehabilitation might be short - lived. Preliminary results indicate that 1 extra h of upper extremity training delivered by early virtual reality (EVR) ($n = 10$) during the 1 month post-stroke can be beneficial when compared to usual care (UC) ($n = 11$) at 1 month after the end of training, but this advantage seems to disappear at 6 months post-stroke (Unpublished data–See **Figure 2**). These findings align with several other studies of early rehabilitation (23, 36, 37) that do not observe longer term benefits in subjects who performed early rehabilitation of their hands. This said, the results in **Figure 2** are more comparable to other studies of technology supported rehabilitation (74, 75) and a study of Constraint Induced Movement Therapy (20) that identified better outcomes than usual care during this early stage. Continued study of rehabilitation during this period is clearly warranted. Subjects in our ongoing trial of early rehabilitation are stratified by corticospinal tract integrity in an attempt to clarify this issue. We are also working toward evaluating an alternate hypothesis that additional high volume training might be necessary after patients are typically discharged from facility-based rehabilitation to preserve and further increase gains made during additional early training. Our group's home based system will offer an opportunity to study this continuation of the rehabilitation process.

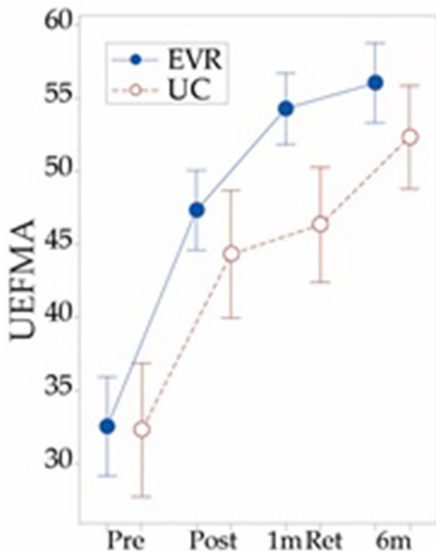

FIGURE 2 | Total UEFMA score for 13 subjects that participated in a 10 session early virtual rehabilitation (EVR) training protocol added to their standard inpatient rehabilitation care, early home or outpatient rehabilitation and 7 subjects that performed usual care (UC) which consisted of standard inpatient rehabilitation care, early home or outpatient rehabilitation only. Both groups demonstrated changes that exceed the minimum detectable change of 5.25 from pre to post-test and from post-test to 6 month retention. Eight of the nine EVR subjects and eight of the 11 UC "subjects" improvements from pre to post-test exceeded the minimum clinically important difference of 10. Measurements taken pre – training and post-training (2–3 weeks after pre test for UC) as well as 1 month post-training and 6 months post-stroke. Note the differences in UEFMA score at 1 month post-training.

COMPARING HOME AND FACILITY BASED REHABILITATION

Our group's study of home based rehabilitation in persons with chronic stroke has demonstrated some interesting new trends. Adherence rates with these subjects has been comparable to other studies of technology supported, home based rehabilitation and better than traditional home based exercise programs in persons with stroke (64, 65). Interestingly, age and previous computer experience did not have an impact on adherence (76), similar to findings of a recent home based rehabilitation study (77). Additionally, our subjects have not demonstrated substantial decreases in compliance over the course of a 12 week intervention program. This diverges with the typical pattern of home exercise adherence which peaks 2 weeks into an intervention and decreases steadily after that point.

Comparing our current, home based virtual rehabilitation system (HoVRS) outcomes with our older work examining therapist supervised lab-based repetitive task practice (RTP) intervention and robot assisted virtual rehabilitation (RAVR), all in persons with chronic stroke offers some insight as well as some considerations for future study. In our 2015 paper comparing a robotically facilitated virtual rehabilitation intervention, to a therapist supervised circuit training intervention of 12 table-top repetitive task practice activities, both groups of subjects demonstrated a mean improvement of 2 points on the UEFMA. Both groups demonstrated inconsistent change patterns with some subjects improving, some staying the same and others regressing (22). This pattern differs from that of our home based subjects who demonstrated across the board improvement from pre to post-test with a mean improvement of more than 5 points (Unpublished data–See **Figure 1**).

The training schedules for these two interventions differed. The two lab based interventions were delivered in a 2 week period with 8, 3 h sessions. Our home based subjects averaged less therapy, closer to 18 total h, but the intervention occurred over 12 weeks. It is possible that a training schedule that distributes training time across a greater time period may be more conducive to motor improvements than a concentrated schedule with a larger volume of training. More rigorous testing will be required to determine if one approach to treatment or treatment schedule was definitively better. This said, the possibility that subjects using inexpensive equipment, in their homes, independently, might make similar to or better gains, than patients performing directly supervised interventions using costly equipment will have important implications for patient access to treatment and the cost of health care delivery. Additional further study will examine the feasibility of adding movement based priming to our home based interventions. Proof of concept testing of a low cost, admittance controlled finger training robot, that will utilize the same platform that presents our home based VR intervention is in progress (78).

CONCLUSIONS

The anatomical and physiological heterogeneity of strokes and persons with stroke, along with the complexity of normal upper extremity movement make the possibility that any single treatment approach will become the definitive solution for all persons with upper extremity hemiparesis due to stroke unlikely. This situation and the non-inferiority level outcomes identified by many studies of virtual rehabilitation are considered by some to indicate that it is time to consider other treatment modalities. Data generated by our lab and others suggesting that (1) persons with stroke may adapt to virtual rehabilitation of hand function differently based on their level of impairment and stage of recovery and (2) that less expensive, more accessible home based equipment seems to be an effective alternative to clinic based treatment that justifies continued optimism and study.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Internal Review Board, Rutgers The State University of New Jersey. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

FUNDING

The lines of inquiry described in this submission have been supported by the NIH/NICHD grants R01HD058301 (Principal Investigators: SA and AMo) and R15HD095403 (Principal Investigator: GF) and the NIDILRR funded Rehabilitation Engineering Research Center grant # 90RE5021 (Director: SA). Open access publishing fees paid by NICHD grant R15HD095403.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2021.623261/full#supplementary-material

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Conflict of Interest: GF, QQ, AMo, AC, AMe, and SA have applied for a patent for the Home Virtual Rehabilitation System. QQ, AMo, and AC have interests in NeuroTech3R, a company working toward bringing the Home Virtual Rehabilitation System to market.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Neurology

ORIGINAL RESEARCH
published: 02 March 2021
doi: 10.3389/fneur.2021.582611

Exploring the Relationship Between Sleep Quality, Sleep-Related Biomarkers, and Motor Skill Acquisition Using Virtual Reality in People With Parkinson's Disease: A Pilot Study

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OPEN ACCESS

Edited by:
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Reviewed by:
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Specialty section:
This article was submitted to Neurorehabilitation, a section of the journal Frontiers in Neurology

Received: *12 July 2020*
Accepted: *20 January 2021*
Published: *02 March 2021*

Citation:
Al-Sharman A, Ismaiel IA, Khalil H and El-Salem K (2021) Exploring the Relationship Between Sleep Quality, Sleep-Related Biomarkers, and Motor Skill Acquisition Using Virtual Reality in People With Parkinson's Disease: A Pilot Study. Front. Neurol. 12:582611. doi: 10.3389/fneur.2021.582611

Background and Objectives: Despite the fact that sleep disturbances are among the most common and disabling manifestations of Parkinson's disease (PD), no study has investigated the effect of sleep quality and sleep-related biomarkers on motor skill acquisition in people with Parkinson's disease (PwPD).

Objective: To examine the relationship between skill acquisition, sleep quality, and sleep-related biomarkers in PwPD using virtual reality (VR) system.

Methods: This is a cross sectional study conducted on 31 PwPD and 31 healthy controls. To assess skill acquisition, each participant practiced a VR game 6 times (blocks). The main outcomes from the VR game were the required time to complete the VR game and the recorded errors. Motor skill acquisition was calculated as the difference of scores between block 6 and block 2 for both outcomes. Sleep was assessed subjectively using Pittsburgh Sleep Quality Index (PSQI) and objectively using the Actisleep. To assess sleep related biomarker, plasma serotonin level was examined.

Results: PwPD and healthy controls demonstrated a practice-related improvement in performance as shown by the main effect of block for each of the VR outcome measures ($p < 0.000$, time required to complete VR game; $p < 0.000$, recorded errors). There was no interaction effect between Block X Group for both outcome measures. There were significant correlations in both groups ($p < 0.05$) between motor skill acquisition (as indicated by the difference of time required to complete the VR game between block 6 and block 2) and PSQI total score, wake after sleep onset, and sleep efficiency. Additionally, a significant correlation was observed in both groups between motor skill acquisition (as indicated by the difference of time required to complete the VR game between block 6 and block 2) and the plasma serotonin level ($p < 0.05$). These correlations in PwPD remained significant, even after adjusting for disease motor severity, cognitive status, depression, and daily dose of L-dopa.

Discussion and Conclusions: Sleep quality may influence motor skill acquisition in PwPD. Healthcare professionals are encouraged to be aware about sleep quality and sleep assessment tools. Therapies may target improving sleep quality which could result in improving motor skill acquisition.

Keywords: Parkinson's disease, motor learning, sleep, rehabilitation, virtual reality

INTRODUCTION

The loss of dopaminergic cells in Parkinson's disease (PD) causes the cardinal motor symptoms of PD and contributes to non-motor symptoms, including autonomic dysfunction, cognitive impairments, and sleep disturbances (1, 2). Currently pharmacological and surgical treatment options are not always effective in managing common motor and non-motor symptoms associated with PD (3, 4). Non-pharmacological rehabilitation treatment options such as physical therapy showed effectiveness and are considered to be important in the journey of managing People with Parkinson's disease (PwPD) (5). Physical therapists play a major role in rehabilitating PwPD by planning activity-focused interventions which emphasize the need for practice and repetition of purposeful motor actions in challenging environments. However, research has indicated that PD would lead to degradation of motor skill learning (6). Therefore, PwPD often have difficulty acquiring and learning new motor tasks affecting therapy outcomes (7, 8). Specifically, studies have demonstrated that different aspects of motor skill learning (i.e., skill acquisition, consolidation, retention, and transfer) are more impacted among PwPD compared to healthy individuals (8).

Overall, the etiology underlying the deficits in motor skill learning in PD is not very clear. However, it is likely to be multi-factorial. For example, the impairments in basal ganglia and reduced dopaminergic neurotransmitter can be a main cause (9). Degeneration in striatum has been linked to deficits in learning motor sequences in PD particularly the consolidation phase (10). Studies have also reported a number of factors related to PD that might have a major impact on motor skill learning such as severity and disease duration (6, 11). In addition, non-motor symptoms including cognitive deficits have been found to affect motor skill learning in PwPD (12).

Recently, there is a growing attention toward the role of sleep on motor skill learning. Sleep may impact each stage of motor skill learning. Good sleep quality was found to enhance the consolidation phase of motor skill learning offline (i.e., when no practice is occurring; "sleep-dependent off-line motor learning") across a wide range of motor tasks in healthy adults as well as in some neurological conditions such as stroke (13). After a night of 8 h sleep, performance on simple motor tasks improved in comparison to same time wakefulness (14). Furthermore, few recent studies found that lower levels of sleep quality before learning the motor task, negatively impacted motor skill acquisition in young healthy adults (14) and in people with sleep disorders (15).

Around more than 3 quarters of PwPD have sleep disorders (16). Excessive daytime sleepiness, REM sleep behavior disorder, and fragmented sleep are frequently reported in this population (17). As yet, there is little knowledge about the role of sleep on motor skill learning in PwPD (18). Terpening et al. (18) demonstrated that sleep is important in the consolidation phase of motor learning. However, this later study did not examine the effect of sleep quality on motor skill acquisition in PwPD. In motor skill learning, successful acquisition results in attaining a certain level of task ability which leads to rapid formation of a memory representation within the brain. Generally, task-related activations in a motor-related network during the initial learning session predicted subsequent consolidation changes in motor behavior (19). Therefore, motor skill acquisition is important stage of motor skill learning and further investigations to understand the impact of sleep on motor skill acquisition in PwPD is warranted.

When assessing motor learning in general, it is important to consider the task under investigation. For example, the study by Terpening et al. (18) used a simple motor task (i.e., finger tapping) to understand motor skill learning in PwPD. However, most daily tasks are more functional and complex. A review by Wulf and Shea (20) state that learning complex motor tasks requires high motor demands, fast reaction to environmental stimuli, and different body parts coordination. Therefore, there is a need to understand motor skill acquisition in PwPD using complex tasks that are functional and simulate tasks similar to real life and rehabilitation settings.

Another aspect of sleep quality that might affect motor skill learning is the role of the hormone serotonin on motor skill acquisition. Previous studies showed low levels of serotonin transporter in parkinsonism within the striatal area (21) and that up to 50% of PwPD have decreased levels of serotonin (22). A recent investigation found significant correlation between reduction of serotonin in midbrain, basal ganglia and hypothalamus, and sleep disturbances in PwPD (23). Furthermore, acute increases in serotonergic transmission could influence skill acquisition during motor learning (24). Therefore, the aims of this study were to: (1) examine motor skill acquisition in PwPD compared to age and gender matched healthy controls using a functional motor task similar to real life, (2) examine the relationship between motor skill acquisition and sleep quality in PwPD, and (3) examine the relationship between plasma serotonin level and motor skill acquisition in PwPD.

MATERIALS AND METHODS

Study Design and Participants

This cross-sectional study was designed to examine motor skill acquisition in PwPD compared to age and gender matched healthy controls using a functional motor task and also to examine the relationship between sleep quality, sleep-related biomarker, and motor skill acquisition in PwPD. Thirty-one PD participants and 31 age and gender matched healthy controls were recruited into the study. PD participants were recruited from King Abdulla University Hospital (KAUH) and additionally from a research database of Jordan University of Science and Technology (JUST). PwPD were screened for eligibility by a neurology consultant at KAUH; who is responsible for their care. Eligible subjects were invited to participate in the study. Inclusion criteria were: (1) a neurologist-confirmed diagnosis of idiopathic PD, (2) capacity to give informed consent, (3) modified Hoehn and Yahr Stage 1–4 during the "ON stage" of medication, (4) maintaining a stable medical regime for 3 weeks prior to initiation of study, and (5) a participant, who had no experience with the motor task implied in this study but still physically able to perform it without physical assistance. Exclusion criteria were: (1) presence of additional neurological disorders that may affect balance and gait (e.g., head injury, stroke, vestibular dysfunction, or peripheral neuropathy), and (2) the presence of severe cognitive deficits or behavioral disorders preventing safe participation.

Healthy controls were recruited from local community and friends of people with PD introduced to us by the patient. Inclusion criteria of the healthy-control participants included: (1) age and gender matched individuals, (2) being functionally independent. Participants were excluded if they had reported (3) untreated sleep disorders, including sleep apnea (4) a history of neurological disorders; and any orthopedic problems or mobility deficits that prevented them from performing the study task (5) taking any medications that may affect sleep and serotonin level.

Participants gave a written informed consent approved from the Institutional Research Committees of Jordan University of Science and Technology (ID: JUST-AA-2018-525).

Study Procedure

Each participant was asked to visit the physical therapy laboratory at Jordan Science and Technology University (JUST) for a single assessment session. At the beginning of the session, blood samples were collected from the participants and stored for later analysis for determining the plasma serotonin levels. In order to eliminate the possible effect of dopaminergic medication on the plasma serotonin levels, fasting blood samples were taken in the early morning (i.e., at 8:00 A.M. $\pm$1 h) after overnight withdrawal of the medication (during the "OFF" phase). Following this, participants took their regularly scheduled morning dose of medication and were provided with a resting period until they were notably on their "ON" stage in which assessments for motor skill acquisition, subjective sleep quality, and cognitive status were undertaken. Collection of basic personal and demographic information such as age, gender, daily use of L-dopa, and disease severity were also obtained from each participant. A sub sample of the PD participants ($n = 22$) were asked to wear an Actisleep (ActiGraph; Pensacola, FL) device a week before the testing session to objectively asses sleep quality (see details below).

FIGURE 1 | Sit to stand game through virtual reality.

Motor Task Description

To assess motor skill acquisition, participants were asked to perform a novel virtual reality (VR) game during their "ON" stage. The novel VR game was developed as part of a previously conducted study (25) and has been validated as an assessment and treatment tool (26). The VR game is part of a non-immersive VR system developed by our research team, which consists of the Microsoft Kinect sensor, large standard LCD monitor, and its software on a research laptop device. Details are published elsewhere (25). In brief, in the VR game, participants were asked to steer a helicopter up and down to collect coins and to avoid specific number of obstacles by moving from chair (the chair is without arm) from sitting to standing and vice versa (**Figure 1**). The aim of the game is to collect as many coins as possible while avoiding specific number of obstacles at the same time by performing the sit to stand movement. The numbers of missing coins (recorded errors) and the time that required to go through the obstacles by the participants determined the game score which was given by the system itself.

Each participant performed VR game for 6 times (blocks) during the session. In order to familiarize the participants with the game, the first block was performed and discarded from analysis. To prevent fatigue, participants were allowed to rest between blocks if needed (in sitting position). In this study, required time to complete the game and errors were recorded from the virtual game for each block performed by the participants. Difference of scores between block 6 and block 2 for both outcomes (i.e., time to complete the block and recorded errors) were considered to represent motor skill acquisition and training-related gains in performance.

Sleep Quality Measures

The Arabic version of the Pittsburgh Sleep Quality Index (PSQI) was used to subjectively assess sleep quality (27). The PSQI is a well-validated and reliable measure of sleep quality which consists of 19 self-rated questions forming a global score ranging from 0 to 21 (28). A global score of 5 or more reflects poor sleep quality for all age groups (28). The PSQI as a generic measure of sleep quality was commonly used in PwPD (29).

To objectively assess sleep quality, we utilized the Actisleep. Only a sub-sample of PD participants ($n = 22$) wore the Actisleep due to the limited number of Actisleep devices available for this study and the limited time allowed to complete this study. Participants were asked to wear an Actisleep (Actigraph wGT3X-BT, Pensacola, Florida, USA) device for 7 consecutive nights until the day the participants came in for the motor skill acquisition testing session. Participants were asked to wear the Actisleep around the non-dominant wrists while maintaining normal lifestyle, especially sleeping habits. Actisleep (30) is a tri-axial accelerometer developed to measure sleep/wake positions in which the following sleep parameters were calculated: sleep efficiency (SE; number of sleep minutes divided by the total minutes the subject was in bed), and wake after sleep onset (WASO; time of wake in minutes after sleep onset). Actisleep was found to be a valid and reliable device for sleep measurement among healthy young adults (31). The clinical utility for using the Actisleep with PD individuals has been proven in several studies (32). Actisleep signals were sampled at 30 Hz. Data from Actisleep was analyzed using Actilife software (ActiGraph; Pensacola, FL) (31).

Other Outcome Measures

To account for confounding variables; data regarding disease motor severity, cognitive status, depression, and anxiety of the participants were recorded. Disease motor severity was assessed using the Movement Disorder Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS)-Part III (33), as well as the Hoehn-Yahr staging system (34). Cognitive status of the participants was evaluated using the Arabic version of the Montreal Cognitive Assessment (MOCA) (35); the total score of the MOCA was used in the analysis. The Arabic version of the Hospital Anxiety and Depression Scale (HADS) was used to evaluate the level depression (36, 37). L-dopa daily dose as well as personal data including age and gender were also collected. All data was recorded in the morning during the "ON" state.

Sleep Related Biomarkers

Fasting blood samples were collected for measurement of plasma serotonin from the PD participants at 8:00 A.M. ±1 h. Plasma serotonin level was examined using the sandwich enzyme-sorbent assay technology (38). After blood collection, all blood samples were centrifuged at 1,500 × g for 15 min in order to collect plasma. Following this, plasma was stored at −80°C until used. A competitive Serotonin/5 hydroxytryptamine (5-HT) ELIZA kits for quantitative analysis of total plasma of serotonin was used (abx257126). All assays were performed according to the instructions provided by the manufacturer Abbexa, Cabridge, UK.

Statistical Analysis

Statistical analyses were performed with Statistical Package for the Social Sciences software (SPSS 20.00). Independent-sample t-tests were used to assess differences in participants' characteristics between groups. Also, independent- sample t-tests were used to assess the differences between participants who wore the Actisleep and those who did not wear it considering the characteristics that might affect the results including the severity of motor symptoms (represented by the MDS-UPDRS Part III) and age. Performance through blocks was examined using a two-factor [Group (PD, healthy control) × Block (2, 3, 4, 5, 6)] repeated measures ANOVAs with time to complete VR game and number of errors recorded were considered the dependent variables. *Post-hoc* analysis was conducted using LSD for multiple comparison between blocks. In all comparisons, significance level was set at 0.05.

Motor skill acquisition was calculated as the differences in performance between Block 6 and Block 2 for time to complete VR game and recorded errors. The associations between subjective and objective sleep measures, sleep biomarker and motor skill acquisition were assessed for both groups using Pearson correlation coefficient (r). In general, $r > 0.50$ indicates large correlation, 0.31–0.49 indicates moderate correlation, and <0.30 indicates poor correlation (39). To account for confounding factors including the severity of motor symptoms (represented by the MDS-UPDRS Part III), the cognitive level of the participants (represented by the MOCA total score), and depression (represented by HADS depression score) and the daily dose of L-dopa, the relationship between sleep measures, sleep biomarker, and motor skill acquisition was examined using partial correlation analysis.

RESULTS

Subject Characteristics

Table 1 demonstrates the demographic and clinical data for both groups (i.e., PwPD and healthy controls). There were no significant differences between groups in term of age ($p = 0.09$) and HADS depression ($p = 0.19$). Significant differences between groups were observed in the PSQI ($p = 0.04$), MOCA ($p < 0.001$), and plasma serotonin level ($p = 0.01$). There were no significant differences in age and MDS-UPDRS Part III between participants who wore the Actisleep and those who did not wear it ($p > 0.05$).

Motor Skill Performance

The participants in both groups demonstrated a practice-related improvement in performance, as shown by the main effect of block for each of the outcome measures ($p < 0.000$, time required to complete VR game; $p < 0.000$, errors recorded) (**Figures 2**, **3**). The extent of improvement in performance across blocks revealed significant differences between PwPD and healthy control in motor skill acquisition as indicated by the main effect of group for time required to complete VR game ($p = 0.04$) and errors recorded ($p = 0.01$). There was no interaction effect between Block X Group for both outcome measures (time to complete VR game $p = 0.31$; errors recorded, $p = 0.42$).

Correlations Between Motor Skill Acquisition, Serotonin, and Sleep Measures

Quality of sleep, as indicated by PSQI, was significantly associated with plasma serotonin level for both groups ($r = -0.519$, $p =$

TABLE 1 | Demographic and clinical data of participants in both groups.

Parameters	*N*	PwPD			Healthy controls		*P*-value (between groups)
	N	Mean	SD	N	Mean	SD	
Gender (F/M)	31	10/21	–	31	10/21	–	–
Age (years)	31	61.06	7.66		57.42	8.98	0.09
MOCA total score (unit)	31	19.89	4.22	31	22.97	3.5	<0.001
HADS Depression	31	7.6	6.1	31	5.7	4.2	0.19
PSQI total score (unit)	31	8.48	4.03	31	5.32	3.32	0.04
		PSQI < 5: (21) PSQI > 5: (10)			PSQI < 5: (16) PSQI > 5: (16)		
WASO	22	15.48	10.75	–	–	–	–
Sleep efficiency (%)	22	69.20	19.66	–	–	–	–
Plasma serotonin level (pg/ml)	31	119.6	24.63	31	177.47	22.7	0.01
MDS-UPDRS- Part III (unit)	31	36.66	12.67	–	–	–	–
Hoehn & Yahr (HY) (unit)	31						
	5	Stage 1		–	–	–	–
	16	Stage 2					
	9	Stage 3					
	1	Stage 4					
Daily dose of L-dopa	31	698.2	262.02	–	–	–	–

MOCA, Montréal Cognitive Assessment; HADS, Hospital Anxiety and Depression Scale; PSQI, Pittsburgh Sleep Quality Index; WASO, Average awaking time after sleep onset (min) deriving from Actisleep. Sleep efficiency, number of sleep minutes divided by the total minutes the subject was in bed deriving from Actisleep. MDS-UPDRS, Movement Disorder Society-Unified Parkinson's Disease Rating Scale.

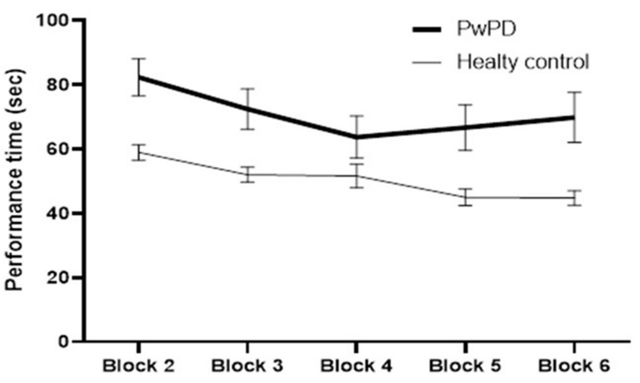

FIGURE 2 | Practice-related improvement in performance (time required to complete the VR game in seconds) across blocks in PwPD and healthy controls. *Post-hoc* analysis indicated significant difference between Block 6 and Block 2 in both groups. In healthy controls, significant differences were also found between (Block 2 and Block 3) and between (Block 4 and Block 5). In PwPD, significant differences were also found between (Block 2 and Block 3) and between (Block 3 and Block 4).

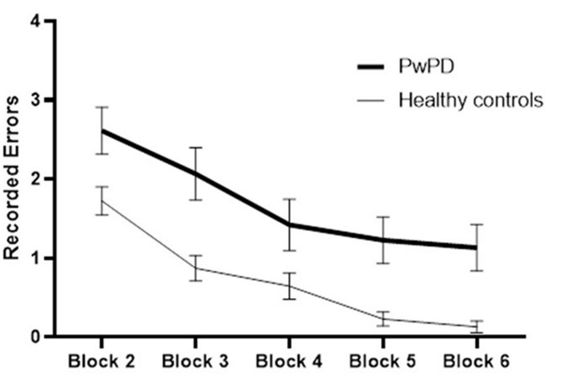

FIGURE 3 | Practice-related improvement in performance (recorded errors) across blocks in PwPD and healthy controls. *Post-hoc* analysis indicated significant difference between Block 6 and Block 2 in both groups. In healthy controls, significant differences were also found between (Block 2 and Block 3) and between (Block 3 and Block 4). In PwPD, significant differences were also found between (Block 4 and Block 5), between (Block 3 and Block 4), and between (Block 3 and Block 4).

0.003, for healthy controls; $r = -0.48$, $p = 0.006$, for PwPD). Poor quality of sleep was significantly associated with lower plasma serotonin level in both groups.

Table 2 summarizes the differences between Block 6 and 2 for both outcome measures (time required to complete VR game and recorded errors) which represent motor skill acquisition for PwPD and healthy control. Also **Table 2** presents the results of *post-hoc* analysis between Block 2 and Block 6. The results indicate significant performance changes between blocks 2 and block 6 in healthy controls and PwPD in both outcome measures.

Table 3 summarizes the relationship between motor skill acquisition, sleep quality measures, and plasma serotonin in PwPD and healthy controls. In healthy controls, there was significant correlation between motor skill acquisition (as indicated by the difference of time required to complete the

TABLE 2 | Motor skill acquisition in PwPD and healthy controls and *Post-hoc* analysis (Pairwise comparison) between Block 2 and Block 6.

Outcome measures	PwPD				Healthy controls			
	Block 2	Block 6	Motor skill acquisition	Pairwise comparison Sig.	Block 2	Block 6	Motor skill acquisition	Pairwise comparison Sig.
Performance time	83.33 (32.16)	68.82 (43.2)	−12.5 (35.6)	$p = 0.001$	58.9 (13.3)	44.8 (12.6)	−14.18 (18.2)	$p = 0.05$
Recorded Errors	2.61 (1.7)	1.13 (1.6)	−1.48 (1.7)	$p < 0.001$	1.72 (0.9)	0.13 (0.4)	−1.6 (1.0)	$p < 0.001$

Motor skill acquisition was calculated as the differences between Block 6 from Block 2 for both outcome measures. Negative motor skill acquisition for recorded errors and performance time in both groups indicate better performance in Block 6 in relative to Block 2.

TABLE 3 | Correlations between motor skill acquisitions and sleep quality measures.in the PD and healthy control participants.

Sleep quality measures	PwPD		Healthy control	
	Performance time	Error recorded	Performance time	Error recorded
PSQI total score	$r = 0.64$ $p = 0.0001$	$r = 0.06$ $p = 0.74$	$r = 0.71$ $p < 0.001$	$r = 0.17$ $p = 0.36$
Sleep efficiency	$r = -0.66$ $p = 0.001$	$r = -0.13$ p =0 0.54	——————	——————
WASO	$r = 0.66$ $p = 0.001$	$r = 0.25$ $p = 0.27$	——————	——————
Serotonin level	$r = -0.48$ $p = 0.006$	$r = -0.15$ $p = 0.42$	$r = -0.63$ p = <0.001	$r = -0.11$ $p = 0.56$

Performance time represents motor skill acquisition outcome which is calculated as the change in the time required to complete the VR task between block 6 and 2. Recorded error represents motor skill acquisition outcome which is calculated as the difference in the error recorded during the VR task between block 6 and 2. PSQI, Pittsburg Sleep Quality Index; WASO, Average awaking time after sleep onset (min) deriving from Actisleep. Sleep efficiency: number of sleep minutes divided by the total minutes the subject was in bed deriving from Actisleep.

VR game between block 6 and block 2) and PSQI total score. Additionally, a significant correlation was observed between motor skill acquisition (as indicated by the difference of time required to complete the VR game between block 6 and block 2) and the plasma serotonin level ($p < 0.05$). These correlations between motor skill acquisition, PSQI total score, and plasma serotonin level in healthy controls remained significant, even after adjusting for cognitive status and depression (**Table 4**).

For PwPD, there were significant correlations ($p < 0.05$) between motor skill acquisition (as indicated by the difference of time required to complete the VR game between block 6 and block 2) and PSQI total score, wake after sleep onset in minutes (WASO; i.e., the total amount of time the participants spent awake after falling asleep), and sleep efficiency. Additionally, a significant correlation was observed between motor skill acquisition (as indicated by the difference of time required to complete the VR game between block 6 and block 2) and the plasma serotonin level ($p < 0.05$) (**Table 3**). These correlations between motor skill acquisition and plasma serotonin level, PSQI total score, average awaking time, and sleep efficiency in the PD participants remained significant, even after adjusting for disease motor severity, cognitive status, and daily dose of L-dopa (**Table 5**).

On the other hand, no significant correlations were noted between the motor skill acquisition as indicated by recorded errors and any of the sleep quality measures nor the plasma serotonin level in both groups.

TABLE 4 | Partial correlation in healthy controls between motor skill acquisition outcomes and sleep quality measures and plasma levels of serotonin controlling cognitive status and depression level.

		Plasma serotonin level	PSQI total score
Performance time	Correlation coefficient	−0.62	0.72
	P-value	0.02	0.03
Recorded error	Correlation coefficient	0.15	025
	P-value	0.48	0.26

Control variables, Montréal Cognitive Assessment (MOCA) total score and Hospital Anxiety and Depression Scale. Performance time represents motor skill acquisition outcome which is calculated as the change in the time required to complete the VR task between block 6 and 2. Recorded error represents motor skill acquisition outcome which is calculated as the difference in the error recorded during the VR task between block 6 and 2. PSQI, Pittsburg Sleep Quality Index.

TABLE 5 | Partial correlation in PD participants between motor skill acquisition outcomes and sleep quality measures and plasma levels of serotonin controlling for disease motor severity, cognitive status, daily dose of L-dopa, and depression level.

		Plasma serotonin level	PSQI total score	Sleep efficiency	Avg. wakening time after sleep onset
Performance time	Correlation coefficient	−0.59	0.66	−0.55	0.62
	P-value	0.04	0.01	0.05	0.02
Recorded error	Correlation coefficient	−0.44	−0.08	0.1	0.3
	P-value	0.1	0.8	0.8	0.3

Control variables: Movement Disorders Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Part III, Montréal Cognitive Assessment (MOCA) total score, Hospital Anxiety and Depression Scale and daily dose of L-dopa. Performance time represents motor skill acquisition outcome which is calculated as the change in the time required to complete the VR task between block 6 and 2. Recorded error represents motor skill acquisition outcome which is calculated as the difference in the error recorded during the VR task between block 6 and 2. PSQI, Pittsburg Sleep Quality Index.

DISCUSSION

To our knowledge, this is the first study to investigate the relationship between subjective and objective sleep quality measures and motor skill acquisition in PwPD. What further makes this study important, is the novel investigation of the relationship between a sleep-related biomarker (i.e., serotonin) and motor skill acquisition in PwPD. The results demonstrated significant associations between subjective (PSQI) and objective (Actisleep measures) sleep measures and the acquisition of the VR game even after controlling for the L-dopa use, disease motor severity and cognitive status. Furthermore, we found that lower plasma serotonin level is significantly associated with poor sleep quality measures and more importantly with decreased motor skill acquisition in our cohort. Also, similar findings were found among healthy controls, in which subjective sleep quality and plasma serotonin levels were significantly associated with motor skill acquisition in this group.

The results of this study have demonstrated that the potential to improve performance of a new motor skill is preserved in PwPD. Understanding improvement in motor performance in PwPD has important practical implications for rehabilitation because the acquisition and reacquisition of motor skills are important parts of motor learning of functional tasks. Importantly, the findings indicated significant associations between subjective and objective sleep measures and the acquisition of the VR game in PwPD and healthy control participants. These findings suggest that impact of sleep quality on motor learning is not limited to simple motor tasks but also extends to a functional motor task that is complex and has direct implications for physical therapists. Although most previous studies that assessed the effect of sleep on motor skill learning utilized simple tasks that focus on fine motor skills (13), evidence suggests that research findings on simple motor tasks cannot be generalized to gross and more complex motor skills (20). This is evident by studies that found the effect of sleep on motor skill learning differs with task complexity (40). In this current study, participants practiced a novel functional motor task that is similar to daily activities and is often practiced in a rehabilitation setting. The VR game utilized in the current study needs gross movements. Gross motor movements require larger body segments involvement and require more complex muscle synergies (41). Therefore, these findings further shed the light on the relationship between sleep quality and performance on functional complex tasks that resembles every day activities in PwPD, and the possible impact sleep quality has on motor learning approaches commonly utilized by physical therapists in rehabilitation settings.

Previous studies reported a number of factors that might have a major impact on motor skill learning in PwPD including disease severity and duration (6, 11), and cognitive deficits (12). Our results extend this earlier research by demonstrating that individuals' sleep quality also impacts subsequent motor skill acquisition in PwPD. The findings of the current study are in line with previously published papers which indicates sleep is an important factor in motor skill acquisition in young healthy adults (42) and in people with obstructive sleep apnea (OSA) (15). Appleman et al. (14) suggested that sleep quality, assessed by actigraphy and quantified as time awake after sleep onset, is associated with subsequent motor skill acquisition. Besides, in extension to previous work investigated the importance of sleep for off-line motor learning and memory consolidation in PwPD (18), the current study found that sleep quality is also important in the online motor acquisition which is considered a very important step for motor memory formation. Bradley et al. (19) found that during the initial learning session of the motor task, the activations in a motor-related network, including the cerebellum, putamen, pallidum, and parietal cortex, forecasted subsequent offline changes in behavior. This suggests that sufficient activation in a motor-related network during motor skill acquisition is necessary to trigger sleep-facilitated consolidation in this population. Therefore, understanding factors that influence motor skill acquisition in PwPD is very important.

The current study demonstrated significant correlations between overall sleep quality as measured subjectively by PSQI and motor skill acquisition. These findings are considered important considering that PwPD have reduced sleep quality. According to PSQI scores, both groups in this study have reduced sleep quality, however, there was a significant difference in the average score of PQSI between PwPD and healthy controls. 68.1% of the PD were poor sleepers compared to 48% in the healthy control participants. These results are consistent and comparable with previous studies, which found reduced sleep quality in PwPD (16). Havlikova et al. (43) found that 73.1% of PwPD were poor sleepers during the nighttime, and the study of Menza et al. (44) demonstrated that sleep problems were very common in PD, affecting about three quarters of these individuals. In addition, the results of this current study support the age-related changes in sleep quality as around half of the healthy control participants were poor sleepers (45–47).

The current study demonstrated significant correlations between objective sleep measures (sleep efficiency and WASO) and motor skill acquisition in PwPD. Studies have confirmed the importance of having a certain amount of sleep continuity (i.e., undisrupted sleep) for motor skill learning (46). Sleep efficiency and WASO are considered important parameters of undisrupted sleep and can detect poor sleep quality especially for those suffering from insomnia (48). Improvement in sleep efficiency has become a gold standard for evaluating insomnia treatment efficacy, sleep restriction therapy (SRT), and cognitive behavioral therapy (CBT) (48). The findings expanded the previous work of Al-Sharman et al. (46) who demonstrated that continuous periods of sleep as indicated by sleep efficiency and WASO are important factors to ensure optimal sleep-dependent consolidation of a functional motor task in young healthy individuals. Also, these findings are in line with Appleman et al. (14) who indicated that WASO, significantly influenced subsequent motor skill acquisition in young healthy individuals.

In line with previous studies among PwPD and other neurological populations, the plasma serotonin levels in the current study were significantly correlated with sleep quality as measured by PSQI in PwPD. Importantly, this is the first study to examine the association between motor skill acquisition and plasma serotonin level. The findings suggest that serotonin level is significantly related to motor skill acquisition. Higher serotonin indicates better motor acquisition, since the time to complete the VR game was lower in participants with higher serotonin level. Studies reported that serotonin plays an important role in fundamental learning mechanisms and in neuroplasticity, referring that to its location in midline raphe nuclei of the brainstem and its role in regulating numerous basic functions which require energy or conserve energy (49). Furthermore, studies have confirmed the role of serotonin on the wake-sleep cycle. Several studies have indicated that serotonergic dysfunction in PwPD is associated with the development of non-motor symptoms including sleep disturbances (50). Thus, this might explain the mechanism behind this relationship (51). Interventions that might help to improve sleep quality and serotonin level might improve motor skill acquisition in PwPD. Aerobic exercise was found to improve serotonin level, and subsequently reduce pain in people with fibromyalgia (52). In multiple sclerosis, a recent study found that aerobic exercise improves sleep quality and that improvement was associated with improvements of the serotonin level (53).

This study is not without limitations. This study was performed without initial power calculations for the sample size, and accordingly the current study findings need to be interpreted cautiously. However, it should be noted that this is a pilot cross-sectional observational study. Overall, in this study, the power was found to be 97% for a sample size of 31 at a level of significance of 0.05 using the correlation coefficient with the PSQI score. Also, the power was found to be 80% for the sample size of 31 at a level of significance of 0.05 using the correlation coefficient with the plasma serotonin level. PwPD participated in this study were moderately affected by the disease [HY mean (SD) = 2.2 (0.74) units]. Replicating this study in a large cohort across the continuum of the disease is warranted. Furthermore, regarding sleep assessment, we used the subjective (PSQI), and objective (the Actisleep) to assess sleep. Both assessments are not designed to capture sleep architecture. Therefore, we cannot determine which sleep stages are associated with motor skill acquisition. Future studies are needed to use higher resolution methodologies such as polysomnography. Also, due to the limited number of Actisleep devices available in this study, only 22 PwPD wore the Actigraph which limits the interpretation of the results. These findings, however, may set the basis for future studies in this area. We assessed only serotonin as a sleep related biomarker. There are other sleep related biomarkers such as melatonin and cortisol that might affect motor skill acquisition. Future studies are required to assess these biomarkers.

The results reported here are of clinical importance considering the high prevalence of sleep disturbances in PwPD. We believe it is important to provide health care professionals mainly physical therapists with recommendations to consider sleep as an important factor affecting motor skill acquisition. It is possible to improve clinical outcomes of rehabilitation by improving sleep quality. In clinical settings, sleep assessment is not considered as a major part of a physical therapists' evaluation. However, due to the important role of sleep on learning and memory, we believe that Sleep assessment should be considered as a major part of a physical therapists' evaluation which might allow clinicians to more effectively individualize interventions to fit specific patients' characteristic to achieve maximum level of motor acquisition. In addition, it is of importance to find interventions that could improve sleep quality in this population.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Institutional Research Committees of Jordan University of Science and Technology (ID: JUST-AA-2018-525). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

AA-S, II, HK, and KE-S contributed to research idea, data collection, managing and analyzing the data, and writing and reviewing the manuscript. All authors contributed to the article and approved the submitted version.

ACKNOWLEDGMENTS

The authors would like to acknowledge Dr. Mayis Aldughmi for reviewing the manuscript. The authors would like to acknowledge all the participants of the study. Acknowledgment for funding support was to Jordan University of Science and Technology (Grant No. AA-20180525), Clinical Rehabilitation Sciences Master Program (CRS) funded project by the Erasmus + Programme of the European Union (Project No: 573758-EPP-1-2016-1-JO-EPPKA2-CBHE-JP).

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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ORIGINAL RESEARCH
published: 15 March 2021
doi: 10.3389/fneur.2021.623200

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Performance Variability During Motor Learning of a New Balance Task in a Non-immersive Virtual Environment in Children With Hemiplegic Cerebral Palsy and Typically Developing Peers

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Edited by:
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Specialty section:
This article was submitted to Neurorehabilitation, a section of the journal Frontiers in Neurology

Received: 29 October 2020
Accepted: 11 February 2021
Published: 15 March 2021

Citation:
Cheng M, Anderson M and Levac DE (2021) Performance Variability During Motor Learning of a New Balance Task in a Non-immersive Virtual Environment in Children With Hemiplegic Cerebral Palsy and Typically Developing Peers. Front. Neurol. 12:623200. doi: 10.3389/fneur.2021.623200

Background: Motor impairments contribute to performance variability in children with cerebral palsy (CP) during motor skill learning. Non-immersive virtual environments (VEs) are popular interventions to promote motor learning in children with hemiplegic CP. Greater understanding of performance variability as compared to typically developing (TD) peers during motor learning in VEs may inform clinical decisions about practice dose and challenge progression.

Purpose: (1) To quantify within-child (i.e., across different timepoints) and between-child (i.e., between children at the same timepoint) variability in motor skill acquisition, retention and transfer in a non-immersive VE in children with CP as compared to TD children; and (2) To explore the relationship between the amount of within-child variability during skill acquisition and learning outcomes.

Methods: Secondary data analysis of 2 studies in which 13 children with hemiplegic CP and 67 TD children aged 7–14 years undertook repeated trials of a novel standing postural control task in acquisition, retention and transfer sessions. Changes in performance across trials and sessions in children with CP as compared to TD children and between younger (7–10 years) and older (11–14 years) children were assessed using mixed effects models. Raw scores were converted to z-scores to meet model distributional assumptions. Performance variability was quantified as the standard deviation of z-scores.

Results: TD children outperformed children with CP and older children outperformed younger children at each session. Older children with CP had the least between-child variability in acquisition and the most in retention, while older TD children demonstrated the opposite pattern. Younger children with CP had consistently high between-child variability, with no difference between sessions. Within-child variability was highest in younger children, regardless of group. Within-child variability was more pronounced in TD children as compared to children with CP. The relationship between the amount of within-child variability in performance and performance outcome at acquisition, retention and transfer sessions was task-specific, with a positive correlation for 1 study and a negative correlation in the other.

Conclusions: Findings, though preliminary and limited by small sample size, can inform subsequent research to explore VE-specific causes of performance variability, including differing movement execution requirements and individual characteristics such as motivation, attention and visuospatial abilities.

Keywords: cerebral palsy, virtual reality, variability, motor learning, virtual environment, children

INTRODUCTION

Cerebral palsy (CP) is the leading cause of physical disability in childhood (1–4). Unilateral spastic CP, or hemiplegia, is the most common subtype, representing 35–40% of new diagnoses (4, 5). Children with hemiplegia have motor, cognitive, sensory and perceptual challenges that limit postural control and activities of daily living, reducing functional independence (6–10). Assisting children to learn new motor skills, improve existing skills, and transfer skills to enhanced function in the real world is a primary goal of rehabilitation (11–13). However, much remains to be understood about motor learning impairments in children with CP (11–13).

Information-processing, attention, motor planning, and motor execution impairments can differ in children with CP as compared to typically developing (TD) peers, influencing the rate and extent of motor learning (12, 13). While children with CP improve in new motor task learning with practice (14–16), they may require greater duration of practice to achieve competency, while demonstrating lower accuracy and greater variability in task performance outcomes over repeated trials as compared to TD peers (14, 16–25). The heterogeneous nature of motor and cognitive impairments in CP allows for significant variability in performance outcomes in children of the same age and Gross Motor Function Classification System Level (24, 26–30).

Variability, traditionally conceptualized as the opposite of stability, is a fundamental characteristic of human performance (31, 32). Sternad defines variability as an umbrella term for "all sets or series of observations that are non-constant" (32). Variability is usually reduced with practice of a new motor skill. A prevalent view is that variability impedes the accuracy and precision required for skill attainment (31, 32). In contrast, some amount of variability may be beneficial to support the search for optimal solutions in differing task conditions (33–35). Indeed, Hadders-Algra defines variability as "the capacity to select from the repertoire the motor strategy that fits the situation best" (36). Ranganathan et al. (31) relate this view of variability to behavioral flexibility, which they define as "the ability to achieve the same task outcome using different movement solutions." Whether adaptive or detrimental, variability can occur at the level of task performance (in performance outcomes) and at the level of movement execution (in kinematic strategies used to achieve the outcome). Exploring both within-child (e.g., variability across different timepoints) and between-child variability (e.g., variability between children at the same timepoint) at both task and movement levels is important to understand differences in children's responses to interventions (37).

Movement execution variability in children with CP is highly correlated with severity of motor impairment (38, 39). Children with CP may demonstrate more movement execution variability because of challenges suppressing normal intrinsic motor system noise (40, 41). Their motor learning impairments may also affect the formation of internal models of movement and the interpretation of feedback mechanisms that could reduce variability (42). Movement execution variability has been investigated in gait (40, 43) and speech kinematics (44–46) in this population. For example, children with CP have a higher stride to stride variability, with more variation in muscle synergies during walking (39). In speech kinematics, Chen et al. (45) found longer coefficients of variation of utterance duration for short speech tasks in children with CP as compared to TD children, with greater variability as task complexity increased. However, movement execution variability in children with CP can decrease with training. For example, interventions in which children adapt to different gait speeds in each leg using a split-belt treadmill can decrease stride to stride variability in children with hemiplegic CP in ways that are significantly correlated with learning improvements (41).

Non-immersive virtual environments (VEs) in which children use body movements to interact with virtual objects displayed on a 2-dimensional (2D) flat-screen display are pediatric rehabilitation interventions that can support motor skill improvement and motor learning (47). There is strong evidence for the effectiveness of VE-based interventions to improve upper extremity functioning (48–51) and postural control (52–54) in children with hemiplegic CP. The unique practice conditions of non-immersive VEs may impact movement execution and performance variability. For example, interactions with virtual objects involve differing perceptual-motor affordances as compared to interaction with objects in the physical environment (55, 56). A lack of 3D depth cues in a non-immersive VE influences distance estimates of where objects are in space, which may increase uncertainty about movement accuracy. In addition, hand-held peripheral controllers that track movement (such as the one required by the Nintendo Wii or the HTC VIVE) may influence task interaction (56) as opposed to direct motion tracking.

Several studies have explored changes in movement execution variability in children with CP who learn a seated reaching task in a non-immersive VE as compared to in a physical environment. Children reduce their movement execution variability in repeated training in non-immersive VE, with some kinematic improvements transferring to improved performance of the same movement in the physical environment (57). Robert et al. (16)

undertook reach-to-grasp training in both physical and 2D flat-screen VEs in children with CP, finding similar improvements in kinematic variables in both training groups. Robert and Levin (58) compared reaching movement kinematics in 2D virtual reality and physical environment in typically developing children and children with CP. Several kinematic variables differed between reaches in the VE and the physical environment for children with CP, with only small clinically insignificant differences between CP and TD children. Overall, children moved more slowly in the VE. When children with CP use a hand-held game controller to interact with a non-immersive VE, they demonstrate both within- and between-child variability in terms of upper-extremity movement patterns used to play a single 2D active video game (59, 60). Some of this variability may be explained by personal and predisposing factors, such as gender, experience with video game play, and upper extremity impairment level (52).

Less is known about task performance variability in non-immersive VEs. Exploring this issue is important to contribute to the ongoing discussion about variability as both an adaptive and detrimental characteristic of motor learning (31, 32). Greater knowledge about within- and between-child variability in performance can provide new information relevant to conclusions about intervention effectiveness and inform sample size considerations for clinical trials. With greater understanding of variability in new task learning in non-immersive VEs, we can better guide therapists who endeavor to adhere to motor learning principles underlying experience-dependent neuroplasticity in rehabilitative strategies (61). For example, decisions about practice dosage, amount of repetition, and timing of progression of difficulty and challenge levels are often made on the basis of consistent performance improvements (i.e., a lack of variability). Understanding children's variability in performance over time is important because non-immersive VEs are often used as home intervention programs (62) and are not directly supervised by therapists; therefore, they cannot observe children's performance to understand how they perform over repeated trials.

The purpose of this study is to (1) Quantify within- and between-child performance variability in motor skill acquisition, retention and transfer in a non-immersive VE in children with hemiplegic CP and TD children; and (2) Explore the relationship between the amount of within-child variability during skill acquisition and retention performance. We hypothesize that children with CP will demonstrate greater between- and within-child variability than TD children, that younger children will demonstrate greater variability as compared to older children, and that variability will differ by learning stage and demonstrate a relationship with learning outcomes.

STUDY DESIGN AND METHODS

We undertook a secondary data analysis of 2 studies undertaken in our lab in which children with hemiplegic CP at Gross Motor Function Classification System (GMFCS) Levels I and II and typically developing children acquired one of 2 new balance skills in a non-immersive VE [the Stability and Balance Learning Environment (STABLE; Motekforce Link, The Netherlands), a 130 degree projection flat-screen VE in which interaction is via a force plate and motion capture cameras]. Forty-seven children participated in Study 1 and 33 children participated in Study 2. All children undertook baseline postural control tests (eyes closed stance, single leg stance, tandem stance, and mediolateral and anteroposterior limits of stability) on the STABLE prior to beginning the task. In both Study 1 and Study 2, children practiced a task requiring them to move their center of pressure (CoP) within a static base of support to control a virtual avatar (Acquisition). Children used CoP movements to control the avatar to follow a predetermined path displayed in the non-immersive VE as closely as possible. In Study 1 (**Figure 1**), the avatar moved along a path in a first-person perspective such that view of the path in the VE emerged according to the children's movements. In contrast, in Study 2 (**Figure 2**); the full path was always visible to the child in a 3rd person perspective. In both studies, VE visual and auditory feedback changed according to children's movements. The tasks are described in more detail in (63, 64). Acquisition involved 20 trials of practice; children returned 2–7 days after acquisition for a retention and transfer session, in which they performed the task in the same condition as acquisition (Retention; 10 trials) and in a more motorically-challenging condition (Transfer; 10 trials).

ANALYSES

Changes in performance score across trials and sessions, as well as differences in performance between children with CP and TD children, and children differing in age (7–10 vs. 11–14 years), were assessed using mixed effects models via the lme4 package in R version 3.6.0. Raw performance scores were converted to z-scores to more closely meet distributional assumptions of the models. A z-score of 0 represents mean performance. Model selection was conducted using an information-theoretic approach based on Akaike's Information Criterion (AIC) (65) [as described in (66)]. Briefly, a set of models is generated based on explanatory variables and higher-order effects (e.g., interactions and/or polynomial terms) of interest. A reduced set of explanatory variables is selected, to prevent overfitting and determine the most important effects in the model. The reduced model is selected using AIC, in which models are ranked in increasing order by AIC values, which are then used to calculate "Akaike weights" for each model. These are commonly interpreted as the probability that the given model is the "best" in the set in terms of minimizing loss of Kullback-Leibler (66) information, providing a straightforward means of comparing relative model fits.

Models in our initial comparison set included both least-square and mixed effects implementations. The full set of explanatory variables and higher-order effects tested included trial number (linear only vs. second-order polynomial), group (TD vs. CP), age group (7–10 vs. 11–14 years), and interactions between group and both age group and the polynomial term for trial. For the top selected models, study was also added as an explanatory variable, as both a main effect and interaction with group and age group, in order to quantify the size of the difference between studies compared with other sources of variation.

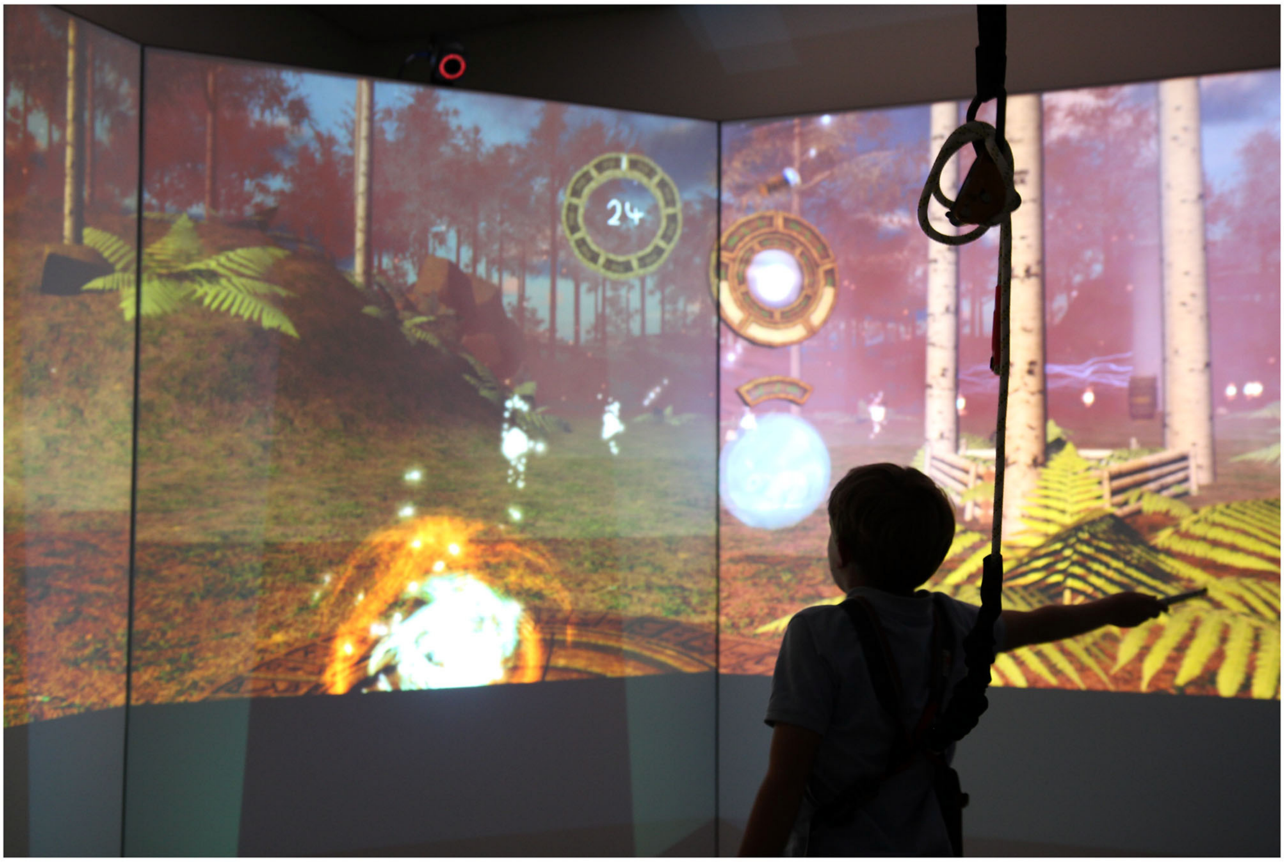

FIGURE 1 | Displays the Study 1 virtual environment, showing the path emerging in front of the participant (the white dots).

Mixed models initially included random parameters for both slope and intercept across trials for each subject. However, for models that included random slope parameters, the numerical search method failed to converge on a maximum-likelihood solution, likely as a result of our relatively small sample size, particularly for the CP group. Mixed-effects implementations of our comparison models therefore only included a random intercept parameter. Differences in mean z-scores among sessions were examined separately using a mixed-effects model that included group, age group, and session as fixed effects, and a random intercept term for subject. Pair-wise differences between groups were examined using Tukey-adjusted *post-hoc* comparisons of estimated marginal means in the "emmeans" package in R.

Because AIC and statistics derived from it only assess relative fit among different models, absolute model fit was also assessed using R^2 values calculated from model deviances using the r.squaredGLMM command from the MuMIn package in R. This generates a "marginal" R^2 which expresses the variance explained by the fixed effects only, as well as a "conditional" R^2 that reflects the variance explained by the whole model (fixed + random factors).

Between-child variability was quantified as the standard deviation (SD = square root of the variance) for each of the 4 groups. We quantified within-child variability as the SD of the trial-to-trial difference in individual z-scores (sdDiff). We tested equality of variance using Levene's test between group and age group among sessions and at each session. Mean sdDiff was compared among sessions, and between groups and age groups, using ANOVA followed by Tukey-adjusted *post-hoc* tests. To examine the relationship between within-child variability (sdDiff) in a session and 2 performance outcomes of that session (maximum z-score and the mean z-score) we ran a multiple regression model for each correlation per study, with group as an explanatory variable, both as a main effect and as an interaction with the performance measure.

RESULTS

Performance Differences Between Children With CP and TD Children and Between Older and Younger Children at Each Session

Table 1 provides the mean and SD of z-scores for each age group across sessions and at each session. **Table 2**

FIGURE 2 | Displays the Study 2 virtual environment, showing the entire path visible to the participant (the blue line).

presents the mean and SD of baseline postural control tests for each age group. **Table 3** presents the effect sizes [Cohen's d (67) and Hedges g (68)] for each age group at each session.

Figure 3 illustrates that children with CP have consistently lower scores as compared to TD children ($t = -7.102$, $p < 0.001$, estimate (CP) $= -1.015$, mean difference $= 0.809$), while the performance for younger participants is consistently below that for older participants ($t = 4.604$, $p < 0.001$, estimate (older) $= 0.5206$, mean difference $= 0.780$). Across sessions, mixed effects models show that the largest effects are associated with trial ($t = 21.027$, $p < 0.001$), with a positive linear effect indicating that most participants improve over time. However, the negative non-linear effect indicates this tendency toward improvement tends to diminish or even reverse as trial number increases within a session. For example, in the acquisition session, performance of the younger participants with CP drops off pronouncedly at the end of the session. Within age and group, the relationship with trial varies widely among participants, ranging from linear (both positive and negative slopes) to unimodal. The models show that the R^2 almost doubles ($R^2 = 0.304$ vs. $R^2 = 0.541$) when accounting for these effects of random between-child variation.

TABLE 1 | Mean and SD of Z-scores for each age group across sessions and within each session.

Group	Age group	N	Mean (SD) Z score	Session	Mean (SD) Z score
TD	7–10 yr	41	−0.090 (SD 0.908)	Acquisition	−0.307 (SD 0.914)
				Retention	0.249 (SD 0.891)
				Transfer	0.056 (SD 0.773)
	11–14 yr	26	0.427 (SD 0.900)	Acquisition	0.141 (SD 0.917)
				Retention	0.909 (SD 0.644)
				Transfer	0.529 (SD 0.856)
CP	7–10 yr	8	−1.308 (SD 0.970)	Acquisition	−1.36 (SD 1.059)
				Retention	−1.084 (SD 0.666)
				Transfer	−1.404 (SD 0.985)
	11–14 yr	8	−0.602 (SD 0.705)	Acquisition	−0.718 (SD 0.589)
				Retention	−0.287 (SD 0.895)
				Transfer	−0.529 (SD 0.759)

TABLE 2 | Mean and SD of baseline postural control tests for each age group.

Group	Age group	Mean (SD) ML* left	Mean (SD) ML* right	Mean (SD) AP* anterior	Mean (SD) AP* posterior	Mean (SD) LOS*
TD	7–10 yr	10.9543 (SD 3.9969)	11.3786 (SD 3.0423)	6.6171 (SD 3.9413)	6.9171 (SD 1.6482)	13.1769 (SD 1.4142)
	11–14 yr	11.5133 (SD 3.1909)	12.5633 (SD 3.5228)	8.9383 (SD 2.6421)	4.5200 (SD 1.4119)	12.1173 (SD 2.3520)
CP	7–10 yr	13.9318 (SD 2.4724)	13.4954 (SD 2.8786)	8.4153 (SD 2.7611)	7.2518 (SD 2.3917)	15.4966 (SD 5.9644)
	11–14 yr	13.2888 (SD 2.2055)	13.8192 (SD 2.1315)	8.9438 (SD 3.0108)	8.0188 (SD 1.8754)	13.9663 (SD 1.7177)

ML, Medio-lateral excursion; AP, Anterior-posterior excursion; LOS, Limits of stability.

TABLE 3 | Effect sizes for between-group differences at each session.

Session	TD-CP All	TD-CP 7–10 yr	TD-CP 11–14 yr	CP 7–10 yr - CP 11–14 yr	TD 7–10 yr – TD 11–14 yr
Acquisition	Cohen's d = 0.947 Hedges g = 0.940	Cohen's d = 1.127 Hedges g = 1.109	Cohen's d = 1.003 Hedges g = 1.980	Cohen's d = 0.752 Hedges g = 0.711	Cohen's d = 0.490 Hedges g = 0.484
Retention	Cohen's d = 1.444 Hedges g = 1.431	Cohen's d = 1.547 Hedges g = 1.522	Cohen's d = 1.694 Hedges g = 1.654	Cohen's d = 1.010 Hedges g = 0.955	Cohen's d = 0.820 Hedges g = 0.811
Transfer	Cohen's d = 1.456 Hedges g = 1.442	Cohen's d = 1.806 Hedges g = 1.777	Cohen's d = 1.256 Hedges g = 1.226	Cohen's d = 0.996 Hedges g = 0.941	Cohen's d = 0.586 Hedges g = 0.579

Between-Child Variability Across Sessions and Per Session: Group (TD vs. CP) and Age (Younger vs. Older) Differences

There is a significant difference in the amount of between-child variability between children with CP and TD children across all sessions [$F_{(1, 81)} = 9.254$, $p < 0.001$, mean difference = −1.071]. Younger children with CP demonstrate the most between-child variability, while older children with CP have the least [$F_{(3, 81)} = 1.888$, $p < 0.001$, mean difference = −0.706]. For TD children, there is no difference in the amount of between-child variability between younger and older children [$F_{(1, 65)} = 1.018$, $p = 0.758$, mean difference = −0.517]. Older TD children and children with CP differ significantly in amount of between-child variability [$F_{(1, 47)} = 1.627$, $p < 0.001$, mean difference = 1.023]. There is no difference in between-child variability between the 3 sessions in younger children with CP [$F_{(2, 5)} = 0.568$, $p = 0.568$], while younger TD children demonstrated significant differences between sessions [$F_{(2, 23)} = 5.375$, $p = 0.005$].

Older TD children show significant differences [$F_{(2, 38)} = 11.843$, $p < 0.001$] between sessions, with the highest variability during acquisition, lowest during retention, and an increase again during transfer. Older children with CP also show significant differences [$F_{(2, 5)} = 9.924$, $p < 0.001$], but opposite to the pattern in the older TD children: lowest variation during acquisition, highest during retention, then a decrease during transfer. Younger TD children show significant differences [$F_{(2, 23)} = 5.375$, $p = 0.005$], with another distinct pattern: a peak in between-child variability during acquisition, followed by a steady decrease throughout retention and transfer. Younger children with CP do not show significant differences [$F_{(2, 5)} = 0.568$, $p = 0.568$] in variability between sessions. There are no significant differences in between-child variability between TD children and children with CP or between younger or older children in the transfer session.

Within-Child Variability Across Sessions and Per Session: Group (TD vs. CP) and Age (Younger vs. Older) Differences

The strongest difference in within-child variability was associated with age, with younger children demonstrating greater within-child variability as compared to older children when pooled across sessions and group ($t = 3.3$, $p = 0.001$, mean difference = 0.157). Children with CP showed a non-significant trend toward lower within-child variability as compared to TD children ($t = 1.9$, $p = 0.06$, mean difference = −0.131). Within-child variability did not differ significantly among sessions ($p > 0.1$). When comparing across groups and age groups within each individual session, there were no significant differences, possibly due to high variability among individuals and low sample sizes. Older TD children displayed a trend toward higher within-child variability as compared to older children with CP in the acquisition session ($t = 1.7$, $p = 0.10$, mean difference = 0.237) and younger children with CP in the transfer session ($t = 1.7$, $p = 0.09$, mean difference = 0.216).

Table 4 provides between- and within-child variability for each age group overall and for each age group at each session.

Figure 4 illustrates the performance score for each individual participant across all trials of the 3 sessions, fit with a quadratic curve.

Relationship Between the Amount of Within-Participant Variability in Acquisition and Performance Outcomes at Each Session

These analyses revealed a strong effect of study as an explanatory variable. In Study 1, there was a significant positive relationship of sdDiff during acquisition with MaxZ score at acquisition ($R^2 = 0.485$, $p < 0.001$); this relationship did not differ between TD children and children with CP. There was no significant relationship with MeanZ. The amount of variability (sdDiff) in acquisition is not significantly correlated with MaxZ or MeanZ in retention or transfer sessions for Study 1.

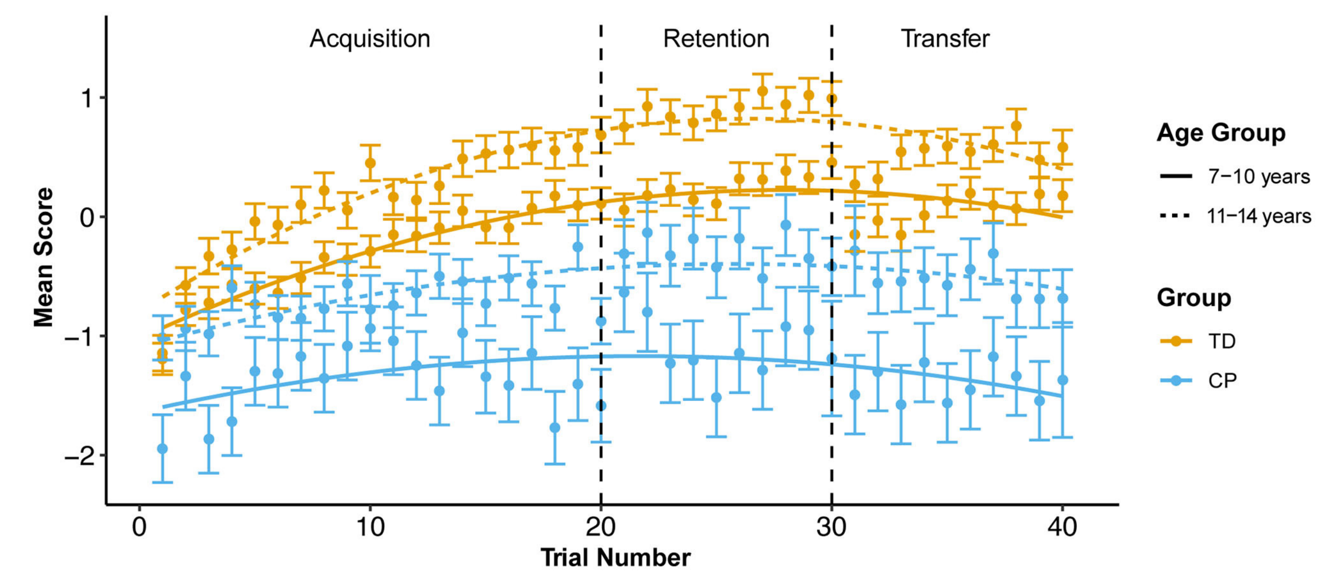

FIGURE 3 | Mean z-score by group and age group across all trials at each session. Error bars use sdDiff (the standard deviation of the pair-wise trial-to-trial differences). SE is calculated by devising the SD by the square root of the number of subjects in each trial.

TABLE 4 | Within- and between-child variability for each age group and for each age group at each session.

Group	Age group	Mean (SD) between-child variability*	Mean (SD) within-child variability**	Session	Between-child variability*	Within-child variability**
TD	7–10 yr	−0.090 (SD 0.908)	0.840 (SD 0.344)	Acquisition	0.914	0.841
				Retention	0.891	0.835
				Transfer	0.773	0.843
	11–14 yr	0.427 (SD 0.900)	0.700 (SD 0.368)	Acquisition	0.917	0.797
				Retention	0.644	0.564
				Transfer	0.856	0.734
CP	7–10 yr	−1.308 (SD 0.970)	0.774 (SD 0.440)	Acquisition	0.106	0.867
				Retention	0.666	0.859
				Transfer	0.985	0.582
	11–14 yr	−0.602 (SD 0.705)	0.527 (SD 0.269)	Acquisition	0.589	0.560
				Retention	0.895	0.438
				Transfer	0.759	0.561

**SD of z-score. **sdDiff (SD of the pair-wise trial-to-trial differences per child).*

For study 2, there was no significant negative relationship of amount of variability in acquisition with maxZ in acquistion ($R^2 = 0.237$, $p = 0.100$). There was a significant negative relationship of amount of variability in acquisition with meanZ ($R^2 = 0.442$, $p < 0.001$) in acquisition, with no difference between TD children and children with CP. In Study 2, the amount of variability in retention is significantly negatively correlated with MaxZ ($R^2 = 0.373$, $p = 0.035$) and with MeanZ ($R^2 = 0.293$, $p = 0.0216$) at retention. The amount of variability in the transfer session is significantly negatively correlated with MaxZ ($R^2 = 0.336$, $p = 0.010$), and MeanZ ($R^2 = 0.503$, $p < 0.001$) at transfer, with no difference in this relationship between TD children and children with CP.

DISCUSSION

This secondary data analysis explored within- and between-child performance variability during practice of a novel postural control task in a non-immersive VE at acquisition, retention and transfer sessions in children with hemiplegic CP and TD children. Consistent with evidence for motor skill acquisition with practice in children with CP [e.g., (69–71)], performance on the task improved over repeated trials during the acquisition session, although it did not reach the same success level as TD children. We observed expected age differences in performance with older children outperforming younger children in each group. Performance decreased at the end of each practice session of our standing postural control tasks, especially for younger

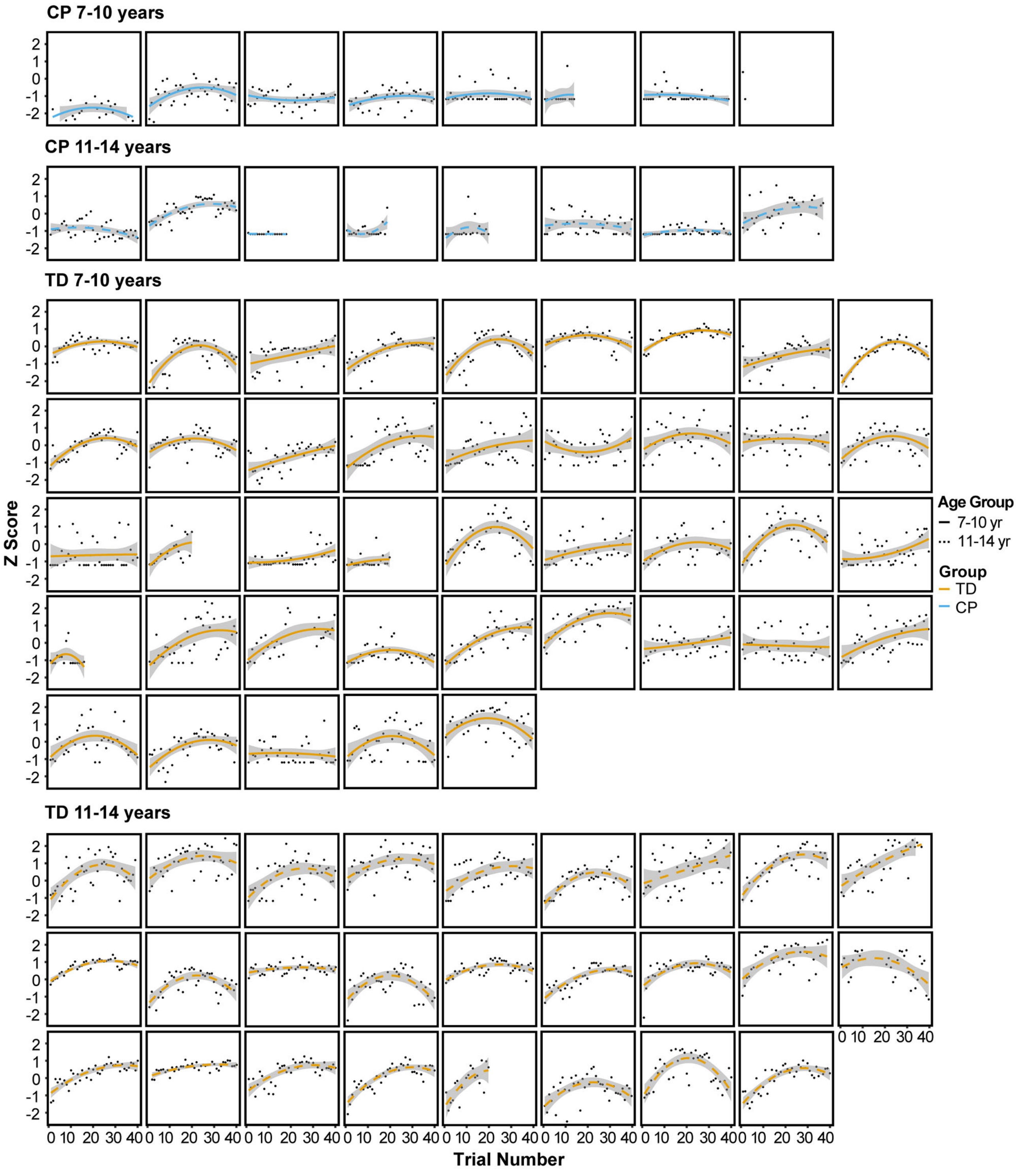

FIGURE 4 | Performance score for each individual participant across all trials of the 3 sessions, fit with a quadratic curve.

children with CP: e.g., from trial 19 to trial 20, the final trial of the acquisition stage, performance decreases by ≥ 0.2, enough for the error bars to exclude the mean curve in both CP age groups, but neither TD age group (**Figure 3**). Fatigue is one possible explanation for this observation. Children with CP demonstrate greater energy expenditure in ambulatory tasks as compared to

TD children (72). Bronton and Bartlett (73) surveyed fatigue in 130 young adults with CP at all GMFCS levels, finding that while fatigue was highest in individuals at higher GMFCS levels (II-V), the majority (92%) of participants reported being fatigued at least a quarter of the day or more.

The amount of between-child variability in performance differed between groups, age groups and sessions. As hypothesized, younger children with CP had the highest between-child variability at each session, likely reflecting the known heterogeneity in motor abilities in children with CP compounded by a lesser amount of motor skill experience at this age. Contrary to our hypothesis, children with CP did not always demonstrate more between-child variability as compared to TD children. Patterns of variability in each session differed for older TD children and children with CP. Older children with CP had the least between-child variability in acquisition and transfer sessions but had highest between-child variability during retention. In contrast, TD children had the most variability in acquisition and the least variability in retention. This finding is explained by the fact that children with CP had consistently lower scores across participants.

The greater amount of between-child variability in retention in children with CP, combined with lower scores in the retention session, may reflect motor learning impairments in children with CP as compared to TD children, who more consistently retained task performance improvements. Information about children's postural control abilities obtained from baseline testing postural control abilities (**Table 1**) shows expected differences between TD children and children with CP due to motor impairment. However, postural control results were not especially heterogeneous among older children with CP, which further explains the low between-child variability. We did not collect detailed demographic data from children as to their current physical activity or sports participation that could help to elucidate between-child variability in task performance at retention in terms of movement experience. High between-child variability in all groups and age groups in the transfer session also suggests the importance of exploring other child factors that influence motor learning. For example, factors such as attention or motivation that were unmeasured here may illuminate between-child performance differences.

With respect to within-child variability, individual children were least variable in their performance across trials in the retention, suggesting that children achieved sufficient task competence to maintain stable performance after a period of no practice. As hypothesized, younger children demonstrated greater within-child variability than older children at each session; however, we were surprised to see lower within-child variability in children with CP as compared to TD children in acquisition and transfer. This finding may be explained again by the overall consistently poorer performance (i.e., lower scores) of children with CP as compared to TD children, limiting the range of scores across which subjects can vary. This is particularly true in the transfer session, which had the lowest scores for children with CP (especially for younger children). A less challenging task and a larger sample size may have resulted in greater information about within-child variability in performance over time. Simple prospective power calculations indicate that, for a balanced design, a sample size of 25 subjects per age group and developmental group would be required to detect our observed difference in the transfer session at alpha = 0.05. Subsequent studies can evaluate within-child variability over longer durations of practice, while considering the challenge of fatigue and motor endurance in this population.

Movement execution variability is one contributor to performance variability across repeated trials. In our studies, performance score was directly based on movement execution: the precision of controlling weight-shifting of the CoP over a static base of support. Studies involving repeated task practice of seated reaching tasks in non-immersive VEs demonstrate that children with CP reduce their movement execution variability with practice (16, 57, 74). However, these studies did not include retention or transfer tasks. In a game play situation, children with CP playing active video games in a non-immersive VE demonstrate within- and between-child variability at a movement execution level during repetitive game play (59, 60). This game play situation has some similarity to our study tasks in having greater opportunities for exploration in movement strategies as compared to studies involving restricted single arm reaching tasks in a seated position. This could have influenced the amount of between-child variability as children tried different strategies to achieve the task goal.

The relationship of within-child variability to performance differed between the 2 studies, with a positive correlation (greater variability in acquisition associated with better scores) in Study 1 and a negative correlation in Study 2. Both studies had similar movement requirements for success and similar visual feedback about how avatar position determined score. However, the visual display differed between the 2 studies, with the full path visible in a 3rd person perspective in Study 2 and the path emerging with movement in a first-person perspective in Study 1. Children with CP found Study 2 more challenging, as scores were lower as compared to Study 1. The path width was narrower in Study 2 as compared to study 1, leading to more penalty for increased variation in CoP position. In Study 1, we can speculate that with a slightly wider path that constantly revealed itself in a first person perspective, children had more tolerance for variation and that those who took advantage of this may have found a more optimal strategy that resulted in higher scores. Differences in the relationship between amount of variability and performance according to task requirements and VE visual display perspective suggest the need for subsequent research to explore the influence of these and other factors on variability.

Our variability metric did not enable us to partition variability into adaptive or error components. Using more sophisticated statistical models to understand the structure of variability can provide more insight into randomness and exploration patterns (31, 32). Example methods that could be useful for exploring the structure of different solutions in simple redundant tasks include the Tolerance, Noise and Covariation Approach (TNC), the Uncontrolled Manifold Approach, and the Goal-Equivalent Manifold approach; readers are directed to Sternad (32) for an overview. Of these, only the TNC method was purposefully developed to evaluate learning processes in changes in variability over time; however, it has not yet been applied to complex 3D tasks, as the model assumes task outcome redundancy from two precisely quantified input variables.

Exploring variability in movement execution during new task learning in non-immersive VEs through kinematic analyses can provide additional insight into this important source of performance variability. To understand how variability differs between virtual and physical environments, subsequent research can use within-participant designs to compare variability in the same task in a VE and an equivalent physical environment. An unexplored area of future research is whether VEs are relevant training paradigms to encourage development of variability/behavioral flexibility (75). Given that task features and task challenge can be precisely manipulated in a VE, these features could elicit practice of variable responses to differing task conditions and adapting to different task constraints. To achieve this goal, more knowledge about the similarity of movements in VEs to the physical environment and how learning transfers to the physical environment in children with CP is important to understand the degree of similarity required to facilitate transfer. Other hypothesized intertwined factors that might influence variability include children's attention, fatigue, effort, and motivation. Indeed, a predominant rationale for the use of VEs is that they elicit and sustain children's motivation and attention to participate in repetitive training (76).

This study has several limitations. Conclusions about variability in performance at retention and transfer sessions are limited by inconsistent rest periods between acquisition and retention/transfer sessions between participants, ranging from 2 to 7 days. These periods were necessary to accommodate family schedules in data collection. Our sample size was small and unbalanced, with the CP group having an especially low number of participants. While the mixed model approach utilized in the lme4 package is designed to be robust to unbalanced data (77), we interpret our results cautiously and would encourage follow-up studies with larger sample sizes.

CONCLUSION

Performance variability can be an important source of information about differences in children's responses to interventions and should be considered in the design of rehabilitation protocols. This study is the first to specifically investigate performance variability over time during learning of standing postural control tasks in a non-immersive VE in children with hemiplegic CP. Findings contribute to the evidence base about differences in motor skill learning in children with CP as compared to TD peers in these novel intervention environments. Between- and within-child performance variability in children with CP is consistent with expected challenges with task performance due to motor impairments and age. A greater understanding of variability in motor skill learning in VEs is important to advance the debate as to the benefits and disadvantages of variability in motor skill learning and to understand whether the affordances of non-immersive VEs may make these interventions appropriate for training behavioral flexibility. Given that the relationship of within-child variability in skill acquisition differs according to the specific demands of the task, other factors that influence performance variability should be explored in subsequent studies, including differences in movement execution in VEs and cognitive factors such as attention and motivation. The design of VE-based interventions for children with hemiplegic CP can consider all these factors and their implications in order to maximize therapeutic benefit.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Northeastern University Institutional Review Board. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin. Written informed consent was obtained from the minor(s)' legal guardian/next of kin for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

DL conceived of the study. MA and MC undertook the analyses and prepared the figures. MC, DL, and MA wrote and edited the manuscript. All authors agree to be accountable for the content of the work.

FUNDING

DL was supported by a K01 Mentored Research Scientist Development Grant (K01HD093838) from the Eunice Kennedy Shriver National Institute of Child Health and Human Development. One of the projects described was supported by the National Center for Advancing Translational Sciences, National Institutes of Health, Award Number UL1TR002544. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH. The second project was supported by a Tier 1 Grant from Northeastern University.

ACKNOWLEDGMENTS

The authors would like to thank the children and families who participated in this research and the research assistants who participated in data collection for the 2 studies.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Neurology

HYPOTHESIS AND THEORY
published: 28 May 2021
doi: 10.3389/fneur.2021.610095

A Clinical Decision-Making Framework for the Use of Video Gaming as a Therapeutic Modality

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Virtual reality and video gaming offer modulation of more exercise and motor learning parameters simultaneously than other modalities; however, there is a demonstrated need for resources to facilitate their effective use clinically. This article presents a conceptual framework to guide clinical-decision making for the selection, adaptation, modulation, and progression of virtual reality or gaming when used as a therapeutic exercise modality, and two cases as exemplars. This framework was developed by adapting the steps of theory derivation, whereby concepts and parent theories are brought together to describe a new structure or phenomenon of interest. Specifically, motor learning theory, integrated motor control theory, Gentile's Taxonomy of Tasks, and therapeutic exercise principles were integrated to develop this framework. It incorporates person (body segment), environmental, and task demands; each demand is comprised of realm, category, choice, and continuum parameters as motor training considerations and alternatives for decision-making. This framework: (1) provides structure to guide clinical decisions for effective and safe use of virtual reality or gaming to meet therapeutic goals and requirements, (2) is a concise and organized method to identify, document, and track the therapeutic components of protocols and client progression over time; (3) can facilitate documentation for reimbursement and communication among clinicians; and, (4) structures student learning, and (5) informs research questions and methods.

Keywords: virtual reality, exergame, motor learning, clinical decision making, clinical framework, exercise therapy, neurological rehabilitation

Edited by:
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Reviewed by:
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Specialty section:
This article was submitted to Neurorehabilitation, a section of the journal Frontiers in Neurology

Received: *25 September 2020*
Accepted: *13 April 2021*
Published: *28 May 2021*

Citation:
Espy D, Reinthal A and Dal Bello-Haas V (2021) A Clinical Decision-Making Framework for the Use of Video Gaming as a Therapeutic Modality. Front. Neurol. 12:610095. doi: 10.3389/fneur.2021.610095

INTRODUCTION

Virtual reality (VR) is the use of computer hardware and software forming interactive simulations to present users with opportunities to engage in environments that feel and appear similar to real world events and objects (1). It is an increasingly accepted modality for physical and cognitive rehabilitation (2–4). The VR environment can be described as non-immersive (i.e., a screen - computer generated environment), semi-immersive (i.e., flight simulator or game with a mix of real and virtual interactive elements), or fully immersive (i.e., HCT Vive) based on the level of immersion and the extent of being present or part of the VR world; the higher level of immersion corresponds to a more realistic VR environment to the user (5). A key feature of VR is the active participation in the VR experience via control interface input into the computer system. As video games, serious games, and virtual environments present a virtual world that users can manipulate, they are technically, and often, included within the scope and definition of VR.

Commercial, off-the-shelf video games and gaming consoles (referred to as gaming in this paper) were initially developed for entertainment purposes, but share some of the same features and advantages of much more expensive, custom VR systems. Commercial games evolved as a means to encourage exercise in the general population (6, 7) and some of these have been adopted as therapeutic modalities for physical rehabilitation (8–10) because of their lower costs (11, 12). Reviews of the evidence of gaming as a therapeutic tool find effectiveness in a number of applications. For example, Chen and colleagues found that in people with Parkinson Disease the use of VR improved Berg Balance Scale (BBS) scores compared to other interventions (13). Similarly, significant improvements in BBS scores were found for VR interventions in people with chronic stroke (14). Laver et al. (3) determined the use of VR and interactive video gaming was not more beneficial than conventional therapy for improving upper limb function but suggested these modalities may be beneficial when used as an adjunct to usual care to increase overall therapy time. While these evidence summaries suggest there are real and potential benefits of VR, they also underscore equivocal conclusions, methodological issues (e.g., small sample size, rigor, quality), large variability in the protocols used (e.g., number of sessions, intervention duration, outcome measures), and the need for further research (15–18).

Gaming and VR are used in rehabilitation because they have several potential motor learning advantages over traditional exercise. They provide the massed motor practice and dosage (3) necessary to induce experience-dependent neuroplasticity (19–22). Multiple repetitions of task practice are essential for motor retraining (23–26) but repetitive practice of a single task is often boring for adults (8, 27, 28). Many individuals find gaming and VR more engaging and enjoyable than traditional exercise programs, thus are motivated to practice more (29, 30) and are less likely to withdraw from VR interventions (17).

The theory of flow highlights that a person's skills and the task demands should align, and that the intrinsic motivation for a task is best when the demands lie ideally along the orthogonal continua of anxiety to flow, and apathy/boredom to relaxation (31). Flow has been described as the optimal experience "when nothing else matters" (32) and conceptualizes dimensions that lead to these positive experiences and pleasurable mental states, such as balance between the skills of an individual and the activity's demands; merging of action and awareness; clear goals; immediate and unambiguous feedback; concentration on the task; perceived control over the activity; and intrinsic motivation toward an activity (autotelic) (32, 33). VR and gaming provide these experiences and the ability to modulate these dimensions.

Video gaming can provide a large range of task demands, allowing finer tuning of the challenge posed by a given intervention. Most significantly for neuro-rehabilitation, VR and active gaming provide rich opportunities for modulating the concurrent motor and cognitive demands of an activity to provide crucial dual- or multi-task therapeutic activities (34, 35). Likewise, VR may provide an enriched environment for problem solving and mastering new skills (35). Potential advantages for cognitive retraining among older adults (34, 36) and increased attention skills resulting from gaming have been reported (37, 38). A randomized controlled trial comparing physical exercise, cognitive exercise, and VR exercise demonstrated significant improvements in cognitive and physical function with VR exercise in older adults; VR exercise was also more favored than physical exercise (39). A recent review and a meta-analysis discussed positive effects of semi-immersive VR on cognition and physical function in people with mild cognitive impairment and dementia (40, 41).

Because VR and gaming are immersive (1, 42), they create a sense of engagement and presence (43), the sense of psychologically leaving the real location and feeling as if transported to a virtual environment for the users. The game's context may be more similar to an actual task, an important component of the ecological approach to cognitive-motor dual task situations (44, 45) which emphasizes that tasks should be as close as possible to real-world scenarios; virtual environments can simulate the crucial sensory cues of complex activities (46). All of these elements may account for the potential transfer of skills to comparable real-world activities (47), a concern in current practice (48).

Despite their advantages, VR and gaming are therapeutic modalities, not therapy in and of themselves. As such, the therapist must identify the specific goals that will be met through the use of gaming; and, gaming tasks need to be chosen to align with those goals and structured to provide the appropriate challenge (49). Performance needs to be monitored, outcomes evaluated, and learning achieved via gaming needs to be linked to the real-world context (49). Further, therapists need to ensure that gaming activities are safe, are not detrimental, and are cost effective.

Lack of time and information have been found to be the biggest barriers to incorporation of VR and gaming into rehab therapies (50–52), while therapist knowledge was found to be a prime facilitator (51). To this end, guidelines, frameworks and clinical practice recommendations are emerging. The "Kinect-ing" With Clinicians format was developed as knowledge translation for physical and occupational therapists integrating the Kinect system into practice (52). A framework has been developed to assist clinicians in choosing VR systems for pediatric patients in neurorehabilitation (53) and a practice guideline has been proposed for VR as an intervention (54). None of these addresses the clinical decision-making process in structuring and using the chosen games and platform though, particularly identifying critical therapeutic elements and their rationale.

Purpose

Broadly, clinical decision-making frameworks guide and enhance the implementation of theory-based rehabilitation practice by providing a systematic approach to organize thinking, observations, and interpretations (55, 56). This paper describes a conceptual clinical decision-making framework and its utilization, through two cases as exemplars, in making and tracking decisions about the therapeutic elements of video gaming and VR modalities in clinical practice, particularly when used to address movement, mobility, balance, and motor relearning goals. Often the terms "framework," "theory," and "model" are used interchangeably, as are the terms "theoretical framework" and "conceptual framework." We have purposefully chosen the term conceptual framework. A conceptual framework explains, graphically or in narrative form, one or more formal theories, in part or whole; as well as key factors, concepts, variables, and empirical findings from the literature to show relationships among ideas (57, 58).

Framework Development

The need for the framework grew out of our laboratory and clinical studies researching off-the-shelf video gaming as a therapeutic tool in balance training and motor relearning for older adults and people post-stroke. We recognized that there are many potential motor-control and learning variables that can be modulated simultaneously with gaming and VR, as well as therapeutic exercise and neuro rehabilitation principles that must be appropriately considered. Our thought was to organize these elements and considerations into a framework that would facilitate clinical decision-making through making explicit the motor control, motor learning, and therapeutic exercise constructs accessible through VR and gaming-based therapy.

Walker and Avant's Theory Derivation (59) procedures were adapted to organize related concepts in a structural manner to illustrate these relationships as a framework. Theory derivation is an iterative process that considers theory and knowledge of the literature within an area of interest to explain possible new concepts and structures. Relevant concepts and structures are borrowed, modified, and redefined from a parent theory, in whole or in part, to explain a phenomenon of interest (59, 60). A theory derivation approach has been used in a wide range of health care literature to develop theories and to adapt existing theories, models, and frameworks (60–62).

We used the steps of Theory Derivation to provide systematic structure to the framework development. Basic steps include: (1) become familiar with the literature on the phenomenon of interest; (2) examine the literature of other applicable fields; (3) choose a parent theory to explain the phenomenon of interest; (4) identify concepts, components, and content from the parent theory to be used; and (5) modify, redefine or refine concepts, components and content from the parent theory (59). Our goal was not to develop a new theory or to adapt a theory, but rather, we developed a conceptual framework to organize and make explicit the therapeutic elements, principles, and considerations that underlie the use of VR and gaming as a motor rehabilitation modality.

Parent theories were carefully examined, and applicable components were extrapolated, and a wide range of literature was utilized for initial framework development, as described in the following section. Drawing on theory, concepts, principles and evidence, we organized these various elements and considerations into an initial framework for therapeutic game selection, adaptation, modulation and progression. The initial framework underwent an iterative process of review and refinement. For example, the framework was applied with 78 individuals, across ages, participating in various research and clinical studies in the laboratory of two of the authors (DE, AR), as well as in the clinical practice of all authors. Iterative application of the framework in this manner was used to refine included concepts and clinical utility such as ease of use, usefulness, acceptability, benefits, meaning, and relevance of the framework (**Figure 1** for overview of the framework).

Parent Theories

In adapting the Theory Derivation Process to this framework development, the parent theories and concepts chosen included: motor learning principles, integrated motor control theory, and basic therapeutic exercise principles, as well as more specific concepts used in neuro rehabilitation. These theories and principles were chosen for this framework because they underpin motor training in neuro rehabilitation.

Motor learning refers to a set of internal processes associated with practice or experience that lead to relatively permanent changes in motor behavior (63). Retention of a learned task or skill is important as permanent changes are the desired outcome. Additionally, transfer of training (63), the ability of the client to draw on past experience to perform a new task or skill, are affected by practice conditions (63). Training parameters that impact retention and/or transfer of skills include repetition, time on task, type and schedule of feedback, locus of attention, context, and variability of practice. Variability in practice is most beneficial for retention and transfer of a motor skill (64).

Integrated motor-control theory conceptualizes movement as a product of the interaction among the *individual*, the *task*, and the *environment* (65), and incorporates many of the concepts of other systems-based theories [i.e., Dynamic Systems Theory (66)] in which movement is thought to be generated by an individual to meet the demands of a specific task performed within a specific environment. Individual, task and environment attributes contribute to the execution of movement tasks. According to Shumway-Cook and Woollacott (65) *individual attributes* may involve action (e.g., motor system, impairments), perception (e.g., factors that affect or limit the internal registration or integration of sensory information), and cognition (e.g., factors such as attention, emotions, motivation, ability to attend to environmental stimuli during the execution of tasks or activities). *Task attributes* define and constrain the execution of a movement task, and are classified into a discrete task with a discernable beginning and ending point (e.g., sit to stand) or a continuous task with a variable ending point (e.g., walking). Whether the base of support (BOS) is stationary or changing is an additional task attribute; and, task considerations include upper extremity (U/E) manipulation requirements, the amount of attention demanded by a task, and the variability of the movement itself. *Environmental attributes* can be divided into regulatory (i.e., factors that shape the movement) and non-regulatory conditions (i.e., factors that may affect performance but do not directly shape the movement, such as background noise or air temperature). In a stationary environment, the regulatory conditions involve a fixed terrain and non-moving objects, and the environment influences only the spatial parameters of the movement. When activities occur in a moving environment, where objects, other people, or the supporting surface are in motion, movements must conform to both spatial and temporal parameters of the environment.

Motor Learning Theory | Integrated Motor Control Theory

Gentile's Taxonomy of Tasks | Exercise Principles

Demand	Realm	Category	Choice	Continuum
Body Segment (Person)	Posture	Base of Support	Standing vs Seated vs Other	Smaller➢ Larger *[standing/one two feet with hands sitting, lying]*
	Trunk	Segments involved Function at Segment	Head, neck, upper, lower Stability Movement	Less ➢More Challenging Small ➢Large; Slow ➢Fast; Single Plane ➢Multi-Plane
	Upper Extremity	Segments involved Function at Segment Overall Mode	Shoulder, Elbow, Forearm/Wrist Stability Movement Open chain vs Closed Chain	Less ➢More Challenging Small ➢Large; Slow ➢Fast; Single Plane ➢Multi-Plane
	Lower Extremity	Segments involved Function at Segment Overall Mode	Hip, Knee, Ankle/Foot Stability Movement Open chain vs Closed Chain	Less ➢More Challenging Small ➢Large; Slow ➢Fast; Single Plane ➢Multi-Plane
	Hand Function	Use Coordination	Free vs In use Unilateral vs Bi-Manual	Free ➢Grasp➢ Manipulate Active Assist ➢Yoked *[symmetrical vs reciprocal]*➢Independent
Environment	Real World	Support Surface Compliance Support Surface Perturbation	Firm vs Compliant Passive *[non-mechanical]* vs Active *[mechanical]*	Stable ➢Unstable *[floor, wobble board, etc]*; Less ➢More Compliant *[floor, foam, etc]* One➢Multi-plane; Small➢Large Amplitude One➢Multi-plane; Small➢Large Amplitude; Predictable➢Random; Low➢High Intensity *[velocity, acceleration, etc]*
	Virtual World	Objects Obstacles Visual Flow Auditory, Haptic Elements	Stationary vs Moving Accommodation Required Stationary vs Moving Present vs Inactivated *[not present]*	Expected ➢Distracting; Predictable ➢Startling By One Body Part ➢By Whole Body Slowly➢ Quickly; Predictable ➢Startling Expected ➢Distracting; Predictable ➢Startling Expected ➢Distracting; Predictable ➢Startling
Task	Performance Characteristics	Type Variability Locus	Discreet vs Continuous Constant vs Variable Motions Timing	Less➢More Variable; Predictable➢Random Self-determined➢Responsive Self-determined➢Responsive
	Accuracy	Spatial Temporal	None ➢Required None ➢Required	Less ➢More Demanding Less ➢More Difficult
	Cognition	Decision making Attention	None required vs Strategy/Planning involved Quiet vs Distractors	Simple➢More Difficult; One Step➢Multi-step Less ➢More distraction *[visual, choices, audio, etc]*

VR Gaming Selection, Adaptation, Modulation, Progression

FIGURE 1 | Clinical Decision Making Framework. The framework synthesizes motor learning and control and exercise science considerations as encountered in the use of VR or gaming technologies as a therapeutic training modality in rehabilitation. It is portioned into demands based on the person (body segment), the environment, and the tasks. The realms specify the potential areas to consider within each type of demand; and the category breaks down each realm into the motor learning, motor control, or exercise-based elements presented within that realm. Within each category, the difficulty of the motor control, motor learning, or exercise element presented can be modulated through discreet choices (Choice) and/or by increasing or decreasing the parameters indicated within "Continuum".

Gentile's Taxonomy of Tasks (67) expands on aspects of the above task and environmental demands and creates a classification for movement activities based on these. The least challenging tasks are those that do not require U/E manipulation and that are performed in a stationary, non-variable environment. Tasks in the taxonomy steadily become more difficult with the addition of mobility requirements, a manipulation component, or increased variability in the environment. The degree of difficulty associated with a movement task and progressing the complexity of a task are determined by changing its taxonomy. When temporal environmental factors are stationary, only the spatial factor of the movement is controlled by the environment—tasks in which temporal environmental factors remain stationary and fixed from trial to trial are termed *closed tasks.* Tasks in which the temporal factors of the environment are stationary but the spatial factors of the task, such as the size or location of objects, vary from trial to trial, are called *variable motionless tasks*. When environmental factors include objects or persons that are moving, both spatial and temporal factors of the movement are determined by the environment. Tasks in which these environmental factors change from trial to trial are termed *open tasks.*

Rehabilitation, especially neuro rehabilitation, largely involves structuring practice to facilitate acquisition or re-learning of skills, with attention to all of the considerations inherent in the above parent theories. Other relevant concepts and principles that underpin therapeutic exercise in neuro rehabilitation include open chain vs. closed chain modes of exercise, considerations of the stages of motor learning, and categories of motor skills including dual-task skills (64).

Framework Structure

In analyzing our use of gaming, the games themselves, and our clinical thought processes in using gaming in therapy, we created an initial structure for the framework around the integrated motor-control theory concept of movement as a product of the interaction among the individual, the task, and the environment (65). As such, our framework is comprised of three types of **demands**: person (body segment), environment, and task (**Figure 1**). Each demand is comprised of one or more **realms**, domains of interest within that demand type. The ***body segment demands*** are person-level and define the postural stability, movements, and necessary interactions between these two, required for successful game play. These are analyzed by body segment **realms**, specifically *posture, trunk, U/E, lower extremity (L/E),* and *hand function*. The ***environmental demands*** include the external characteristics of the *real-world* **realm** in which the player (person) is gaming, as well as the environmental context provided by the *virtual* (game) **realm**. The ***task demands*** characterize additional motor learning and motor control constraints and affordances related to the specific game, such as attentional and cognitive requirements. Each **realm** is comprised of **categories**, specific factors to consider that are reflective of the **realm**. Within a **category,** a judgement is rendered as to the relative difficulty of the item as presented in the specific person/game/set-up under consideration. In some cases, it is a **choice** (yes/no, present or not); in others it is a **continuum** (from less to more difficult or complex).

Framework–Theory Integration

Person/Body Segment Demands

Gaming and VR platforms dictate, to a greater or lesser degree, the functional requirements of a game, for example, avatar-based systems often require full body participation, while accelerometer or inertial measurement unit (IMU) based systems can respond to single segment motion, allowing but not requiring full body motion. The functional requirements of a game that intersect with the individual's attributes include overall posture, BOS, and specific combinations of joints providing stability or movement. While some games can be played, for example, in sitting or standing, others dictate one particular posture. Base of support can be dictated by certain games (e.g., kicking in single limb stance), but others do not respond to foot placement at all, allowing any stance for play. Certain games and platforms allow or can be adapted to be played from sitting or with one or both upper extremities in weight bearing.

Stability and *mobility* are categories of motor skills: stability involves maintenance of a posture at rest or during movement, and mobility involves controlled movement of the body or segment from one posture to another (64). In the given posture, with the given BOS, the activity may engage the full body or any segments in stability or mobility motor skills. Segmental analysis reveals whether a segment is stable or mobile, allowing for both therapeutic emphasis and avoidance. The lower extremities (or single leg) in stance must provide stability and the trunk may be required to provide a stable base for arm motions. In contrast, one lower extremity may be in motion (kicking) while the other provides stable support, or the trunk may move with the arms to complete the activity (e.g., trunk rotation with arm swing in a racket sport). Segments can be required to provide stability and movement simultaneously. Mobility is further graded by its amplitude or arc of motion, the speed of movement, and the planes of motion involved in the game. Extremities can be used in both open and closed chain fashions, with some modifications to the experience often needed for closed-chain upper extremity use. Open chain motion involves a freely moving distal segment while, in closed chain motion, the distal segment is fixed (64). Modulating this parameter allows some specificity of training to the eventual, real world tasks of interest.

With some platforms and games, hand use may be minimal to unnecessary, while others require it. Accelerometer-based games typically require enough dexterity to manage the controller. Cases in which hand use is a therapeutic goal may require adding various manipulanda, which are included in certain games and can be easily adapted by the clinician in others. Hand function required by a game to stabilize, grasp, or manipulate the controller and object can be bilateral or unilateral, and can often be done in a variety of active assisted fashions. Finally, some games require elements of symmetrical or reciprocal arm activity, such as swinging a golf club, while others require independent left vs. right hand use, such as playing a guitar.

Environmental Demands

Active games and VR create virtual environments that must be considered along with the real-world environmental constraints of any activity. There are no real consequences if the constraints of the virtual environment are not met, though they may be felt as "real" by players engaged in the game. The real-world environment, however, can present real constraints. Thus, the model delineates real and virtual environmental constraints.

Aligning with Gentile's taxonomy (67), the framework identifies whether the real environment is stable or in motion, whether this varies between trials, and if the variability is predictable. Specifically, the weight bearing surface can be firm or compliant on a continuum of being more stable (less difficult), such as standing on the floor, to less stable (more difficult), such as standing on a Bosu ball. Induced perturbations can be caused by a passive surface, such as a wobble board, or by an active mechanical surface, such as a motorized platform. Surface perturbations can also be: unidirectional (e.g., wobble board) or multidirectional (e.g., Bosu ball), smaller to larger amplitude, lower to higher intensity (velocity/acceleration), and predictable vs. random.

The framework classifies the virtual environment into four broad categories: objects, obstacles, visual flow, and auditory or haptic components. There are objects in the virtual world (visual field) that do not need to be accommodated; these are one type of non-regulatory conditions (67). These objects can be stationary or moving, related to the task (expected) or unrelated (distractors) that must be ignored, and predictable or startling. For the virtual obstacles on the other hand, accommodation by one body part or by the whole body (regulatory) is an aspect of the game. These can be stationary (relative to the overall motion of the virtual environment) or in motion (moving distinctly from the rest of the virtual environment), and they can move slowly to quickly and predictably to unpredictably. A visual flow is created in the virtual environment giving the sense of moving directionally, including looming or receding as appropriate (68). This flow can be as expected (i.e., matches the movement of the player/avatar appropriately) or unexpected (mis-matched) and predictable or startling. Finally, auditory or haptic elements can be active or de-activated, and when active, can range from expected to distracting and from predictable to startling.

Task Demands

The ability to modulate motor learning and performance characteristics are an advantage of gaming over standard modalities. Game tasks may be discrete or continuous. Consistent with motor learning theory, discrete tasks provide breaks for rest, hypothesis testing, feedback, or attention (63). Continuous tasks demand more endurance (motor, attentional, cardiopulmonary, et cetera), and potentially more automaticity in task performance, consistent with more mature stages of motor learning (64). They also provide more overall practice repetitions and the higher dosage necessary for motor retraining (23–26). Tasks may also be variable or not, as described in Gentiles's taxonomy (67); if variable, they are graded as minimal to extensive and predictable to random. In the early stages of learning, blocked practice enhances motor learning, while retention is better in later stages of learning with random practice (63). The contextual interference introduced with more variability enhances retention, learning, and likely transfer, but must be adjusted to the skill level of the learner (69).

Timing and motion responsiveness range from self-determined, in which the player chooses the specifics of the timing and motions, to responsive, in which the game dictates all of these parameters. Therapeutically, both modes demand motor planning and initiation, while a responsive mode also promotes perseverance, endurance, faster responses, and automaticity – corresponding to progression through stages of motor learning (64). More impaired individuals may master game play more easily when both timing and motions are self-determined because they can slow the pace and are allowed more motion options. Games may have no accuracy demands or may require a high degree of spatial and/or temporal accuracy. Both of these are components of Gentile's taxonomy and can be regulatory (essential to meet) or non-regulatory (67). When temporal and spatial accuracy demands are simultaneous, one component typically predominates (63).

The requirement to maintain specific postures and motions while also attending to a game mean that gaming and VR are inherently dual tasks, the most challenging category of motor skills (64). A range of motor and/or cognitive elements can be added, or their difficulty modulated through game choice. The cognitive domain includes decision-making requirements, and attentional demands (70). Decision-making demands may be none to simple choices (e.g., to swing or not at a pitched baseball) to multiple choices (e.g., best route to avoid an obstacle in a racing game.) to requiring multi-step strategic planning for successful play. Finally, games have few to many distractors (non-regulatory elements) which may or may not be relevant to the game and, if present, are an additional decision-making requirement (i.e., to be ignored or attended to).

DISCUSSION

This framework has been developed for use by rehabilitation clinicians working with clients with mobility, movement, and motor re-learning goals. It is designed for VR or gaming-based movement and practice based therapeutic exercise, particularly motor learning and control. It is useful for games that present and respond to full or large body motions, and it is not technology specific. The framework can be applied across gaming and VR platforms, including newly developing technologies, because it is non-system specific in its design and terminology and it incorporates well-established theoretical concepts and principles. It is, however, a *motor* rehabilitation framework and is not designed to be used with games that emphasize cognition or strategy, especially those played primarily via a joystick, buttons, keyboard, et cetera. It also does not address gaming targeted at fitness, or primarily cardiovascular/pulmonary interventions.

Framework Use

In every therapeutic activity, the clinician must intentionally prioritize the critical active ingredients to address or to avoid, including body segments and movements, correct levels of challenge, and specifics about the physical environment. Gaming has significantly more elements to consider than typical therapeutic activities; virtual features can provide additional challenge, level and type of task constraints, and motor learning and control components that should be emphasized. The clinician must choose and tailor the game effectively to align the therapeutic aspects with the client's treatment goals. The framework guides the clinician in considering all of the critical variables, specifically in the context of gaming. It also facilitates evaluation of gaming-specific factors that might not be an issue in a non-gaming context, for example, overload of cognitive demands, startling elements, and/or additional virtual obstacles to accommodate.

It is important to be able to modulate the difficulty of any therapeutic exercise or activity. In gaming, adding or removing motor control elements increases or decreases the difficulty of the activity. Likewise, within categories, adding or eliminating the yes/no elements increases or decreases the active therapeutic elements impacting the player (client), as does moving toward the harder or easier end of the continuum in graded elements. For example, to increase the challenge of an activity, temporal or spatial accuracy demands can be added then increased, expected movement excursions can be increased, and dictated base of support can be decreased. It should be noted that moving through the game options or levels may increase or decrease the difficulty and those differences can be identified through the framework.

The framework guides decisions about modifications to the real or virtual environment or task. Game analysis, through the framework, identifies elements that the client may not be able to tolerate, or which may be detrimental, for example a game may be overly challenging or specific gaming variables may interfere with the therapeutic session. Some aspects may be contraindicated or unsafe for an individual, such as altered visual flow (Realm–Virtual World, Category–Visual Flow) or stepping requirements (Realm–Lower Extremity, Category–Function at each Segment, Choice–Movement). Analysis through the framework can point to needed real or virtual modifications, such as instructing the client to ignore certain obstacles, turning off the sound, or changing the support surface from standing to sitting.

Context in Which It Is Useful

Clinicians must document the therapeutic interventions that clients experience, not the games they play. The framework helps to articulate (document) the segments involved, the movement or stability requirements of the activity, the concurrent cognitive demands, and the other therapeutic elements of the treatment session. This then facilitates recording the added elements or progression within elements as well as any areas being avoided and the reasons. This treatment documentation is important for communication among providers, reimbursement, and to note and guide progress toward goals. Likewise, in gaming or VR research, this structure facilitates protocol design for and documentation of the impactful elements and levels of a gaming intervention, which allows accurate investigation and comparisons of gaming-based interventions. In the educational setting, the framework can help students identify and articulate the many considerations behind the use of gaming as a therapeutic modality and offers a structure for examining the theory-based therapeutic elements. Below are two examples illustrating use of the framework in two settings, a clinical research study and a clinic.

Case #1: Research Application

The framework was used to develop a gaming progression algorithm for a randomized controlled trial examining intense harnessed balance training for individuals post stroke. Five categories of **Person demands** represented the variety of standing/stepping balance challenges encountered during typical daily mobility activities: (1) anterior posterior stepping (AP stepping); (2) medial lateral stepping (ML stepping); (3) feet in place AP/ML/vertical center of mass (COM) weight shift (weight shift); (4) feet in place trunk turning (rotation); and (5) alternating single leg stance with dynamic kicking (SLS). A four-level progression of Kinect (Microsoft) video games combined with varied standing support surfaces was used to gradually increase the intensity demand within each balance activity category, systematically maintaining high intensity practice demands.

In the **Person demand** ***Lower Extremity Realm***, the framework was followed to vary activities in *Overall Mode* and *Function at Each Segment* from closed chain with stability demands (weight shift and rotation), open chain with mobility demands (ML and AP stepping), or a combination of both (SLS, with closed chain SLS and open chain LE kicking). In the ***Posture realm***, the games were chosen to vary in terms of smaller to larger *COM* control demands (rotation → weight shift → stepping → SLS). The ***Upper Extremity realm*** was varied in the need for open chain shoulder and elbow activity being required or not required in a given game.

The ML stepping progression illustrates how the framework guided **Environment** and **Task demand** modulation to increase training intensity using two games. In the first game, 20,000 Leaks (Leaks), the player had to plug a varying number and placement of leaks in a surrounding aquarium. In the second game, Reflex Ridge (RR), the gamer rode a moving mining cart while dodging various obstacles. In the **Environment**, all ***realms*** were varied. In the ***Real World realm,*** the *support surface* was changed by moving from solid (floor) to compliant (gym mats) surfaces. In the ***Virtual World realm***, the *objects* were moving, distracting, and unpredictable in both games, however RR demanded speedy, full-body accommodation for random *obstacles*. RR also added managing *visual flow* while riding the moving cart. The **Task** was varied across three r**ealms.** For the ***Performance characteristics,*** the *locus* was self-initiated in Leaks and responsive in RR, and *spatial* **accuracy** only was required in Leaks while both *temporal and spatial* ***accuracy*** were needed in RR. ***Cognitively***, both games required *decision-making* and *attention*, but the demands of RR were more complex and required speed.

Case #2: Clinical Application

In the clinical case example, the therapist and client with left hemiplegia first established a collaborative treatment goal: reaching the left arm to a table top in sitting with less than 30 degrees of elbow flexion in order to stabilize objects for various bimanual tasks. This was currently effortful and accomplished very slowly, with shoulder abduction and 90 degrees of elbow flexion. The critical **Person** component was in the ***Upper Extremity realm***, with the *Segments, Function,* and *Overall Mode* requiring open chain shoulder and elbow movement. The goal defined the ***Posture realm*** as seated and the ***Lower Extremity*** and ***Hand Function realms*** were deemed not essential, however rotation *movement* of all *segments* of the ***Trunk realm*** was desired. A racket type game was chosen but modified for play in sitting and for holding the racket with both hands. This "yoked" reciprocal pattern was chosen to decrease left arm task intensity, with the right arm/hand actively assisting the left during dynamic racket swinging. A variety of game options existed using the Wii and Kinect games of baseball batting practice, tennis/table tennis, and golf. While tennis/table tennis involved both a forehand and backhand swing, both of which were desired movement practice motions, golf and batting could be varied similarly by requiring a right vs. left-handed swing, so **Environment** and **Task demands** were considered next in determining initial game choice.

The **Environment** was least critical in this case; to keep the task at an optimum level of difficulty for this client, no ***Real World realm*** *support surface compliance* or *perturbation* was desired and no ***Virtual World realm*** *obstacles, visual flow,* or *haptic/auditory elements* were selected since it was known that distractors made movement very difficult for this individual. The ability of the client to manage *moving objects,* however, needed to be assessed along with additional **Task demands** in all ***realms***. In the ***Performance Characteristics realm,*** tennis/table tennis were a more *continuous type* than the *discreet* batting practice or golf swing. Golf had the least *variability* and was the only *self-determined locus*. It required *spatial*, not *temporal* ***Accuracy***, while the *spatial accuracy* in batting practice was less difficult (less amplitude and variability) than tennis/table tennis. Finally, in the ***Cognitive realm***, golf required the least *decision-making* and *attention,* and tennis/table tennis the most. Since this client was initially able to manage the *spatial/temporal* ***accuracy*** demands of batting but not tennis/table tennis, practice began with batting and later progressed to table tennis. In addition, **Environment** ***Virtual World*** *auditory distractor elements* were later added to better meet the client's goal of movement performance in noisy environments.

Limitations and Conclusions

It must be noted that this framework does not address feedback explicitly. Feedback is a crucial and complex component of motor learning (63, 64). Video games provide greater or lesser degrees of feedback about current play (knowledge of performance) through the avatar and visuals of the game itself. They also provide knowledge of results through points, scores, sounds, and visuals of cheering crowds, et cetera. This feedback is of variable scheduling, accuracy, and utility, depending on the platform and the game. While these both may be utilized at the clinician's discretion, the clinician should be providing feedback specific to the therapeutic tasks or movements, not to the game play. This is especially important for transfer or generalizability of the motor learning to real world conditions. Finally, this framework does not explicitly guide the process of taking the skills mastered in the gaming environment into real-world contexts. As with any motor learning intervention, the clinician must structure treatment sessions to include practice ultimately in real world contexts, out of the therapeutic environment (71). This framework does facilitate explicit identification of the therapeutic components involved in the gaming intervention which will need to be matched to the necessary real-world activities, practiced in the gaming environment, then practiced and assessed in the real-world environment.

Frameworks exist for many aspects of clinical decision-making within rehabilitation: for types of treatment (72, 73), for aspects of practice, such as goals and content of exercise interventions (74); or for decision-making (55, 75). Holden (47) noted the need for designers and users of VR in rehabilitation to know VR technology *and* motor learning principles, and to match VR features to those principles. This framework facilitates this necessary clinical decision making with the client's needs and goals foremost.

DATA AVAILABILITY STATEMENT

The original contributions generated for the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

All three authors contributed to this conceptualization/idea of the Framework as well as the research and model development. DE and AR completed iterative testing of the model. All authors assisted in writing the manuscript.

FUNDING

This work was funded in part through a Cleveland State University Undergraduate Research Engaged Learning Grant to DE and AR.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Neurology

ORIGINAL RESEARCH
published: 03 June 2021
doi: 10.3389/fneur.2021.597404

Postural and Head Control Given Different Environmental Contexts

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OPEN ACCESS

Edited by:
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Reviewed by:
Antonino Naro, Centro Neurolesi Bonino Pulejo (IRCCS), Italy
Dara Meldrum, Trinity College Dublin, Ireland

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Specialty section:
This article was submitted to Neurorehabilitation, a section of the journal Frontiers in Neurology

Received: 21 August 2020
Accepted: 07 May 2021
Published: 03 June 2021

Citation:
Lubetzky AV, Kelly JL, Hujsak BD, Liu J, Harel D and Cosetti M (2021) Postural and Head Control Given Different Environmental Contexts. Front. Neurol. 12:597404. doi: 10.3389/fneur.2021.597404

Virtual reality allows for testing of multisensory integration for balance using portable Head Mounted Displays (HMDs). HMDs provide head kinematics data while showing a moving scene when participants are not. Are HMDs useful to investigate postural control? We used an HMD to investigate postural sway and head kinematics changes in response to auditory and visual perturbations and whether this response varies by context. We tested 25 healthy adults, and a small sample of people with diverse monaural hearing ($n = 7$), or unilateral vestibular dysfunction ($n = 7$). Participants stood naturally on a stable force-plate and looked at 2 environments via the Oculus Rift (abstract "stars;" busy "street") with 3 visual and auditory levels (static, "low," "high"). We quantified medio-lateral (ML) and anterior-posterior (AP) postural sway path from the center-of-pressure data and ML, AP, pitch, yaw and roll head path from the headset. We found no difference between the different combinations of "low" and "high" visuals and sounds. We then combined all perturbations data into "dynamic" and compared it to the static level. The increase in path between "static" and "dynamic" was significantly larger in the city environment for: Postural sway ML, Head ML, AP, pitch and roll. The majority of the vestibular group moved more than controls, particularly around the head, when the scenes, especially the city, were dynamic. Several patients with monaural hearing performed similar to controls whereas others, particularly older participants, performed worse. In conclusion, responses to sensory perturbations are magnified around the head. Significant differences in performance between environments support the importance of context in sensory integration. Future studies should further investigate the sensitivity of head kinematics to diagnose vestibular disorders and the implications of aging with hearing loss to postural control. Balance assessment and rehabilitation should be conducted in different environmental contexts.

Keywords: sensory integration for postural control, Head Mounted Display, vestibular disorders, hearing loss, balance

INTRODUCTION

The ability to adapt to changes in the sensory environment is considered critical for balance (1). Healthy individuals are able to maintain their balance with their eyes closed, for example, because they will rely on other senses (e.g., vestibular, somatosensory) for postural control (2, 3). An inability to reweight sensory information may lead to loss of balance with environmental changes, e.g., darkness, rapidly moving vehicles (due to visual dependence), or slippery surfaces (due to somatosensory dependence) (2, 4). Historically, the inputs considered for balance consisted of visual, vestibular, and somatosensory, but recent studies suggest that auditory input may serve as a 4th balance input (5). The presence of stationary white noise has been shown to be associated with reduced postural sway, particularly during challenging balance tasks such as standing on foam or closing the eyes (6). To understand the role of sounds in postural control, it is important to combine different levels of auditory and visual cues to better reflect day-to-day postural responses in healthy individuals.

Context has been shown to have an important impact on balance performance, potentially induced by cognitive and emotional aspects, such as postural threats, fear of imbalance or symptoms related to past experiences within specific environments (7). This top-down modulation can interact with the multisensory integration process to affect the motor plan and cannot be captured without providing an environmental context. To facilitate transfer of balance control, it is imperative that we test and train individuals in conditions as close as possible to those commonly encountered during daily activities (8). The importance of context may be analogous for auditory stimuli. While limited research exists on the relationship between auditory input and postural control, a few studies incorporated natural sounds (e.g., a fountain) and suggested that differences in response to natural sounds relate to the properties of the sounds (greater variety of binaural and monaural cues including static and moving features) (9) and the innate emotional/cognitive responses of the individual (5). The majority of studies, reporting that balance is context-dependent, however, refer to the task (single or dual, static or dynamic) or the surface type (10–13). Current virtual reality technology allows context-based testing of multisensory integration and balance using Head Mounted Displays (HMDs) (14).

A novel HMD-based sensory integration paradigm where visual and auditory cues are manipulated in different contexts could be of particular importance to people with sensory loss. Individuals with vestibular dysfunction appear to develop a substitution strategy whereby the remaining sensory inputs (e.g., vision) are weighted more heavily (15–21). Such a strategy is problematic in hectic environments (22). Indeed, individuals with vestibular dysfunction complain of worsening dizziness and balance loss in complex settings such as busy streets (23–25). Data are accumulating regarding the importance of sounds for balance (6). Likewise, several studies suggested an independent relationship between hearing loss, balance impairments and increased risk for falls (26, 27). At present, the mechanism underlying imbalance in patients with hearing loss who do not present with vestibular symptoms is not clear; potential mechanisms include a common inner ear pathology, abnormal sensory weighting/reweighting, cognitive processing or a combination of these (6). Additional research is necessary to explore these and/or other mechanisms mediating imbalance in these groups.

Postural responses to visual perturbations and the contributions of sounds to balance are typically quantified *via* postural sway (6). HMDs, designed to move the virtual scene according to the participant's head movement, accurately (28) record head position at 60–90 Hz with no additional equipment (29). Some studies, however, found differences in head kinematics, and not in postural sway, between patients with visual sensitivity or vestibular dysfunction and controls in response to visual perturbations (30–33). Indeed, people with vestibular loss demonstrated increased head movement compared with controls in response to head perturbations, potentially associated with excessive work of their neck muscles in order to control the head in space (34, 35). In related work we observed that responses to visual cues were magnified at the head segment also among healthy young adults. Head kinematics may provide an important additional facet of postural control beyond postural sway.

The aims of this study were as follows:

1) Determine how postural sway and head kinematics change in healthy adults in response to auditory perturbations when combined with visual perturbations. We expected more movement in response to the visual perturbations, particularly around the head but also for postural sway. Based on prior studies showing a significant reduction in head movement among healthy adults with broadband white noise via speakers (36) or a reduction in head movement with 2 speakers projecting a 500 Hz wave in people who are congenitally blind (37) we hypothesized that head movement will also increase with the sound perturbations.
2) Determine whether the response to sensory perturbations (*via* postural sway and head kinematics) varies by context. Given that balance is known to be context-dependent, we expected the responses to sensory perturbations to be magnified in a semi-real contextual scene.
3) Explore the feasibility of this novel HMD assessment in individuals with vestibular loss and hearing loss and establish a protocol for future research.

METHODS

Sample

Healthy controls ($N = 25$) were recruited from the University community. Adults with chronic (>3 months) unilateral vestibular hypofunction ($N = 7$) participating in vestibular rehabilitation for complaints of dizziness or imbalance were recruited from the vestibular rehabilitation clinic at the New York Eye and Ear Infirmary of Mount Sinai (NYEEIMS). Adults with monaural hearing ($N = 7$) for various reasons who had no current vestibular issues or self-reported imbalance were recruited from the Otolaryngology clinic at the NYEEIMS. We defined monaural hearing as an ability to hear on one side only due to a single-sided hearing loss or due to bilateral profound hearing loss corrected with a single cochlear implant (CI). Inclusion criteria for all groups were: 18 or older, normal or corrected to normal vision, normal sensation at the bottom of the feet, and ability to comprehend and sign an informed consent in English. This study was approved by the Institutional Review Board of Mount Sinai and by the New York University Committee on Activities Involving Human Subjects.

System

Visuals were designed in C# language using standard Unity Engine version 2018.1.8f1 (64-bit) (©Unity Tech., San Francisco, CA, USA). The scenes were delivered via the Oculus Rift headset (Facebook Technologies, LLC) controlled by a Dell Alienware laptop 15 R3 (Round Rock, TX, USA) with a single sensor placed on a tripod 1.6 meters in front of the participant. The rift has a resolution of 1,080 × 1,200 pixels per eye and uses accelerometers and gyroscopes to monitor head position with a refresh rate of 90 Hz. It has a field of view of 80° horizontal and 90° vertical. Environmental auditory cues were captured with the Sennheiser Ambeo microphone in first order Ambisonics format. The background sounds merged with a sound design process which involved simulating the detailed environmental sounds that exist within the natural environment to develop a real-world sonic representation. Abstract sounds were generated in Matlab. The audio files were processed in Wwise and integrated into Unity.

Scenes

Stars

The participants observed a 3-wall (front and 2 sides) display of randomly distributed white spheres (diameter 0.02 m) on a black background (See **Figure 1A** and **Supplementary Material**) (38). Each wall was 6.16 by 3.2 m with clear central area of occlusion of 0.46 m in diameter to suppress the visibility of aliasing effects in the foveal region (39). Similar to Polastri and Barela (40) the spheres were either static or moving at a constant frequency of 0.2 Hz with either a "low" amplitude (5 mm, AP5) or "high" amplitude (32 mm, AP32). The sounds were developed as rhythmic white noise, scaled to the visual input (**Table 1**).

City

The city scene simulates a street with buildings at randomly generated heights, cars and pedestrian avatars (See **Figure 1B** and **Supplementary Material**). The difference between "low" and "high" visuals was the amount of avatar pedestrians and the addition of moving cars. Pre-recorded sounds were also scaled "low" and "high" levels of complexity (**Table 1**).

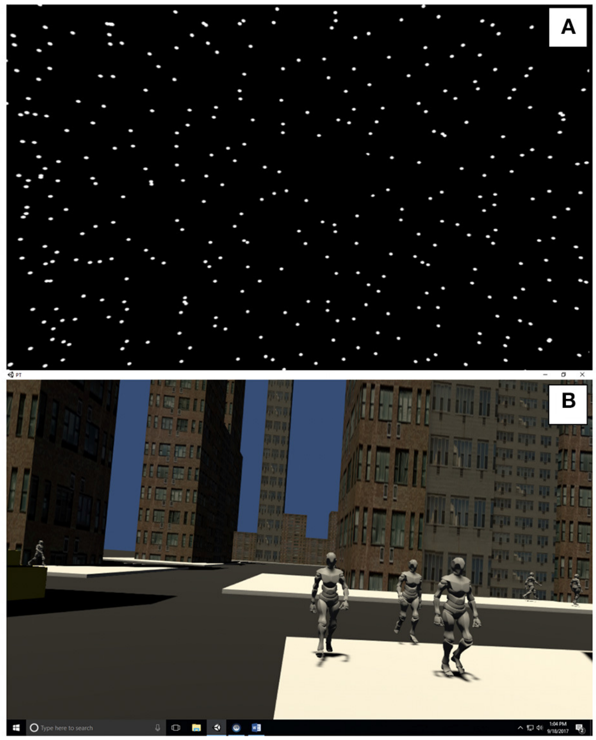

FIGURE 1 | A screenshot of the Stars scene **(A)** and the City scene **(B)**.

TABLE 1 | Description of the auditory and visual stimuli in each scene.

The scene	Stars	City
Low visual	0.2 Hz, 0.005 m, in the anterior-posterior direction (AP5)	1–4 avatars are moving from front and back at a speed of 0.51–1.40 m/s.
Low sound	White noise that cycles from 0 to 0.25 dB above played intensity at 0.3 Hz	Ambient sounds include people chatting and city rumbling sounds, mainly caused by traffic.
High visual	0.2 Hz, 0.032 m, in the AP direction (AP32)	4–8 avatars, moving in the same speed and direction as "low." Ten yellow cars are circling around the street.
High sound	White noise that cycles from 0 to 1 dB above played intensity at 0.3 Hz	Complex sounds include footsteps, car horns honking, a jackhammer, and sirens.
Static, no sound	Display of stars with no movement or sounds	Display of the "high" city with 0 speed (no movement) and no sound.

Each scene lasted 60 s.

Testing Protocol

Participants stood hip-width apart on a stable force-platform wearing the Oculus Rift and were asked to look straight ahead and do whatever felt natural to them to maintain their balance. Participants were guarded by a student physical therapist. Two quad canes were placed on either side of the force-platform for safety and to help with stepping on and off the force-platform. Most participants completed 3 repetitions of each dynamic combination (low, low; low, high; high, low; high, high) and 1 of the "static visuals/no sound" scene per environment. To monitor cybersickness, the Simulator Sickness Questionnaire (SSQ) (41) was administered at baseline, breaks and at the end of the session. The Dizziness Handicap Inventory (DHI), (42) the Activities Specific Balance Confidence Scale (ABC), (24) and a demographic questionnaire were completed during their rest breaks.

Data Reduction and Outcome Measures

The scenes were 60-s long and the last 55 s were used for analysis (38). Postural sway was recorded at 100 Hz by Qualisys software for a Kistler 5233A force-platform (Winterthur, Switzerland). Head kinematics was recorded at 90 Hz by a custom-made software for the Oculus Rift headset. The criterion validity of the Oculus Rift to quantify head kinematics within postural tasks as compared with a motion capture system has been established (28). We applied a low-pass 4th order Butterworth filter with a conservative cutoff frequency at 10 Hz (43). Directional Path (DP) (44) was calculated as the total path length of the position curve for a selected direction. DP is a measure of postural steadiness and is used as an indication of how much static balance was perturbed with a given sensory manipulation. DP was calculated in 2 directions for force-platform data (AP, ML in mm) and 5 directions of head data [AP, ML in mm, pitch (up and down rotation), yaw (side to side rotation), roll (side flexion) in radians]. DP derived from a force platform is a valid and reliable measure of postural steadiness (45). We previously demonstrated the test-retest reliability of postural sway DP within a similar protocol without the sounds (46).

Statistical Analysis

Aim 1

We generated box plots for each outcome measure (postural sway DP AP and ML and head DP AP, ML, pitch, yaw, roll) per environment across the 5 conditions (**Table 1**). We conducted a visual inspection of the box plots to determine whether the distributions differed by sensory perturbations among healthy adults.

Aim 2

Given that Aim 1 showed complete overlap of the box plots for the 4 dynamic conditions regardless of environment or variable, we combined all dynamic scenes into a single level (dynamic). For each of the 7 variables, we fit a linear mixed effects model (47, 48). Linear mixed-effect models were used to estimate overall differences between environments (Stars, City) and 2 levels of sensory perturbations (static, dynamic) in healthy adults. Based on initial inspection of the residual plots for these models we used a log-transformation of the response variable to limit the impact of heteroscedasticity. These models account for the individual-level variation that is inherently present when repeated measures are obtained from individuals through a random intercept for each individual. No random slopes were used. We present the model coefficients and their 95% confidence interval (CI) for each environment (stars, city) and level (static, dynamic). P-values for each fixed effect are calculated through the Satterthwaite approximation for the degrees of freedom for the T-distribution (49). In addition, for ease of clinical interpretation, we provide the estimated marginal means for each of the 4 conditions on the original response scale (mm or radians) along with their confidence intervals. Analyses and figures were created in R Studio version 1.1.423 (50).

Aim 3

We used descriptive statistics and inspected violin plots to explore how the patients are distributed around the controls' mean performance. The violin plot depicts the kernel density estimate where the width of each curve corresponds with the frequency of data points in each region. A box plot is overlaid to provide median and interquartile range. Individual data points are represented as black dots.

RESULTS

For a description of the sample see **Table 2**.

Aim 1

Across all outcome measures and all conditions, box plots of the scenes that included dynamic visual and auditory perturbations showed a complete overlap. Representative examples from postural sway and head data can be seen in **Figures 2**, **3**, respectively.

Aim 2

Given the lack of difference between "low" and "high" perturbations, we combined all perturbations data into a single "dynamic" category and compared it to the static level. All model coefficients are presented on the log scale whereas estimated marginal means in the response scale are presented in **Table 3**.

Postural Sway ML

We observed no significant main effects of sensory perturbations or environment, but a significant sensory perturbation by environment interaction such that the increase in Sway ML was larger between static and dynamic conditions in the city (β = 0.124, 95% CI 0.028, 0.221, $P = 0.012$) compared with the stars.

Postural Sway AP

We observed a significant increase in Sway AP between static and dynamic for both scenes (β = 0.051, 95% CI 0.006, 0.096, $P = 0.025$), with no main effect of environment or sensory perturbations by environment interaction.

Head ML

There were no significant differences between static and dynamic for Head ML for the stars scene. A significant main effect of environment was observed, such that that Head ML was significantly lower in the city compared with the stars (β = −0.191, 95% CI −0.311, −0.07, $P = 0.002$) and a significant sensory perturbation by environment interaction (β = 0.274, 95% CI 0.148, 0.399, $P < 0.001$) such that there was a significant increase with the dynamic condition in the city.

Head AP

We observed a significant increase in Head AP DP between static and dynamic for both scenes (β = 0.073, 95% CI 0.015, 0.13, $P = 0.013$), a significantly lower Head AP DP with city compared with stars (β = −0.244, 95% CI −0.322, −0.166, $P < 0.001$) and a

TABLE 2 | Sample demographics.

	Control	Vestibular hypofunction	Monaural hearing
Sex	17 women (68%)	5 women (71%)	2 women (29%)
	8 men (32%)	2 men (29%)	5 men (71%)
Age	Mean 28.40 (SD = 8.48)	Mean 53.7 (SD = 18.0)	Mean 52.57 (SD = 19.50)
DHI	Mean 0 (SD = 0)	Mean 26 (SD = 10.46)	Mean 12 (SD = 18.97)
ABC	Mean 100% (SD = 0)	Mean 74.55% (SD = 18.56)	Mean 90.56% (SD = 16.07)
SSQ baseline	Mean 0.20 (SD = 0.50)	Mean 4.86 (SD = 6.74)	Mean 2 (SD = 2.08)
SSQ final	Mean 0.90 (SD = 1.2)	Mean 7.43 (SD = 6.85)	Mean 2.14 (SD = 3.53)

DHI, Dizziness Handicap Inventory; ABC, Activities Specific Balance Confidence; SSQ, Simulator Sickness Questionnaire pre- and post-testing.

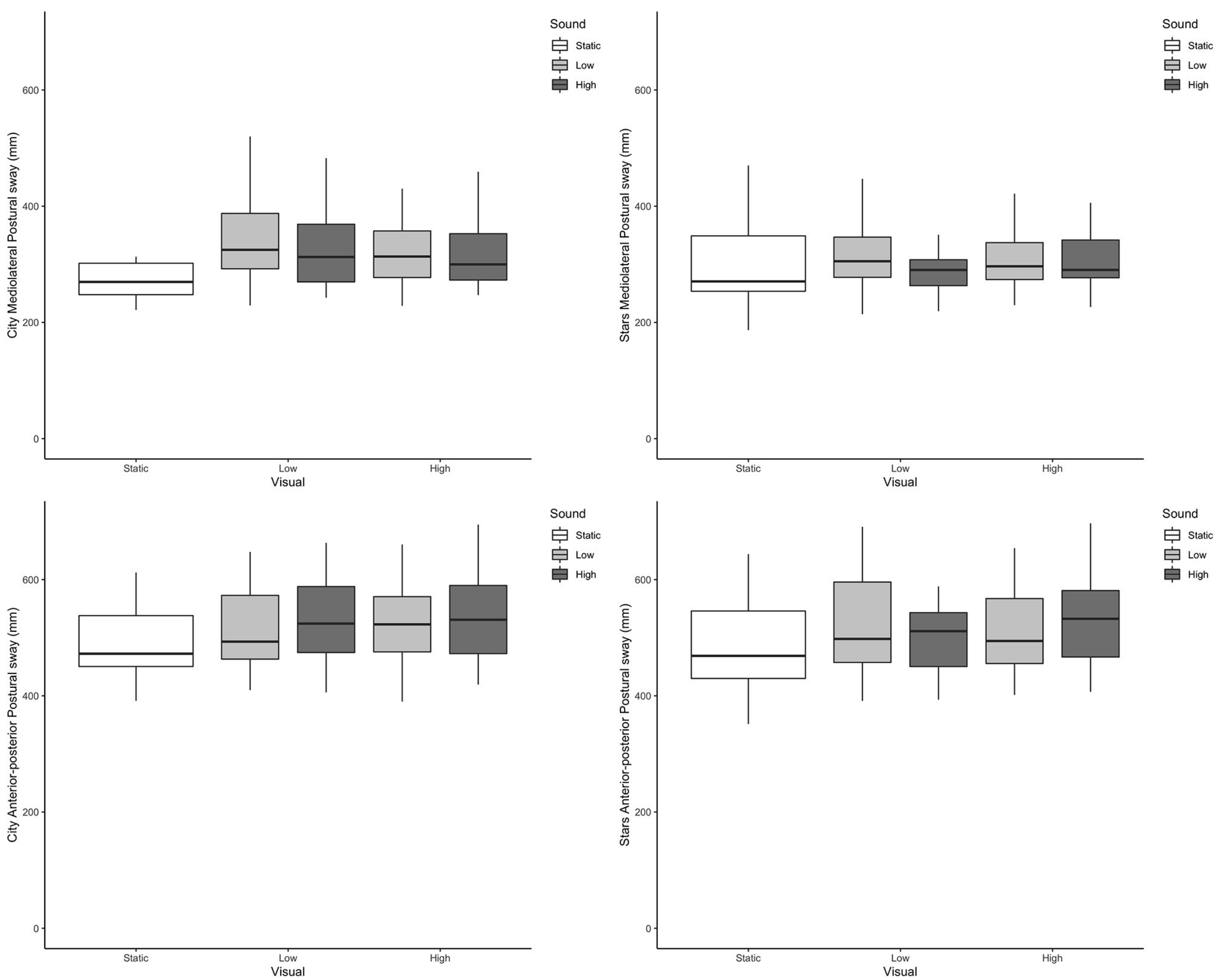

FIGURE 2 | Boxplots of postural sway directional path in mm (Y axis) across the different visual and auditory levels for the city scene (left-hand side) and stars scene (right-hand side) in the medio-lateral direction (top) and anterior-posterior direction (bottom).

significant sensory perturbations by environment interaction ($\beta = 0.172$, 95% CI 0.09, 0.253, $P < 0.001$) such that the increase with the dynamic condition was higher in the city compared with the stars.

Head Pitch, Yaw, and Roll

There were no significant main effect of sensory perturbations for pitch, yaw or roll. We observed a significant main effect of environment for pitch ($\beta = 0.628$, 95% CI 0.519, 0.737, $P <$

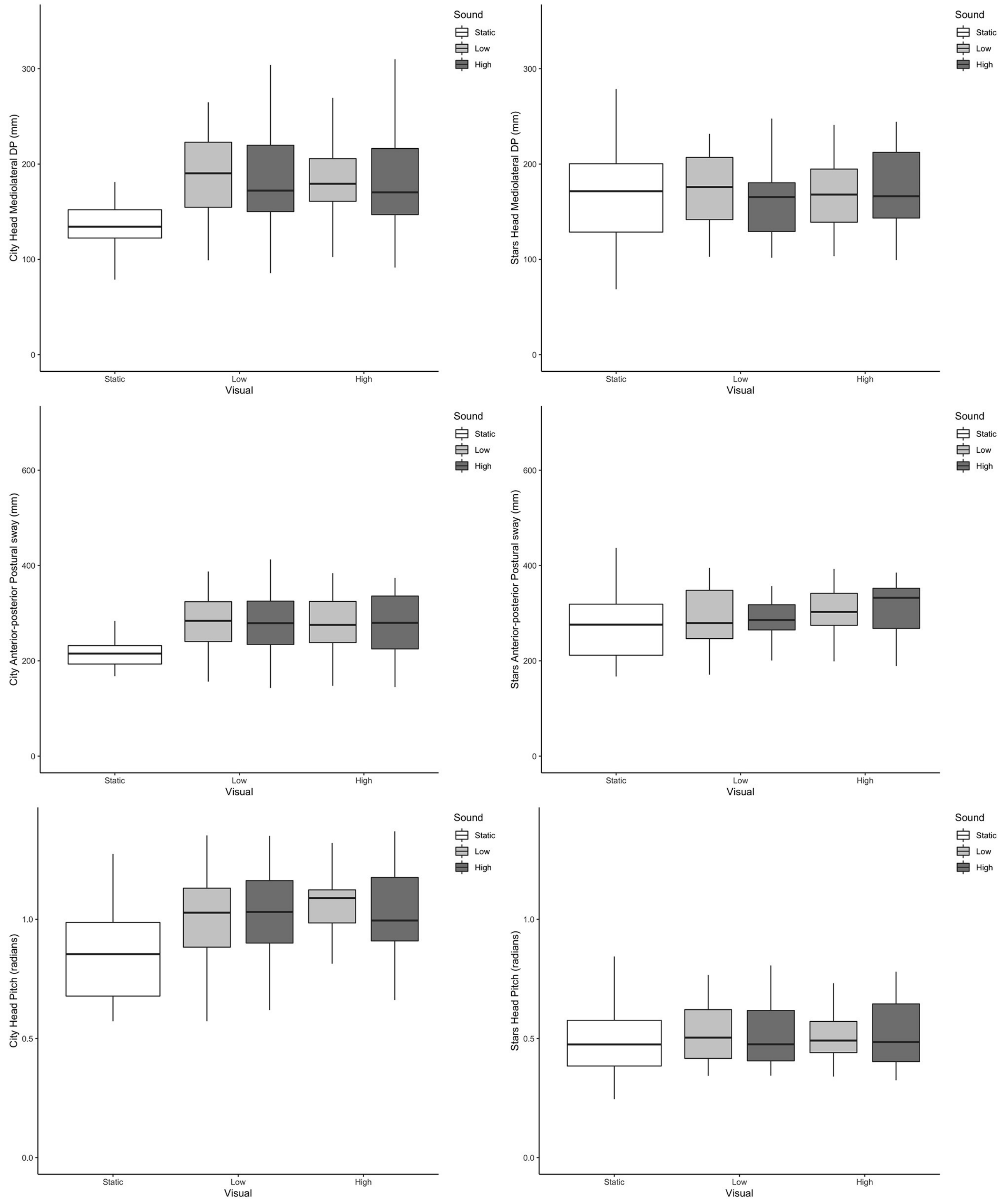

FIGURE 3 | Boxplots of head directional path (Y axis) across the different visual and auditory levels for the city scene (left-hand side) and stars scene (right-hand side) in the medio-lateral direction (top, mm); anterior-posterior direction (middle, mm) and pitch (bottom, radians).

TABLE 3 | Directional path estimated marginal means in the response scale with 95% confidence intervals.

	Stars static	Stars dynamic	City static	City dynamic
Postural sway ML (mm)	301 (274, 331)	304 (282, 327)	281 (255, 309)	321 (298, 345)
Postural sway AP (mm)	487 (454, 523)	513 (484, 544)	482 (449, 517)	532 (502, 564)
Head ML (mm)	161 (141, 183)	162 (146, 179)	133 (117, 152)	176 (158, 195)
Head AP (mm)	268 (242, 297)	288 (264, 315)	210 (190, 233)	268 (246, 293)
Pitch (radians)	0.47 (0.41, 0.53)	0.50 (0.45, 0.55)	0.87 (0.77, 0.98)	1.11 (1.01, 1.23)
Yaw (radians)	0.37 (0.32, 0.42)	0.40 (0.36, 0.45)	0.76 (0.67, 0.87)	0.91 (0.82, 1.02)
Roll (radians)	0.30 (0.26, 0.34)	0.32 (0.29, 0.36)	0.56 (0.49, 0.63)	0.71 (0.63, 0.79)

TABLE 4 | Description of the clinical groups.

Mean (SD) hearing loss onset in years	Type of hearing loss	Positive bedside vestibular testing	History of vestibular rehab	History of vertigo		
MONAURAL HEARING						
15.75 (8.61)	4 Bilateral SNHL with a unilateral cochlear implant	1 (2012)	1 (2012)	2 (2012, 2015)		
3 unknown	2 SSD (unamplified)					
	1 SSD + ARHL (unamplified)					
Mean (SD) vestibular hypofunction onset in years	**Hearing loss**	**VNG**	**Bedside head thrust**	**Head shaking nystagmus**	**Spontaneous nystagmus without fixation**	**Gaze evoked nystagmus without fixation**
VESTIBULAR HYPOFUNCTION						
2.38 (2.59)	1 symmetric bilateral ARHL (unamplified)	4 positive 0 negative 3 NT	3 positive 1 negative 3 NT	5 positive 2 negative	2 positive 5 negative	3 positive 4 negative

SNHL, Sensorineural Hearing Loss; SSD, Single-sided Deafness (>70 dB, 3-frequency pure-tone average with normal, <25 dB PTA contralateral ear); ARHL, Age-related Hearing Loss (SNHL beginning at 4 KHz with normal, <25 dB PTA in lower frequencies); NT, Not Tested.

0.001) and roll (β = 0.623, 95% CI 0.521, 0.726, $P < 0.001$) but not for yaw. Significant sensory perturbations by environment interactions were also observed for pitch (β = 0.177, 95% CI 0.063, 0.291, $P = 0.002$) and roll (β = 0.171, 95% CI 0.065, 0.278, $P = 0.002$), but not for yaw.

Aim 3

Table 4 includes a detailed description of the clinical groups. Representative violin plots can be seen in **Figure 4** (city ML, postural sway, and head), **Figure 5** (stars AP, postural sway, and head) and **Figure 6** (pitch). All descriptive statistics per group can be found on **Appendices A, B**.

Generally speaking, the majority of the vestibular group moved more than controls when the scenes were dynamic, particularly in the city scene. The monaural hearing group was more diverse. While 4 out of 7 performed similarly to controls, 3 patients emerged outside of the group on dynamic scenes. Of the 3, 1 had prior vestibular rehab, 1 had reduced hearing compared to the rest of the sample. Two of the 3 were elderly CI users (above 70 years of age), but 2 other younger CI users performed similarly to controls. Two of the three had the worst DHI (above 30 when the rest of the group was at 0) and ABC (the only 2 below 90%) scores (for averages see **Table 2**).

DISCUSSION

This pilot study provided insights into the inquiry of sounds for postural control, the importance of context, and provided further support for head kinematics as an important additional metric (32, 33) that goes beyond the information provided by postural sway alone. The headset used for this scientific inquiry, the Oculus Rift, allows for simultaneous manipulation of high-quality visuals and sounds while obtaining accurate head kinematics. The study also generated hypotheses for future research investigating postural control in people with monaural hearing and contextual sensory integration in people with vestibular loss.

The first question of this study was how postural sway and head kinematics change in healthy adults in response to auditory perturbations when combined with visual perturbations. We expected to see changes in postural sway between the "low" and "high" visual environments based on previous research using similar visual conditions (38, 40). We also hypothesized that head

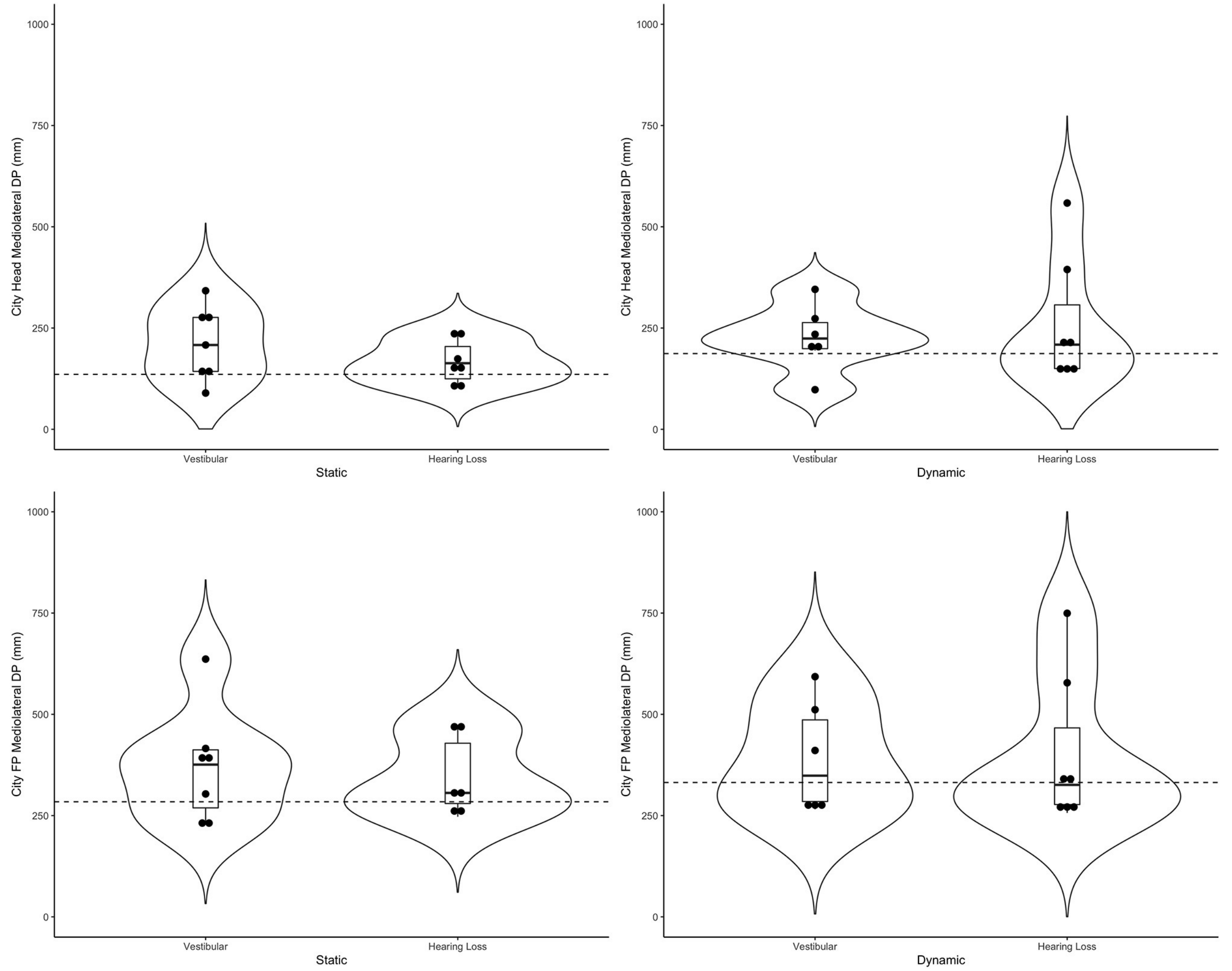

FIGURE 4 | Violin plots representing the distribution of both clinical groups around the mean of the control group (represented by the dashed line) for the city scene in the medio-lateral direction. Top plots show head data and bottom plots represent postural sway data (FP = forceplate). Left-hand side represents the static scenes and right-hand side represents the dynamic scenes.

movement will increase with the sound perturbations. However, these hypotheses were not met as in the current study, the "low" and "high" levels of auditory and visual stimulation did not make a difference in participants' movement when they were standing on the floor with their feet hip-width apart (based on descriptive statistics as well as median-based comparisons not shown). By combining the "low" and "high" data, we were able to explore the role of context, but no longer study the contribution of sounds to balance alone. It is possible that the addition of sounds, which were developed for this study, masked those differences. While all patients noticed the subtle differences between the dynamic scenes, most healthy adults could only detect a difference between the static and dynamic environments.

Our second question was whether the response to sensory perturbations (*via* postural sway and head kinematics) varies by context. Several observations with respect to this question should be discussed. First, medio-lateral postural sway increased with sensory perturbations in the city scene more than the stars scene. Anterior-posterior postural sway increased with sensory perturbations similarly in both environments. This is probably because the visual perturbation in both environments was in the anterior-posterior plane (flow of people or stars), and so a greater response in this direction is expected with an increased visual weight (51). As expected, further insights into people's motor behavior can be obtained from the head segment. For both medio-lateral and anterior-posterior head directional path we observed less movement on the static city environment vs. the static stars. This could be explained by the fact that a static street may feel more natural to people as compared with the "space" feeling many participants reported within the stars scene. This finding highlights the importance of including a static baseline scene to every environment to be studied. Interestingly, the

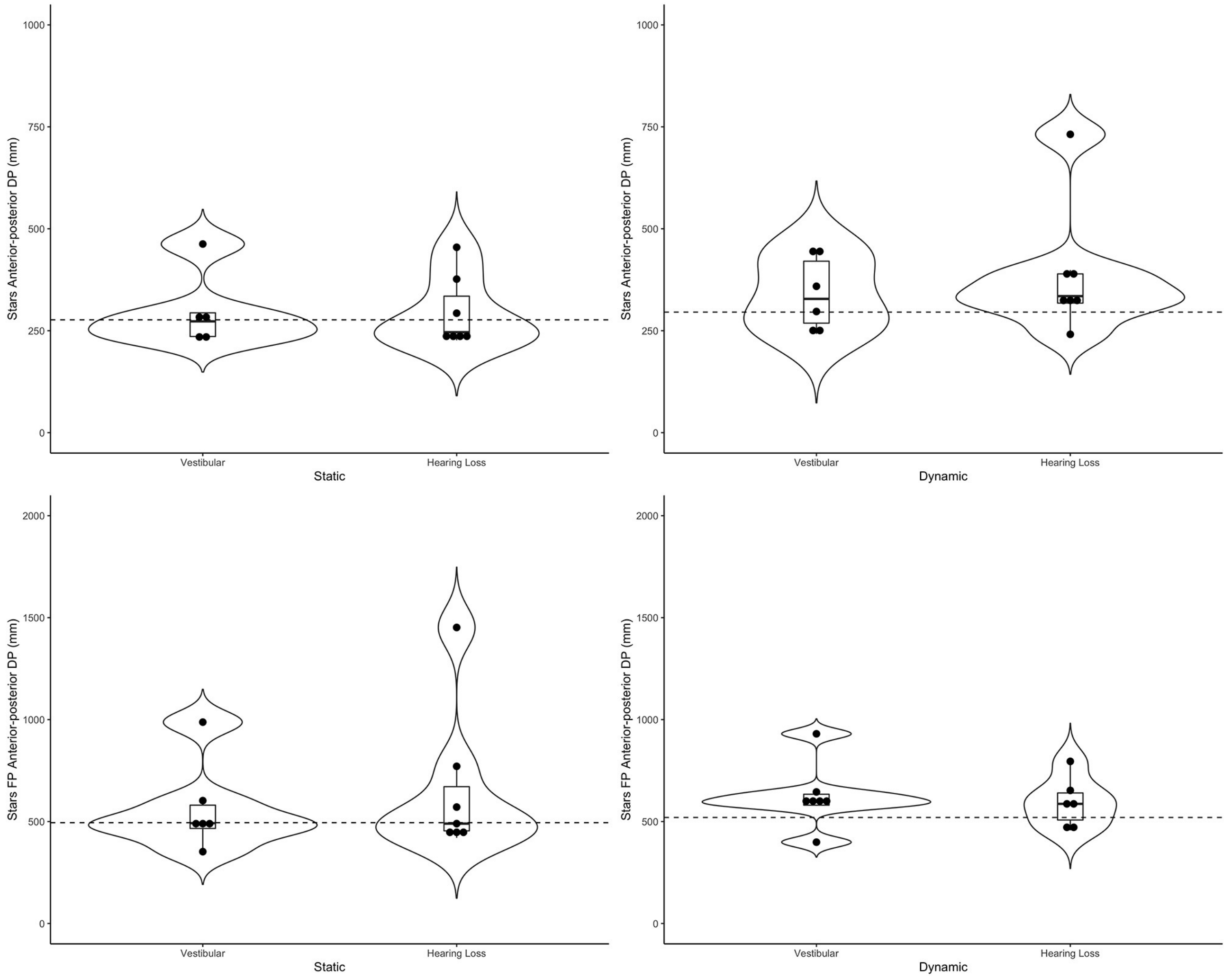

FIGURE 5 | Violin plots representing the distribution of both clinical groups around the mean of the control group (represented by the dashed line) for the stars scene in the anterior-posterior direction. Top plots show head data and bottom plots represent postural sway data (FP = forceplate). Left-hand side represents the static scenes and right-hand side represents the dynamic scenes.

transition from static to dynamic perturbations was larger in the city scene. Our sample also showed significantly more head pitch and roll on the city vs. stars environment. Potentially the participants were more influenced by the moving avatars than the moving stars, and perhaps felt a need to look away or avoid the flow of avatars that were moving toward them.

Our clinical sample was small and diverse, and the analysis of this sample was exploratory. Vestibular and auditory anatomy are closely linked (52), and peripheral vestibular hypofunction is often accompanied by various degrees of hearing loss. The current study did not include diagnostic vestibular testing on patients with hearing loss, so it is possible that these patients with hearing loss had an undiagnosed (or well-compensated) vestibulopathy. Patients with vestibular hypofunction were recruited from a physical therapy clinic whereas patients with monaural hearing loss were recruited from the physician's office where they were seen for their hearing. Patients with vestibular hypofunction also had higher level of simulator sickness than the other 2 groups, particularly after testing. Clinically, diagnostic vestibular testing is not routinely done in people with hearing loss unless they complain of dizziness. Interestingly, the two patients with monaural hearing loss that consistently showed much larger movement in response to sensory perturbation than the rest of the group (particularly AP postural sway and head movement, mostly in the stars scene) were the oldest in the group and had the worst DHI and ABC scores. It is possible that issues related to balance and hearing loss emerge in older age. It also suggests that all people with hearing loss should be regularly queried regarding dizziness and balance. The vestibular group had increased ML postural sway and head movement, particularly in the dynamic city scene. Even though the visual flow of the avatars was in the AP direction, it is possible that

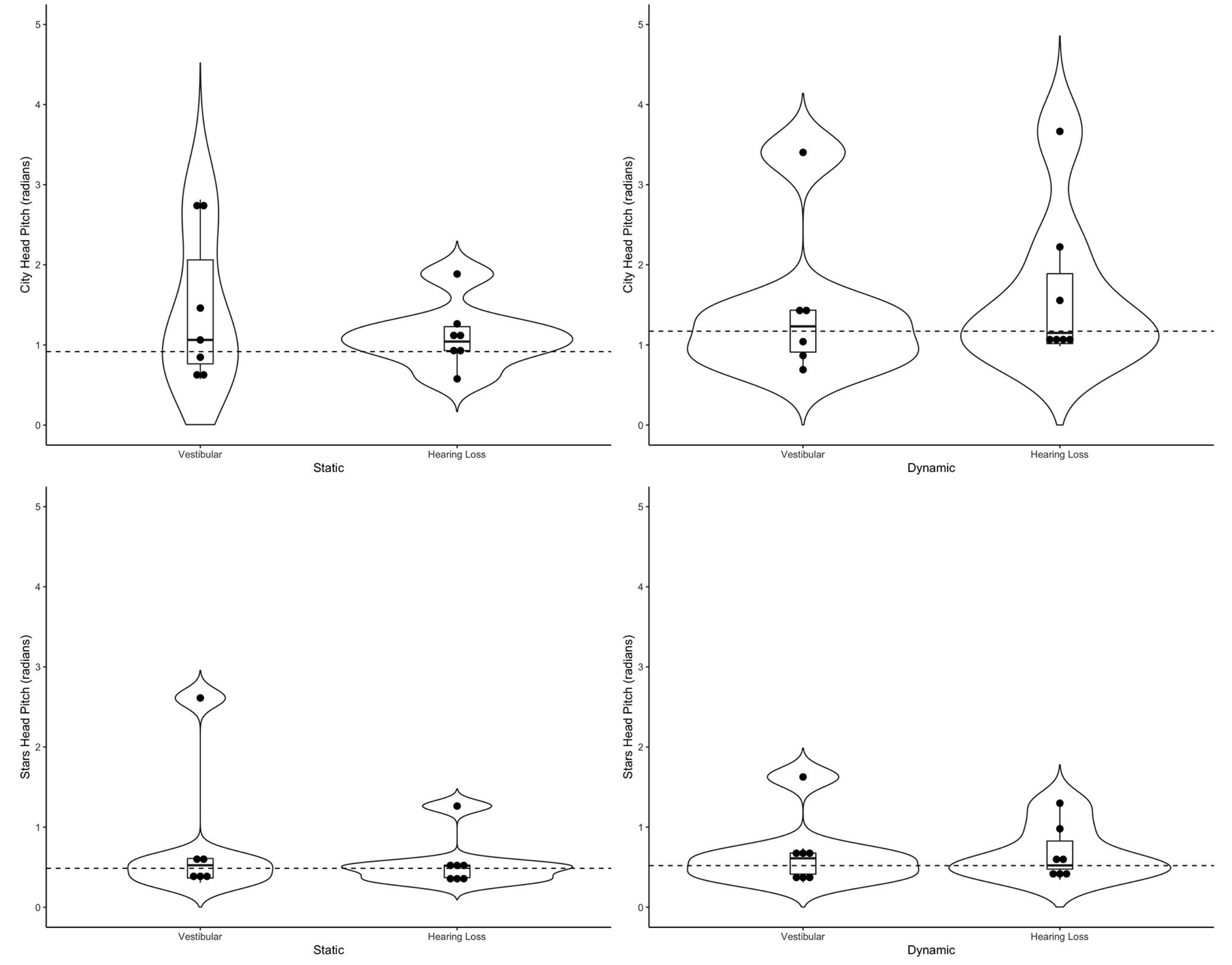

FIGURE 6 | Violin plots representing the distribution head pitch (radians) of both clinical groups around the mean of the control group (represented by the dashed line) for the city scene (top) and stars scene (bottom) Left-hand side represents the static scenes and right-hand side represents the dynamic scenes.

patients with vestibular dysfunction attempted to avoid collision by increasing lateral movement, even more than controls did, despite the fact that they were not asked to do so. All participants were asked to "do whatever feels naturally to them to maintain their balance." Anecdotally, patients in the vestibular group were more likely to report some fear and discomfort with the avatars walking toward them (see **Supplementary Video**). In our prior work, we observed that participants with unilateral vestibular hypofunction had larger head movement than controls on different dynamic scenes (32, 33) but we did not include a static scene. The current pilot work suggests that larger head movement in the vestibular group particularly occurred in response to the dynamic scene and is not a constant difference (movement was closer to controls on the static scenes). It is important to consider that the descriptive differences observed between the clinical groups and controls were seen despite the fact that the current protocol was done when the patients were standing on a stable surface in a comfortable hips-width stance and the visual perturbations themselves were quite mild. Therefore, any behavior observed in response to the dynamic scenes could be potentially interpreted as excessive visual dependence associated with other sensory loss. To tap into somatosensory dependence we could add a challenging support surface to the paradigm (53). It is likely that further differences would arise between the vestibular group and controls when the surface does not provide stable, reliable somatosensory cues (19).

In addition to the small sample, other design limitations should be mentioned. Given that the study was designed with multilevel sensory load, the static/no sound scene was only repeated once. In the future, we will separate the auditory load from the visual load and include abstract as well as ecological sounds and perform the same number of repetitions on all scenes. Because previous studies did not find loudness/volume of the sound to be a factor in postural sway (6, 54–57), we used the same volume with a range of 62 db (stars) to 68 db (city) for all participants. It is therefore possible that some participants, particularly in the hearing loss group, were not impacted by the addition of the sounds because the sounds were not loud enough for them. In the future, in order to assess individual responses to sounds we will project the sounds at the "loudest that is still comfortable" level. Baseline levels of postural sway and head movement without an HMD were not obtained and could further contribute to the interpretation of the data. The lack of diagnostic vestibular testing on all groups is a limitation as well and needs to be added in future studies.

CONCLUSION AND FUTURE RESEARCH

The current settings were too subtle to test differences between responses to visuals and sounds. Future studies should isolate each modality at the presence of the other. Our data show the importance of context in the study of sensory integration and the feasibility of an HMD setup to do so. In addition, a static baseline scene should be included for each environment. We hypothesize that a varying context will show particular importance in people with vestibular disorders who may be anxious due to the flow of avatars in the immersive contextual environment. The head is an extension of postural sway and responses to HMD-derived sensory perturbations will be magnified around the head segment. While the clinical importance of this observation should be further investigated, it currently appears that HMD-based head kinematics augment data derived from a force platform, and could potentially provide a distinct characteristic of people with vestibular loss. This should be further studied, potentially in combination with electromyography (EMG) of the neck muscles. Fall risk in people with hearing loss has been shown in older adults and our pilot data suggest balance impairments in people with single-sided hearing are more likely to arise in older participants with moderate DHI scores. Future studies utilizing HMDs should further assess aging with and without hearing loss and its impact on postural performance in a larger sample with a more cohesive diagnosis. Vestibular testing needs to be conducted for a clear separation between vestibular-related and hearing-related pathologies and to clarify whether observed performance deficits relate to an underlying vestibular problem or directly to their hearing loss.

DATA AVAILABILITY STATEMENT

The datasets generated for this study are available at: Lubetzky, Anat (2020), "Auditory Pilot Summer 2020", Mendeley Data, v1 http://dx.doi.org/10.17632/9jwcp78xzf.1.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Institutional Review Board of Mount Sinai; The New York University Committee on Activities Involving Human Subjects. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

AL, JK, BH, DH, and MC: substantial contributions to the conception or design of the work, or interpretation of data for the work. JK, BH, and MC: recruitment of participants. AL: data acquisition and drafting the work. DH and JL: statistical analysis of the data. All authors revising the work critically for important intellectual content, final approval of the submitted version, and agreement to be accountable for all aspects of the work.

FUNDING

This research was supported in part by the Hearing Health Foundation Emerging Research Grant 2019. AL and DH were funded by a grant from the National Institutes of Health National Rehabilitation Research Resource to Enhance Clinical Trials (REACT) pilot award. The sponsors had no role in the study design, collection, analysis and interpretation of data; in the writing of the manuscript; or in the decision to submit the manuscript for publication.

ACKNOWLEDGMENTS

We thank Zhu Wang, PhD candidate, NYU Courant Future Reality Lab and Tandon School of Engineering, for the development of the testing applications. We thank Susan Lunardi and Madison Pessel, physical therapy students at NYU, for their assistance with data collection.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2021.597404/full#supplementary-material

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Conflict of Interest: MC reported unpaid participation in research on cochlear implants and other implantable devices manufactured by Advanced Bionics, Cochlear Americas, MED-El, and Oticon Medical outside the submitted work.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Neurology

ORIGINAL RESEARCH
published: 25 August 2021
doi: 10.3389/fneur.2021.615242

Gait Speed Modulations Are Proportional to Grades of Virtual Visual Slopes—A Virtual Reality Study

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Gait is a complex mechanism relying on integration of several sensory inputs such as vestibular, proprioceptive, and visual cues to maintain stability while walking. Often humans adapt their gait to changes in surface inclinations, and this is typically achieved by modulating walking speed according to the inclination in order to counteract the gravitational forces, either uphill (exertion effect) or downhill (braking effect). The contribution of vision to these speed modulations is not fully understood. Here we assessed gait speed effects by parametrically manipulating the discrepancy between virtual visual inclination and the actual surface inclination (aka visual incongruence). Fifteen healthy participants walked in a large-scale virtual reality (VR) system on a self-paced treadmill synchronized with projected visual scenes. During walking they were randomly exposed to varying degrees of physical-visual incongruence inclinations (e.g., treadmill leveled & visual scene uphill) in a wide range of inclinations (−15° to +15°). We observed an approximately linear relation between the relative change in gait speed and the anticipated gravitational forces associated with the virtual inclinations. Mean relative gait speed increase of ∼7%, ∼11%, and ∼17% were measured for virtual inclinations of +5°, +10°, and +15°, respectively (anticipated decelerating forces were proportional to sin[5°], sin[10°], sin[15°]). The same pattern was seen for downhill virtual inclinations with relative gait speed modulations of ∼-10%, ∼-16%, and ∼-24% for inclinations of −5°, −10°, and −15°, respectively (in anticipation of accelerating forces). Furthermore, we observed that the magnitude of speed modulation following virtual inclination at ±10° was associated with subjective visual verticality misperception. In conclusion, visual cues modulate gait speed when surface inclinations change proportional to the anticipated effect of the gravitational force associated the inclinations. Our results emphasize the contribution of vision to locomotion in a dynamic environment and may enhance personalized rehabilitation strategies for gait speed modulations in neurological patients with gait impairments.

Keywords: virtual reality, gait speed, visual-physical conflict processing, rod and frame, subjective visual vertical, uphill and downhill locomotion

OPEN ACCESS

Edited by:
Judith Erica Deutsch, The State University of New Jersey, United States

Reviewed by:
Wendy A. Powell, Tilburg University, Netherlands
Mukul Mukherjee, University of Nebraska Omaha, United States

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Specialty section:
This article was submitted to Neurorehabilitation, a section of the journal Frontiers in Neurology

Received: *08 October 2020*
Accepted: *14 July 2021*
Published: *25 August 2021*

Citation:
Benady A, Zadik S, Zeilig G, Gilaie-Dotan S and Plotnik M (2021) Gait Speed Modulations Are Proportional to Grades of Virtual Visual Slopes—A Virtual Reality Study. Front. Neurol. 12:615242. doi: 10.3389/fneur.2021.615242

INTRODUCTION

Walking is a complex process that requires specific adaptations when transitioning to inclined surfaces (1–4). These adaptations are thought to be regulated by an *Internal Model of Gravity* (IMG) that is composed of three input components (5–8): *proprioception, vestibular* (together known as body-based), and *visual* inputs. Body-based inputs are sensitive to real gravitational forces exerted on the body when walking on inclined surfaces. Visual inputs however, are assumed to be influenced by top-down expectations likely based on prior visual experience during walking on inclined surfaces (4, 9). The sensory reweighting mechanism suggests that each of the sensory inputs has a specific "weight." The weighted inputs are added up to produce a behavioral modulation. Reweighting of the cues is constantly taking place with respect to the relevancy of each modality afferent cues (6, 10). In real life, visual and body-based inputs are typically synchronized and provide congruent information about the overall sensory experience, except for in very rare situations [e.g., the train illusion (11)]. Therefore, to evaluate the contribution of visual inputs to locomotion there is a need to artificially manipulate them in an independent manner from the body-based inputs and examine their relative "weight." While reweighting changes have been broadly described under steady-state conditions, evidence is lacking regarding the dynamics of reweighting following transitions to various intensities of sensory inputs during locomotion. To that end, we used a novel paradigm recently presented by our lab, which allows dissociating visual inputs from body-based inputs (4, 9). We transitioned the visual scene's apparent inclination independently of the physical inclination of the treadmill. This was done using a fully immersive VR system where participants walked on a treadmill that was operated in a self-paced mode and were presented with virtual visual scenery projected on a large dome shaped screen. Our previous studies show that while walking on a leveled treadmill (i.e., 0° inclination), uphill virtually visually simulated transition of 10° is followed by a temporary increase in gait speed, while downhill virtually visually simulated transition of 10° is followed by a temporary decrease in gait speed. These visually guided gait speed modulations represent the *exertion* and *braking* effects seen in physical uphill and downhill walking, respectively. During uphill walking, the exertion effect counteracts the gravitational forces that would eventually bring a freely moving body to a stop, allowing an individual to maintain a roughly stable walking speed, typically slower than their self-selected speed during leveled walking (3, 12, 13). For downhill walking, the braking effect prevents uncontrolled speeding up (as would occur in the case of a freely moving body) and allows the individual to descend in a stable walking speed, either faster or slower than the self-selected speed on a leveled surface (3, 12, 14).

Visual field dependence is deemed as the level of reliance on visual inputs in comparison to body-based inputs (15, 16). The rod and frame test is a common method to assess visual field dependency, which is considered to evaluate the extent of subjective misperception of visual verticality (17–19). Visual field dependency varies across healthy individuals (20, 21), and it has been suggested to be higher in patients and populations with balance related disorders (22–25).

Previous studies examined gait speed modulations to inclinations of $\pm 10°$. Yet, it is unknown whether the extent of speed modulation is proportionally related to the degree of virtual visual scene transition. In the present study we aim to demonstrate that the predictions of gravitational force related consequences while walking on a slope mediated merely by visual cues are subtle and take into account the steepness of the slope. In other words, that the internal model of gravity quantifies the visual information with reference to its physical dimensions. To that end we parametrically manipulated the virtual visual scene between $-15°$ to $+15°$ in steps of 5° (i.e., $\pm 15°$, $\pm 10°$, $\pm 5°$ and 0°), while the treadmill either remained leveled or transitioned uphill/ downhill. Our main hypothesis was that gait speed modulation is proportional to virtual visual inclination slopes during incongruent walking conditions (i.e., provoking visually induced braking (during downhill) or exertion (during uphill) effects). Specifically, given the expected gravity induced acceleration forces acting upon the body when walking on actual inclined surfaces, we anticipated smaller visually induced braking/exertion effects for smaller slopes ($\pm 5°$) as compared to the effect expected when walking under the illusion of bigger slopes ($\pm 15°$). We defined an additional objective for this study, to confirm our previous observation (9), that the magnitude of visual modulation on gait speed during virtual surface inclination changes of 10 degrees varies across people and is related to the individual's subjective visual misperception of verticality, as measured by the rod and frame test.

MATERIALS AND METHODS

Participants

Fifteen young healthy adults (mean age $\pm$ SD: 27.45 $\pm$ 4.1 years old, 8 men) participated in this study. Exclusion criteria (confirmed through a questionnaire prior to recruitment) were physical restrictions, visual problems, sensorimotor impairments, or cognitive and psychiatric conditions that could potentially affect locomotion or the capability to comply to instructions. The Institutional Review Board for Ethics in Human Studies at the Sheba Medical Center, Israel, approved the experimental protocol (Approval Number 9407–12) and all participants signed a written informed consent prior to entering the study. Three participants are lacking data in the treadmill leveled vision $-15°$ condition, and one participant is lacking data in the treadmill leveled vision $-5°$ condition. There were four values missing from the analyses, two due to technical problems and two were excluded as outliers (more than three standard deviations from the average).

Apparatus

The different experimental apparatuses were elaborately described in our previous work (4, 9). Herein is a brief description:

Virtual Reality System

Experiments were conducted in a fully immersive virtual reality (VR) system (CAREN High End, Motek Medical, The Netherlands) containing a moveable platform with six degrees of freedom. A treadmill that operates in self-paced mode, allowing participants to adjust treadmill speed to preferred gait speed, was embedded in the moveable platform (26).

VR Version of the Rod and Frame Test

We used the rod and frame paradigm published by Bagust et al. (20) in a VR format, which was based on the original computer screen rod and frame test (27). This test is commonly used to estimate subjective visual verticality misperception. Specifically, the test measured how visual perception of the orientation of a central bar (rod) is influenced by the orientation of a peripheral visual reference frame around it. It was implemented in our lab using Unity software and C# scripting. The participants sat upright wearing VR glasses (HTC VIVE, New Taipei City, Taiwan) and were told not to move or tilt their heads during the test. The VR environment consisted of a white frame ($\sim 16^{\circ} * 16^{\circ}$) at a certain orientation and a white rod ($\sim 11^{\circ}$ long) inside it with its own orientation, both presented on a black background (refresh rate of 90 Hz). A sequence of 28 trials was presented during which the frame was initially rotated (relative to a vertical line) to one of seven possible random orientations: $0/\pm 10/\pm 20/\pm 30$ degrees (0 was vertical, + was clockwise), and each of these initial frame positions was presented four times. The initial rotation angle of the rod was also random (sampled from 0–180 degrees range distribution). The participants' task was to rotate the rod until it becomes perpendicular to the true horizon (i.e., vertical) while ignoring the surrounding frame. This was achieved using the VR system's remote control that allowed the participants to rotate the rod around its center in a clockwise or counterclockwise direction while the surrounding frame was unchanged. When the participants perceived the rod's orientation as vertical, they were supposed to respond by pressing a button on the remote control, after which the display was cleared and another trial immediately began.

Procedure

VR Rod and Frame Test

The first part of the experiment after filling the informed consent was the rod and frame test. After assuring that the participant felt comfortable with the VR head mount device (HMD), a short practice trial was conducted to confirm that the participant understood the task and then the 28 test trials began. The test was not limited in time and typically lasted 10 min, including the practice trial.

Gait Trials in a Large-Scale VR System

Habituation Period to Walking in Self-paced Mode During Leveled and Inclined Surfaces

The participant was secured by a safety harness to a metal frame on the moveable platform (**Figure 1**). The first part of the habituation included familiarizing the participant with the self-paced mode of the treadmill which involved 10–15 min of leveled walking, with practicing to decrease and to increase speed until he/she mastered the walking. In the second part of the habituation, the participant performed three walking trials, one of each of the three possible inclinations (i.e., leveled, uphill and downhill walking, at this order) when the visual and the gravitational cues were synchronized ("congruent" conditions; see more details below). Each trial lasted 3–4 min.

Gait Experiments

The participants were informed that they would perform several gait trials, each lasting several minutes, with around 20 second intervals between them. They were instructed to walk "as naturally as possible" and were told that inclination changes may occur during walking. All trials in all conditions began from a standstill position and participants began walking with both the treadmill and the visual scene leveled until reaching steady state velocity, after which a 5 s long transition of the treadmill and/or visual scene occurred. Post transition, participants walked for additional 65 s until the treadmill slowed down and stopped. By convention, we refer to the transition start time as time zero ($t = 0$).

Experimental Conditions

The protocol included fifteen experimental conditions which the participant encountered in a random order and comprised of combinations of the treadmill and visual scene inclinations. Each condition started with leveled walking until the participant reached steady state velocity (SSV) and maintained it for 12 s. Following that, a transition of 5 s occurred to one of the fifteen different conditions, lasting 65 s. The treadmill (T) either transitioned uphill (U) to $+5^{\circ}$ (T_{U5})/$+10^{\circ}$ (T_{U10}), remained leveled (L) at 0°, or transitioned downhill (D) to -5° (T_{D5})/-10° (T_{D10}), and due to safety purposes the treadmill was not transitioned to $\pm 15^{\circ}$. The visual scene (V) transitioned to $+5^{\circ}$, $+10^{\circ}$, or $+15^{\circ}$ uphill (V_{U5}, V_{U10}, V_{U15}), remained leveled at 0° (L) or transitioned to -5°, -10°, or -15° downhill (V_{D5}, V_{D10}, V_{D15}). Treadmill and visual scene *congruent* conditions that served as baseline were (i) leveled ($T_L V_L$), (ii) uphill ($T_{U5} V_{U5}$), or (iii) downhill ($T_{D5} V_{D5}$) walking. Note that in terms of civil engineering guidelines a 10° walking slope is considered a steep inclination for walking (28). Treadmill-visual scene *incongruent* conditions included the following visual scene manipulations: for the leveled treadmill, vision was $+5^{\circ}$ ($T_L V_{U5}$), $+10^{\circ}$ ($T_L V_{U10}$), $+15^{\circ}$ ($T_L V_{U15}$), -5° ($T_L V_{D5}$), -10° ($T_L V_{D10}$) or -15° ($T_L V_{D15}$). "*Double*" *incongruent* walking conditions included: For treadmill uphill at 5°, vision was downhill at -5° ($T_{U5} V_{D5}$), for treadmill uphill at 10°, vision was downhill at -10° ($T_{U10} V_{D10}$) or -15° ($T_{U10} V_{D15}$). For treadmill downhill at -5°, vision was uphill at $+5^{\circ}$ ($T_{D5} V_{U5}$), for treadmill downhill at -10°, vision was uphill at $+10^{\circ}$ ($T_{D10} V_{U10}$) or $+15^{\circ}$ ($T_{D10} V_{U15}$). **Figure 1** depicts the experimental setup and the virtual visual scene experimental manipulations.

Predictions of Gait Speed Modulations

A free body placed on an inclined surface is influenced by two gravitational force components, one perpendicular to the surface which is balanced by the normal reaction force, and another parallel force acting on the body in parallel to the surface

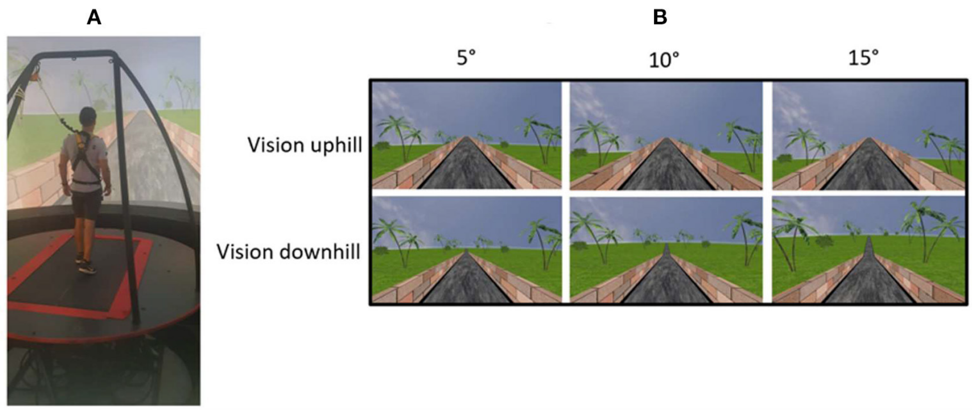

FIGURE 1 | Apparatus **(A)** and visual scene manipulations **(B)**. **(A)** A participant in the VR system. A fully immersive virtual reality system containing an embedded treadmill synchronized with projected visual scenes, wherein this example the treadmill is leveled and the vision is leveled ($T_L V_V$). **(B)** Main visual manipulations regardless of the treadmill inclination. Following leveled walking and after reaching steady state velocity (SSV) and maintaining it for 12 s, a transition (5 s) occurred to one of fifteen different conditions presented in random order, lasting 65 s, in which the inclination of the treadmill (T) and/or visual scenes (V) transitioned to +5°, +10°, or +15° uphill ($_U$), remained leveled ($_L$), or transitioned to −5°, −10°, or −15° downhill ($_D$). Visual scene inclination effect was achieved by the road appearing above (uphill), below (downhill) or converging (leveled) with the line of the horizon and in addition, the peripheral greenery is exposed more (downhill) or less (uphill) by the road. Upper row represents visual scene uphill and lower row visual scene downhill. First, second and third columns represent transition of ±5°, ±10°, and ±15°, respectively.

and pushing the body downhill (assuming no friction or other external forces). The parallel force acting on the body is given by $Fp = g * \sin(\alpha)$, where g is the gravitational acceleration and α is the slope angle. Since the sin function is relatively linear for small degrees (including in the range of [−15°, +15°]), such that $\sin(A^*\alpha) \approx A^*\sin(\alpha)$ (provided that $|A^* \alpha| < 15°$), the anticipated parallel forces are relatively linear, and therefore we hypothesized that the magnitude of the visually triggered braking and exertion effects will be proportional to the slopes (i.e., steeper slope—stronger anticipated forces—higher exertion/braking effect). Specifically, if X stands for the exertion effect measured in a virtual 10° slope, we predicted exertion effects of 0.5X for virtual inclinations of 5° and 1.5X for virtual inclinations of 15°. Similar predictions were made for negative virtual slopes with braking effects.

Outcome Measures

The outcome measures were elaborately described in our previous work (4, 9). Below is a brief description:

Gait Speed Related Variables

To assess the post transition effects on gait speed we assessed (i) the magnitude of the peak/trough of gait speed relative to the steady state velocity (SSV; presented in %); and (ii) the time of this peak from the start of transition (seconds). Gait speed was estimated directly from a tachometer in the treadmill motor that provides the velocity signals from the treadmill belts. For full derivation of these parameters see **Supplementary Methods**.

Standardized Response to Virtual Inclination

To compute this metric, we used data from the incongruent $T_L V_{U10}$, $T_L V_{D10}$, $T_{D10} V_{U10}$, $T_{U10} V_{D10}$ conditions, similar to our previous study (9). For each participant the absolute values of the maximal relative (i.e., percent) change with respect to the SSV were calculated.

Calculation of ratio of gravity induced behavior- We first calculated the Area Under the Curve (AUC) separately for every second between 1s to 60s from a free body's velocity V(t) and walking speed (WS) of the congruent uphill and downhill walking conditions. Then we defined the ratio: $R = (AUC(WS_i)/AUC(V_{(t)t=i}))^*100$. The index i refers to the time (in seconds) post-transition, with zero being the start of the transition. The equation is multiplied by 100 to avoid extremely small numbers. The ratio quantifies the extent to which WS estimates the velocity of a free body. A positive ratio indicates that both parameters were in the same direction (either accelerating or decelerating), while a negative ratio indicates the opposite direction. A ratio further from zero indicates greater gravitational influence on walking.

Subjective Verticality Misperception Index

For each trial the degree of deviation of the rod from the true vertical was measured and recorded as the rotation error. For each participant the mean rotation error for each of the 7 frame angles was calculated (20). We defined the rod and frame individual index to be the average angle of deviation of the rod from the true vertical when the frame was projected at ±20 degrees (8 trials in total, 4 trials of +20° and 4 trials of −20°). This parameter allows for evaluation of individual differences in gravitational misperception.

Statistical Analyses

Values are represented by their group mean values (± SE). We used the repeated measures General Linear Model (GLM) to analyze groups of related dependent variables (amplitude and timing of the gait peaks) that represent different measurements

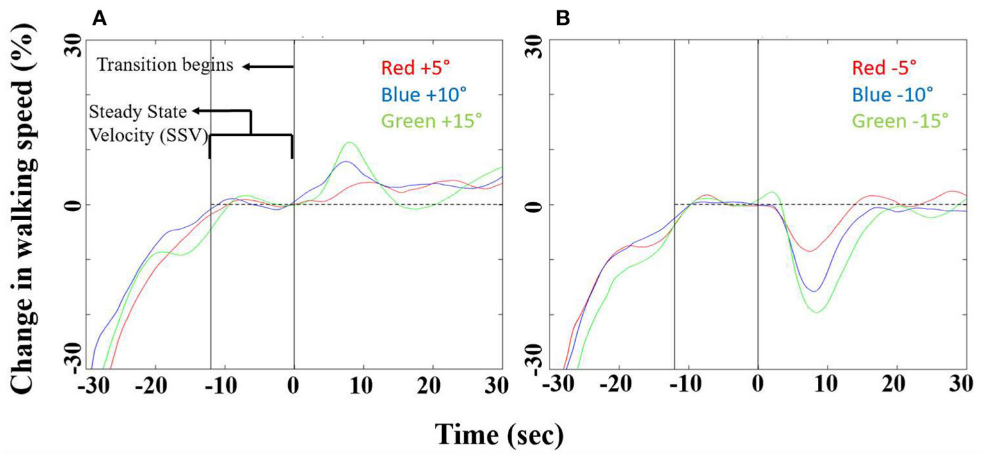

FIGURE 2 | Walking speed modulations following uphill (virtually induced exertion effect) and downhill (virtually induced braking effect) virtual inclinations ($N = 15$). Speed modulations before and after **(A)** uphill or **(B)** downhill virtual inclination changes (leveled treadmill, in red for ±5°, in blue for ±10°, and in green for ±15°). X-axis represents time (seconds), 30 s pre- and post-transition. Y-axis represents the relative change in gait speed from steady state. See text for details on statistical comparisons.

of the same attribute (i.e., gait speed modulation). We defined two within-subject factors for the GLM analyses. The first GLM factor was the *condition class* (4 levels: T_LV_U, T_LV_D, T_DV_U, T_UV_D), and the second GLM factor was the visual inclination (3 levels: 5°,10°,15°). We further conducted GLM contrasts attempting to reveal the source of any effects that were observed in the GLM analyses. For testing how our estimates predicted true behavior, two-way repeated measures ANOVA was used. This was done by comparing observed values vs. predicted values (see section on predictions for gait speed modulations above) for treadmill leveled conditions with vision up, down or leveled. For all the above, a p-value equal or lesser than 0.05 was considered significant. Pearson correlation coefficient was computed to evaluate the relationship between (i) predicted and measured values and (ii) subjective verticality misperception index and the standardized response to virtual inclination (see *outcome measures* for more details). As the subjective verticality misperception index was compared between two distinct studies (see **Figure 7**), we transformed the indices into Z-scores so the results would be comparable.

RESULTS

For the averaged gait speed magnitude peak, the GLM showed a significant effect for the condition class (factor 1), [$F_{(3,36)} = 36.07$, $p < 0.001$] and for the visual inclinations (factor 2), [$F_{(2,24)} = 23.79$, $p < 0.001$]. The model also revealed a significant condition class*visual inclination interaction [$F_{(6,72)} = 10.79$, $p < 0.001$]. The following contrasts were found to be statistically significant: (1) For the condition class factor, T_LV_U vs. T_UV_D [$F_{(1,12)} = 64.98$, $p < 0.001$]; (2) For the visual inclination factor, 5° conditions were significantly different from both 10° conditions [$F_{(1,12)} = 27.53$, $p < 0.001$] and from 15° conditions [$F_{(1,12)} = 45.08$, $p < 0.001$]; (3) For the condition class*visual inclinations interaction, T_LV_U and T_UV_D showed significant interactions between the 5° and 10° visual inclinations [$F_{(1,12)} = 36.33$, $p < 0.001$] and between 5° and 15° visual inclinations [$F_{(1,12)} = 19.13$, $p = 0.001$]. For the averaged gait speed peak time, the GLM showed no significant difference between the condition class levels (factor 1), [$F_{(3,10)} = 2.59$, $p = 0.110$] and between the visual inclinations (factor 2), [$F_{(1,12)} = 2.23$, $p = 0.150$].

Gait Speed Modulations by Visually Induced Inclinations at Leveled Treadmill

In order to address our main hypothesis that gait speed modulations are linearly correlated to the degree of visual inclination, we measured gait speed while treadmill was leveled and visual scene inclination was set to +5°, +10°, +15° (**Figure 2A**), −5°, −10°, or −15° (**Figure 2B**). **Figure 2** depicts the averaged relative change in gait speed from steady state velocity for each of these conditions in a time window of 60 s centered around the transition. The mean magnitude peaks ±SE of walking speed changes following virtually induced uphill slopes (the exertion effect, **Figure 2A**) were 6.7 ± 0.9% for +5°, 10.9 ± 1.5% for +10°, and 17.2 ± 1.7% for +15°. The mean values (±SE) of peak relative changes of walking speed changes in response to virtually induced downhill slopes (the braking effect) were −9.4 ± 2.3% for −5°, −15.8 ± 2.6% for −10° and −23.7 ± 2.7% for −15°. The timing of the gait speed peaks after transition were not significantly affected by virtual positive inclinations (mean ± SE): V_{U5} = 9.3s ± 4.5s, V_{U10} = 8.2s ± 3.7s, V_{U15} = 8.9s ± 1.7s), or by virtual negative ones (mean ± SE):V_{D5} = 8.2s ± 3.8s, V_{D10} = 8.3s ± 1.0s, V_{D15} = 8.4s ± 1.1s.

Predicted vs. Measured Virtually Induced Exertion and Braking Effects

To test our hypothesis that the extent of walking speed modulation by virtually inclined surfaces is dependent on the

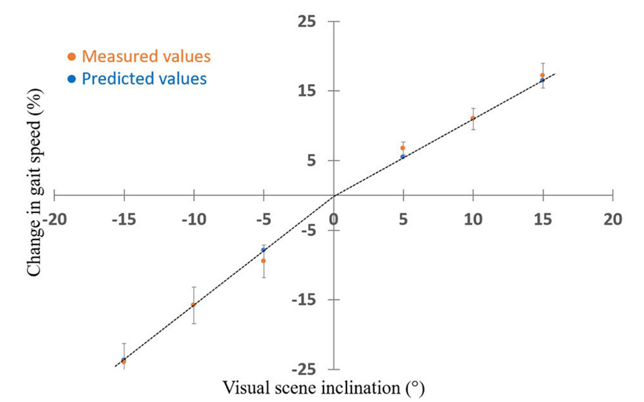

FIGURE 3 | Predicted measures closely match measured gait speed at various virtual inclinations ($N = 15$). X-axis represents the virtual inclination of the visual scene (°); in all conditions the treadmill remained leveled. Y-axis represents the relative change in gait speed from the steady state (%). Orange and blue circles represent measured and predicted values (see Methods for calculation of predicted values), respectively. Error bars represent the standard error for the measured values. Dashed lines represent the slope for the predicted values. Two-way ANOVA showed no significant difference between predictive and measured values. These results support our hypothesis that the gait speed modulation is linear in this range of inclinations. Note that the positive and negative predictions are both linear with different slopes.

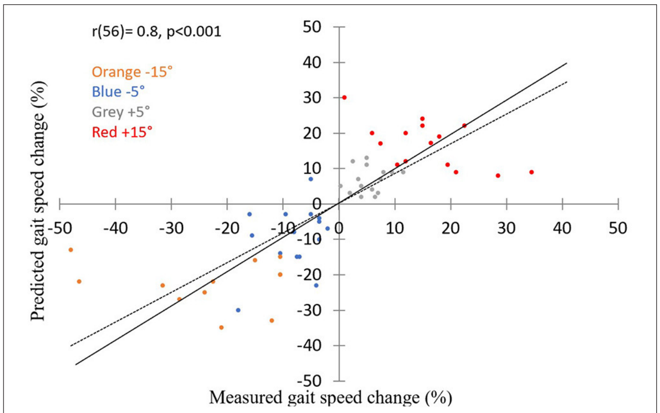

FIGURE 4 | Predicted and measured changes in walking speed correlate during virtual inclinations at leveled treadmill ($N = 15$). X-axis represents the measured gait speed change from the steady state (%); Y-axis represents the predicted gait speed change from the steady state (%). For each color, a circle represents one participant (orange, blue, gray, and red circles depict T_LV_{D15}, T_LV_{D5}, T_LV_{U5}, and T_LV_{U15}, respectively). Thus, each participant is represented by 4 circles. Predicted gait speed is highly correlated with measured gait speed across virtual scene inclinations. Pearson correlation ($r = 0.8$, $p < 0.01$). Solid line represents the unity line, dashed line represents the regression line. Note that the data points are scattered roughly equal below and above the unity line.

slope size, we estimated the expected speed modulation for slopes of ±5° and ±15° based on the results of ±10° slopes, and compared these estimates to the real modulations. **Figure 3** shows how the expected results closely matched the measured ones. A two-way repeated measures ANOVA with inclination (−5, −15, 5, 15) and predicted vs. measured as factors revealed, as expected, a significant effect of inclination [$F_{(3,33)} = 0.968$, $p < 0.001$] and substantiated our observation that the predicted measures were not significantly different from the measured ones [$F_{(1,11)} = 0.001$, $p = 0.914$]. No interaction was found [$F_{(3,33)} = 0.146$, $p = 0.684$]. Furthermore, a high correlation [$r_{(13)} = 0.8$, $p < 0.01$] was seen in an individual analysis between the expected and the measured results across the four virtual inclinations measured (**Figure 4**).

Relative Change in Gait Speed for Double Incongruent Walking Conditions

In addition to measuring virtually simulated exertion and braking effects, we also manipulated both the treadmill and the visual scene in different directions to further examine the role of vision during walking. **Figure 5A** presents the walking speeds during conditions where the treadmill transitioned upward with inclinations of +5° or +10°, while the visual scene transitioned downward with inclinations of −5°, −10°, or −15°, respectively. **Figure 5B** presents the same concept but in the opposite direction, where the treadmill transitioned downwards, and the visual scene transitioned upwards. The mean magnitude peaks ±SE of walking speed changes following the transition (treadmill up, **Figure 5A**) were −23 ± 3% for $T_{U5}V_{D5}$, −60 ± 7% for $T_{U10}V_{D10}$ and −63 ± 7% for $T_{U10}V_{D15}$. The mean magnitude peaks ±SE of walking speed changes following the transition (treadmill down, **Figure 5B**) were 13 ± 3% for $T_{D5}V_{U5}$, 9 ± 4% for $T_{D10}V_{U10}$ and 20 ± 3% for $T_{D10}V_{U15}$. The timing of gait speed peaks after transition to uphill treadmill inclinations while the vision transitioned downward were (mean ±SE): $T_{U5}V_{D5}$ = 8.47s ± 2.97s, $T_{U10}V_{D10}$ = 7.87s ± 3.14s, $T_{U10}V_{D15}$ = 9.23s ± 4.55s and for downhill treadmill inclinations while the vision transitioned uphill were (mean ± SE): $T_{D5}V_{U5}$ = 11.7s ± 4.9s, $T_{D10}V_{U10}$ = 9.42s ± 4.0s, $T_{D10}V_{U15}$ = 9.51s ± 3.99s.

Ratio of Gravity-Induced Behavior in Congruent Uphill and Downhill Walking Conditions

Our next step was to compare the changes in exertion and braking effects over time (post-transition). To that end, we computed the normalized ratio between the areas under the curve of gait speed for the ±5° congruent conditions [for ±10° see Cano Porras et al. (4)], divided by free body velocity at the same inclination [i.e., V(t) = g*sin±5*t] (**Figure 6**). The higher the ratio (i.e., further from zero), the stronger the effect of gravity and the weaker the exertion and braking effects are. The analysis revealed a robust differential response to gravity in uphill vs. downhill walking ($p = 0.034$), reflecting a weaker accelerating influence of natural gravity and a strong braking effect. Yet, both uphill and downhill walking initially showed an increasing ratio, which suggests increasing natural gravity influence. For uphill walking, the turning point occurred at 8 s, while for downhill walking the turning point occurred at 13 s from the transition. Beyond this point participants expended more effort (the exertion effect) or braked themselves (the braking effect) to maintain gait speed during uphill and downhill walking, respectively.

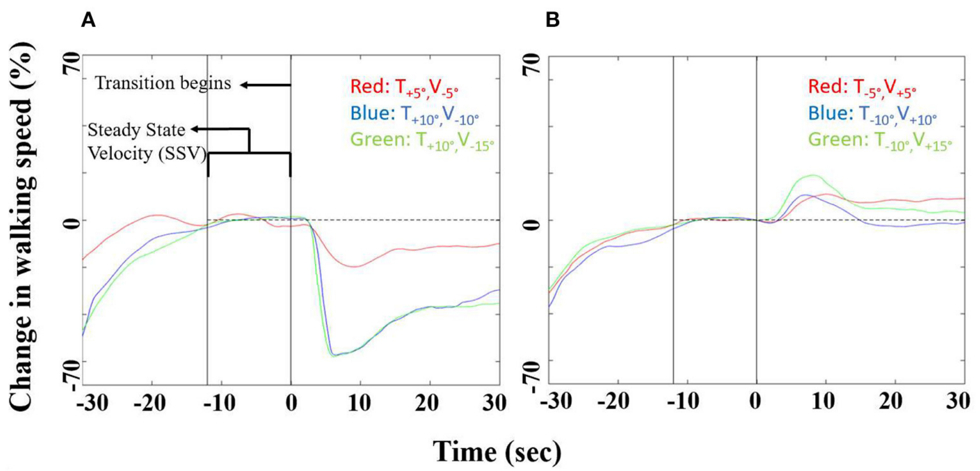

FIGURE 5 | Gait speed modulations in the double in congruency walking conditions ($N = 15$). Speed modulations before and after **(A)** treadmill up vision down or **(B)** treadmill down vision up walking conditions (red lines for ±5°, blue lines for ±10°, and in green lines for treadmill ±10° and vision ±15°). X-axis represents time (seconds), 30 s pre- and post- transition. Y-axis represents the relative change in gait speed from steady state (%). See text for details on statistical comparisons.

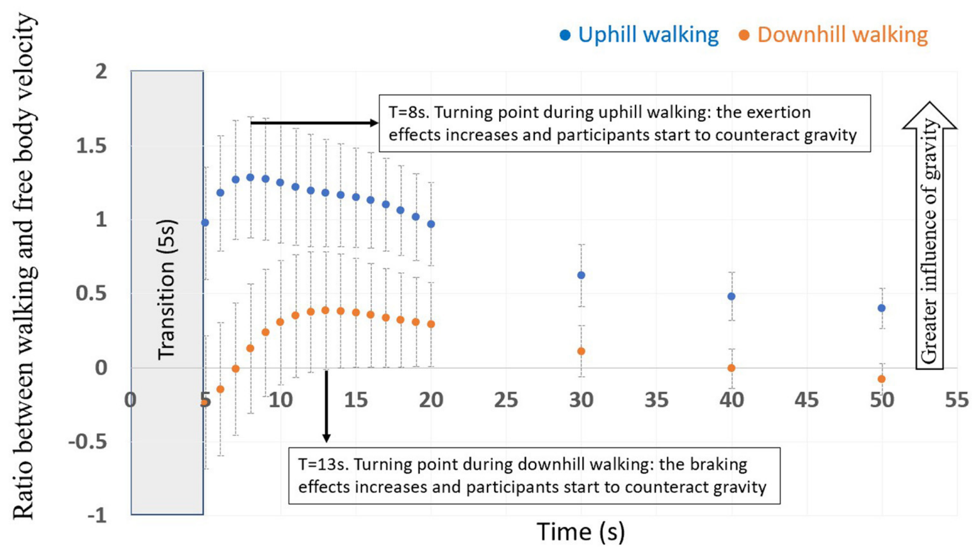

FIGURE 6 | Ratio of gravity-induced behavior in uphill and downhill walking. The average ratio between gait speed and velocity of a free-moving body over time for ±5° downhill and uphill congruent conditions ($N = 15$), error bars represent standard error. The turning points represent the time (seconds) in which the participants applied the exertion effect to counteract gravitational deceleration in uphill walking (8 s) and conversely, applied the braking effect to counteract gravitational acceleration in downhill walking (13 s).

Relation Between Visual Modulation of Gait Speed During Visual-Physical Incongruent Conditions and Subjective Misperception of Verticality

Finally, we hypothesized that the magnitude of visual modulation on gait speed varies across people and may be related to the individual's visual field dependency. Therefore, for each participant we calculated the magnitude of visual modulation on gait speed and the visual field dependence index. The former was calculated based on the changes in gait speed for the ±10° incongruent conditions (see Methods) and the latter based on the rod and frame test which estimates the visual field dependence. As can be seen in **Figure 7**, which combines data from two separate studies with the same protocol (9), when we compared these 2 measurements together we found that they were significantly correlated ($r = 0.542$, $p = 0.005$), and this was also the case when each subgroup was measured separately. This indicates that people with higher visual field dependency are likely to have stronger walking speed modulations during virtual

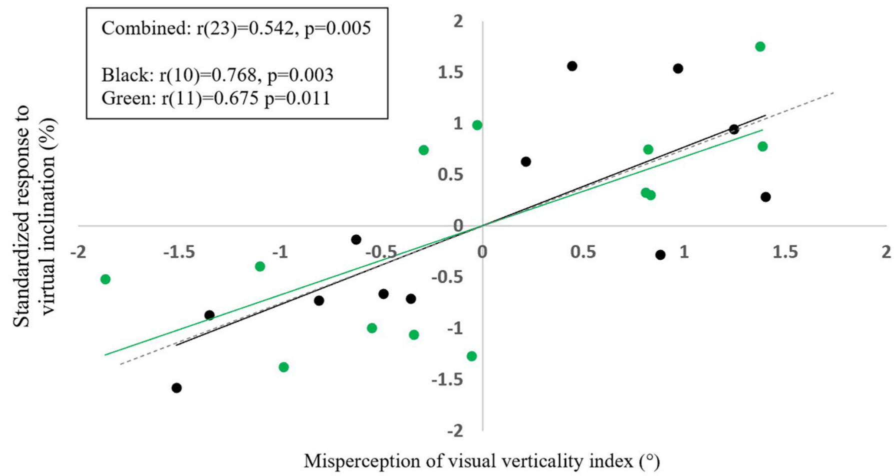

FIGURE 7 | The extent of visual dependence during locomotion on inclined surfaces is linked to misperception of visual verticality. X axis represents the z-score for misperception of visual verticality index as assessed by the rod and frame test; Y axis represents the z-score for standardized response to ±10° virtual inclination based on incongruent walking conditions. Each circle represents one participant obtained from two separate experiments with the same protocol [green ($N = 13$) and black ($N = 12$)]. A significant correlation was found between these measures either for both cohorts combined: $N = 25$, $r = 0.542$, $t_{(23)} = 3.09$, $p = 0.005$, and for each cohort separately (i) $N = 13$, $r_{(11)} = 0.675$, $t_{(11)} = 3.03$, $p = 0.011$, (ii) $N = 12$, $r_{(10)} = 0.768$, $t_{(10)} = 3.79$ $p = 0.003$. The dashed line represents the combined linear regression line (Y = 0.71X + 6E−16), the black and green line represent the regression lines of each cohort separately as can be seen the 3 regression lines almost overlap.

inclination changes, suggesting that these processes may rely upon associated mechanisms. No correlation was found between the changes in gait speed for inclinations of ±5° and ±15° and the index of subjective visual misperception of verticality estimated by the rod and frame test.

DISCUSSION

Summary of Findings

In this study we investigated how gait speed is modulated by the visual virtual inclination slopes. As hypothesized, we showed that when a larger conflict was created between the sensory inputs, larger visually induced braking and exertion effects were measured (**Figure 2**), as expressed by gait speed modulations. The response-intensity relations of the visually induced braking and exertion effects were linear and proportional to the theoretical gravity induced tangential downhill and uphill acceleration levels, respectively (**Figures 3**, **4**). We did not find any difference in the timing of the peak/trough of gait speed modulations when different virtual inclination levels were introduced. Furthermore, as previously described (9) we observed that the inter-subject variability in the virtually induced braking and exertion effects (at ±10°) can be explained in part by the individual's visual field dependency as measured by the rod and frame test (20).

The Relative Weight of Visual Cues During Locomotion Modulations

Although we found a significant linear effect for visual inputs on gait speed modulations while walking at physical leveled inclinations when only the visual scene was transitioned, we did not find an effect on the timing of the gait speed peaks across the virtual visual induced transitions, suggesting that the timing of the peak effect of visually induced braking and exertion effects is similar regardless of the inclination. This result points us to two mechanisms regarding human locomotion: (i) indirect prediction, which is a process controlling locomotion patterns based on accumulated experience, promptly activating pre-programmed gait patterns in the presence of a perturbation (in our case the transition to an inclined slope). (ii) Sensory reweighting which is an iterative mechanism of recalibration of the relevant cues. This finding demonstrates that the sensory reweighting processes (6, 10, 29) which balance between vision (which in this case is influenced by a "faked" visual incline), and body-based cues (which are influenced by the physical treadmill inclination) occur at similar times, independent of the intensity of the sensory input conflict (for the discrepancy levels used in the present study). Adapting the hypothesis that the central nervous system (CNS) is using a weighted summation model of the sensory cues in execution of motor control, we assume that when there is a conflict between the inputs, the more reliable cues become more heavily weighted. In other words, the visual cues are likely to affect the indirect prediction mechanism (29) in proportion to the conflict size created by the visual inclination, but the time it takes for the sensory reweighing to "kick in" is apparently constant for virtually induced uphill walking (∼8.8 s) and for virtually induced downhill walking (∼ 8.2 s). This study strengthens the sensory reweighting theory by showing that once this mechanism governs, quantitative estimates of sensory weights are modulated regardless of the amplitude of perturbations provided by visual manipulations. To further compare the weight of vision contribution in uphill and downhill walking, we conducted two types of double incongruent setups ($T_U V_D$, $T_D V_U$). In both $T_U V_D$ and $T_D V_U$ conditions, the vision did not significantly affect gait speed. In conclusion, visual inputs predominantly affect gait speed during leveled (neutral) inclinations proportionally to the degree of virtual visual inclination. The proportional weight of visual inputs is reduced when gravitational cues (physical inclination) oppose the virtual visual cues.

Inter Participant Variability

The relation between subjective visual vertical (SVV) that is assumed to represent visual field dependency (17–19) and postural stability in the healthy population is well established (15, 30–32). Yet, the locomotive responses, which are behaviorally expressed by changes in gait speed is not fully understood. While the present finding confirms earlier findings with this specific paradigm (at ±10°) (9), it is unclear why these findings were not generalized to the other inclinations (±5° or ±15°). These seemingly conflicting results might be explained by assuming that visual field dependency varies across healthy individuals within a certain range (9, 20, 21). In extreme scenarios where the conflict is up to 15° (e.g., treadmill 0° and vision +15°), it may be that visual field dependence no longer plays a role in affecting perception, which may explain why no correlation was observed between the rod and frame test and locomotive response. Although we did find a behavioral change in virtually induced inclinations of ±15°, which was relatively bigger than inclinations of ±10°, we could not predict those changes by the rod and frame index. These behavioral changes may suggest that in cases with extreme discrepancy, the integration of sensory cues follows another mechanism. A possible mechanism could be directed to instinctively prevent us from falling backwards while walking uphill (or in the case of the visual scene transitioning downward, decreasing the speed to maintain stability and prevent forward acceleration). The same was true when the conflict was small (i.e., virtually induced inclination of ±5°). We suggest that humans adapt their gait speed according to the virtually induced inclination, but the mechanism relies on different sources rather than the traditional visual dependence. This analog was also seen in our analysis of the rod and frame index itself, as well as for Bagust et al. (9, 20). When the frame was tilted at ±30°, or when the frame was not tilted (0°), no significant change was seen across individuals. The only difference was seen when the frame was tilted at ±10° and ±20°. These findings suggest that the visual dependence, as measured by the rod and frame index is not susceptible to extreme discrepancies.

Exertion and Braking Effects as Measured in Congruent Conditions

The braking and exertion effects were previously quantified in our lab for congruent inclinations of ±10° (4). Here we quantified the modulations related to inclinations of ±5° (**Figure 6**). Our results confirm the role of vision in the initiation of the exertion effect during real uphill walking, since the timing of the deflection point (i.e., turning point, which symbols the time that took the participants to accommodate to the new inclination) ($t = 8$ s) was almost similar to the peak of the gait speed increase in response to virtual uphill walking (9.3 s). Overall, the accommodation to uphill walking is faster for smaller inclinations (5°, $t = 8.0$ s) as compared to greater inclinations (10°, $t = 11.0$ s). These findings are consistent with the notion that people try to minimize their energetic cost while walking (29, 33), and thus when walking on steeper inclination, more energy is used and it will take more time to reach the new steady state (34). For downhill walking at −5°, the braking effect started at 13 s post transition. Surprisingly, the trough of the virtually induced braking effect was at 8.2 s. This time difference indicates that when no sensory discrepancy exists, the accommodation time to a downhill slope is longer, emphasizing the role of body-based cues to maintain locomotion and adjust the body according to the gravitational laws of physics. We also note that subtle influences of the self-pace control parameters employed in this experiment may interfere with these estimations (e.g., forward/backward translations on inclined surfaces provides reduced feedback to the speed controller as compared to leveled walking), as well as the individual ability to control gait speed alterations under this self-paced paradigm.

Clinical Implications

As natural continuation to traditional physical therapy base interventions, VR advantages were emphasized in light of its ability to incorporate motor learning principles such as real-time multisensory feedback, task variation, objective progression, and task-oriented repetitive training (35–38). VR systems allow to simulate scenarios from real life, and yet provide therapists a unique opportunity to work in a risk-free environment, and train patients in motor rehabilitation paradigms (39–41). We posit that the VR media provides additional substrates for developing new motor learning strategies. For example, targeting salient physiological processes such as *indirect prediction* and *sensory reweighting* (6, 10, 29), which are adopted by humans during the course of development and can be recruited for treating locomotion impairments. For example, Lamontagne et al. show that using optic flow manipulations, stroke patients instantaneously increased their walking speed by 44%, for comparison the healthy control group increased their speed by 32% (42). Combining these findings with Bonan et al. (22, 23), which show that stroke patients have increased visual dependency, we can suggest that people with higher visual field dependency will have greater speed modulation following an optic flow manipulation. These findings are in line with our present study (**Figure 7**) in a young healthy population, showing this relation between visual field dependency and the magnitude of gait speed change following an optic manipulation (either optic flow or virtual inclination transition). Decreased sensorimotor integration is an essential characteristic of neurological patients suffering from gait impairments (43). As inclined walking is part of our daily living, better understanding the physiology in young healthy populations is a first step in harnessing the present, or similar (4, 9), paradigms for clinical use. For example, as a relatively ecological tool employed for diagnosis of sensorimotor integration impairment. Such approach would imply establishing norms (of outcomes such as those presented in the present work) based on data from healthy participants. These norms can be contrasted with data recorded from participants with pathological conditions such as persons with Parkinson's disease or persons post stroke. As done in the present contribution, such potential diagnosis can address whether the graded response pattern to virtual inclination intensity is preserved in these cohorts. Along these lines, our paradigm could also evaluate the success of conventional therapies by comparing the multisensory integration pre- and post- therapies and examine whether there was any progress and to what extent. Finally, by "recruiting" this manipulation as a clinical therapy, and repeating the manipulation continuously over longer periods, it can be used to alter the impaired coupling between perception and action, and enhance gait adaptation and sensorimotor integration. Moreover, based on the present study, a new tool which unites a short walking period in a visual conflict paradigm and the rod and frame test can potentially estimate visual dependency in locomotion. Such a tool will help to identify those who may benefit from visual conflicts paradigms, hence facilitating personalized rehabilitation program. For example Brady et al. (44), showed that highly visually dependent people successfully trained to one set of visual conflicts, but were not able to apply their adapted skills to a new discordant environment in comparison to lower visually dependent people. It is yet unclear whether the gait speed modulations we found in a young healthy population will be replicated in populations with gait impairments. To the best of our knowledge, although there are studies that measured the effect of optic flow training (45), none of these paradigms have been effectively translated to clinical practice. Both theoretical and clinical studies are needed to harness the ability of VR to introduce sensory incongruence for rehabilitation benefits.

LIMITATIONS

We note the following limitations associated with this study: (1) Treadmill inclinations of $\pm 15^\circ$ could not be included due to safety restrictions, thus limiting the ability to reach conclusions about gait speed modulations at these walking inclinations. (2) The experimental design did not include all the possible walking conditions, and by that prevented us from computing the proper statistical tests. The limiting factor was the presumed maximal number of walking trails (i.e., 15) that can be presented without causing fatigue. We included the main conditions where the treadmill is leveled and the visual scene transitioned. (3) The third limitation is related to the fact that the visual slope transition times in the incongruent conditions were always 5 s in all conditions (i.e., $\pm 5^\circ$, $\pm 10^\circ$, or $\pm 15^\circ$). This means that, e.g., the 15° transition change was 3X faster than of the 5° transition. This adds a potential confounder (i.e., visual slope transition speed). We acknowledge that this point should be addressed in future studies.

CONCLUSIONS

Virtually induced braking and exertion effects which are expressed by gait speed modulations are linearly related to the degree of virtual inclination. Furthermore, these modulations are highly correlated to the individual visual field dependency assessed by the rod and frame test while walking at virtual inclinations of $\pm 10^\circ$. Our findings add another stratum to the understanding of sensorimotor integration during locomotion in healthy populations and has the potential to contribute to develop VR based rehabilitation strategies in the future.

DATA AVAILABILITY STATEMENT

The datasets generated for this study are available upon reasonable request from the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by The Institutional Review Board for Ethics in Human Studies at the Sheba Medical Center. The participants provided their written informed consent prior to entering the study.

AUTHOR CONTRIBUTIONS

MP, SG-D, and AB conceptualized the study. AB and SZ collected the data. GZ supervised recruitment and ethical aspects. AB analyzed the data and was the primary writer. All authors participated in reviewing, editing, and approving the final manuscript.

FUNDING

This study was supported in part by the Israel Science Foundation (ISF) grant #1657-16. SG-D was supported by the ISF grant #1485/18.

ACKNOWLEDGMENTS

We thank the participants for their time and efforts, Mr. Yotam Bahat for his technical assistance and Dr. Nira Koren-Morag for her advice on concerns on statistics raised during the revision process.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2021.615242/full#supplementary-material

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