Inducing Visuomotor Adaptation Using Virtual Reality Gaming with a Virtual Shift as a Treatment for Unilateral Spatial Neglect

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Abstract: Unilateral spatial neglect after stroke is characterized by reduced responses to stimuli on the contralesional side, causing significant impairments in self-care and safety. Conventional visuomotor adaptation (VMA) with prisms that cause a lateral shift of the visual scene can decrease neglect symptoms but is not engaging according to patients. Performing VMA within a virtual reality (VR) environment may be more engaging but has never been tested. To determine if VMA can be elicited in a VR environment, healthy subjects (n=7) underwent VMA that was elicited by either wearing prisms that caused an *optical* shift, or by application of a *virtual* shift of the hand cursor within the VR environment. A low cost VR system was developed by coupling the Kinect v2 gaming sensor to online games via the *Flexible Action and Articulated Skeleton Toolkit* (FAAST) software. The adaptation phase of training consisted of a reaching task in online games or in a custom target pointing program. Following the adaptation phase the optical or virtual shift was removed and participants were assessed during the initial portion of the de-adaptation phase for the presence of an after-effect on their reaching movements, with lateral reaching errors indicating the successful induction of VMA. Results show that practicing reaching in a VR environment with a virtual shift lead to a horizontal after-effect similar to conventional prism adaptation. The results demonstrate that VMA can be elicited in a VR environment and suggest that VR gaming therapy could be used to improve recovery from unilateral spatial neglect.

Keywords: Sensorimotor learning, plasticity, stroke, spatial attention, engagement.

1. INTRODUCTION

Each year 795,000 individuals in the United States experience a stroke, and many survivors have chronic sensory, motor, and cognitive symptoms that significantly impact their ability to perform routine functional tasks and limit their independence [1]. The incidence of unilateral spatial neglect (USN) is high, with reports ranging from 40% to 80% of persons who suffer a right hemisphere lesion [2-4]. USN is a deficit of spatial awareness characterized by a reduced tendency to respond to stimuli on the contralesional side of space [5-7]. Clinically, patients with USN may ignore the contralesional side of their body, miss details on the contralesional side of objects, are slow to orient toward the contralesional side and fail to scan the contralesional side of space. While left USN is more frequent among patients with right hemispheric lesions than is right USN after left hemispheric lesions [8], right USN has also been reported [9, 10]. USN also interferes with rehabilitation after stroke [2, 11]. While spontaneous recovery occurs in some cases during the acute stage of stroke, many individuals will suffer from unresolved chronic neglect [12, 13]. USN can cause significant impairments in functional performance, specifically in regard to self-care, socialization, mobility, and safety. Consequently, neglect has been associated with higher levels of impairment and longer rehabilitation hospitalizations, causing poor motor and functional recovery in the long term [2, 14]. Safety concerns arise when individuals ignore important information on the left side of space, such as a fire on a stove or a car approaching from the left. Neglect also leads to performance deficits in activities of daily living (ADLs), such as basic hygiene and grooming, and instrumental activities of daily living (IADLs) like transportation and meal preparation [15]. Participation deficits may also occur, impeding social and leisure activities, communication, and relationships. Thus, it is paramount to adequately address neglect to promote safety, independence, and participation.

Numerous interventions have been explored for the treatment of USN [4, 16-18]. Top-down strategies require the patient to self-initiate the implementation of a learned strategy. Bottom-up approaches seek, through repeated practice, to restore the lost function at the impairment level. Limitations of top-down strategies include that they require constant attention for their implementation and are not suited for patients with other cognitive impairments that interfere with their ability to learn and remember new rules [19]. Bottom-

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up approaches for USN have consisted primarily of various forms of stimulation applied to the contralesional neglected side [20]. While these can have some effect, typically the effect lasts only as long as the stimulus is being applied [21]. Currently, one of the most effective, but not widely used, methods for inducing long-lasting improvements in USN is prism adaptation (PA) therapy [21]. PA therapy relies on the well-studied phenomenon of visuomotor adaptation (VMA) [22-24]. One of the first published reports of the induction of VMA using prisms dates back to von Helmholtz in 1867 [25] who had a healthy subject make quick reaching movements to an object while looking through laterally deviating prisms. The subject missed the target on initial reaches but eventually compensated for their error after multiple attempts. Most importantly, subsequent removal of the prisms resulted in a transient reaching error in the opposite direction, this after-effect indicating that, via yet unknown mechanisms of brain plasticity, VMA had taken place.

Since Helmholtz's seminal experiments, prism-induced VMA continues to be intensively studied in healthy subjects. VMA is readily induced with either left shifting [26] or right shifting prisms [27]. VMA induction requires interaction with the environment and does not occur with passive wearing of prisms [28] and may be dependent on aging [29]. Furthermore the amplitude of the after-effect and its duration have been shown to depend respectively on the prism strength and the number of reaching movements performed [26]. Recently, the pointing error associated with VMA has been shown to last at least 40 min after a single PA session [30]. Also, interesting asymmetries in VMA transfer have also been shown in that training the arm transfers to the leg, but training the leg itself does not transfer to the arm [31]. Training walking however, does generalize to reaching [32]. In other studies, partial generalization has been reported [33].

More important for the rehabilitation of USN is the evidence of the cognitive after-effects of prism adaptation on space representation. Interestingly, reported cognitive after-effects are asymmetric in that they appear after using a leftward but not rightward optical shift resulting in a right spatial advantage that mimics some of the features of left USN [34]. Training with left shifting prisms can cause healthy subjects to have a rightward bias that can be seen in perceptual line bisection tasks [30, 35], in mental number line bisection tasks [36], and in an alphabetic line bisection tasks [37]. Other induced abnormalities include impaired visuospatial remapping (demonstrated with the double-saccade test) [38], and increased local versus global information processing of visual stimuli [39, 40]. Studies investigating changes in lateralized spatial attention or awareness in healthy subjects have reported more complex results [41] that may depend not only on the direction of the optical shift during training but also on the subject's baseline attentional bias (such as whether they have pseudoneglect at baseline) [42]. Given the evidence that PA influences spatial cognition in healthy individuals, it is likely that similar processes contribute to its efficacy in the rehabilitation of USN [43, 44].

In stroke patients, a study showing that prism adaptation could improve performance on a line bisection task and a line cancellation task in a mixed stroke population with homonomous hemianopsia or hemineglect [45] was the first to suggest that prism adaptation could be used to treat USN. This was confirmed in a seminal study showing behavioral improvements that lasted over two hours after a single session [46], longer than any other intervention for neglect to date. Since then numerous studies have demonstrated that after multiple rounds of prism adaptation effects may last for weeks [47-49] or months [50, 51]. The intervention is effective even in chronic stroke [48, 52-55]. Effects are manifest well beyond visuomotor performance to visual imagery [56, 57], visuo-verbal tasks [58], bisection of a mental number line [59], body representation [60] and other aspects of cognition [43, 44]. Crucially, from the rehabilitation perspective, prism adaptation has been shown to improve the performance of functionally meaningful tasks [50, 51, 61, 62].

In standard PA therapy protocols, patients wear wedge prism glasses that shift their vision 10-12 degrees to the right, causing objects in their visual field to appear at a displaced position. Thus, when the patient reaches toward a target, he or she must adapt to the difference between the real and displaced positions of that target. During treatment, the patient is instructed to perform numerous ballistic reaching movements to a target. Initially, the patient will exhibit a large pointing error to the right. As the participant adapts, this error will return to zero. When the patient removes the glasses, they display a compensatory over-correction to the left, or after-effect, demonstrating that adaptation has taken place [26, 63]. In the clinical setting typical protocols may have a patient with USN perform PA therapy for 15-20 minutes once per day for 2 weeks (https://www.youtube.com/watch?v=aj8D4SXeXZs).

Although this after-effect eventually wears off (de-adaptation), studies examining the long-term treatment benefit of PA therapy have shown the effect to last up to 6 months with multiple sessions [64]. Limitations of PA therapy include visual disorientation, nausea, and boredom leading to lack of engagement and motivation [65].

Virtual reality (VR) environments have been gaining popularity as therapeutic tools to promote stroke recovery [66-69]. VR is an attractive option for creating a highly engaging task and has been successfully used as an engaging intervention for improving upper extremity function in individuals with cerebral palsy (CP) and hemiplegia after stroke [70-73]. Increasingly, VR is being used as a tool to assess and treat unilateral spatial neglect [74-80]. A number of studies have taken advantage of the VR environment's ability to safely train the subject with USN to perform an otherwise dangerous real-world scenario such as street-crossing [81-84]. Of the larger interventional trials looking at the effect of VR training on USN, there is some evidence to suggest a modest benefit from training on virtual street crossing [82] and reaching for objects in the VR environment [77, 85]. However, these, and multiple smaller studies, are not very mechanistically motivated with regard to understanding their active therapeutic ingredient. A recent exception is a study that trains visual scanning in a VR environment. Visual scanning is a well-established top-down technique that can help some patients with USN [86, 87]. Fordell *et al.* reported that chronic stroke patients with USN who underwent a 5 week course of training in visual scanning in the VR environment had improved scores on measures of neglect at the impairment and functional levels that were maintained for up to 6 months [88]. Before promoting the development of a VR environment that relies on VMA for the treatment of USN it is crucial to demonstrate the induction of VMA within the VR environment. Traditional PA therapy drives sensorimotor rearrangement by a misalignment of the visual input through prisms. This study seeks to test the hypothesis that misalignment of the motor output of the virtual hand with normal visual input can also lead to VMA. Our hypothesis predicts that training under conditions of a virtual shift that shifts the virtual hand to the right will also lead to VMA as demonstrated by the presence of a measurable leftward after-effect upon removal of the virtual shift. To the best of our knowledge, there are no other mechanistically driven studies of the rehabilitation of USN using VR, and none that have tried to use specific principles of brain plasticity to promote recovery. The results of this project represent essential knowledge for developing a VR gaming therapy to improve functional recovery in individuals with left USN.

2. MATERIALS AND METHODS

The study was approved by the Washington University School of Medicine Internal Review Board and all procedures were conducted in agreement with the 1975 Helsinki Declaration.

2.1. Participants

The participants were seven neurologically intact individuals who lived in the St. Louis metro area (Table **1**). Neurologically intact individuals were chosen for the purpose of testing the feasibility of inducing VMA within the VR environment. If VMA is successfully induced in healthy individuals, those results could be translated to individuals with neglect as an intervention in future studies. The inclusion criteria for this study were: having full range of motion in the right arm (shoulder flexion and abduction), normal vision or corrected to normal vision, and ability to provide informed consent. The exclusion criteria for this study were history of neurologic or psychiatric illness and previous participation in a VR study with a virtual shift. Participants were six females and one male, ages 23-27 years. All participants were graduate students who had completed at least 16 years of education.

2.2. Study Design

This study investigated the induction of VMA in each of four experimental conditions within a low-immersion VR environment. Each condition consisted of 3 sequential phases during which participants made a fixed number of ballistic reaching movements to a target on a computer screen: pre-adaptation (30 reaches), adaptation (100 reaches), and de-adaptation (30 reaches). Each reach constituted a single trial. The four conditions differed from each other only with regard to the adaptation phase where different methods of inducing VMA were used. Visuo-motor congruence was disrupted either by having participants wear prism goggles that introduced a horizontal optical shift (OS) of the scene, or by computerized manipulation of the on-screen hand cursor that introduced a horizontal virtual shift (VS) relative to where their real hand was pointing (2 conditions). In addition, participants got to experience each of these two manipulations (OS and VS) in two different VR environments: one was a simple pointing error detection (PED) program requiring the participant to reach to either a red dot or a black dot that appeared at fixed locations on either side of the monitor; the other was a free online version of the games “Whack-a-mole” or “Darts” (Game). Consequently the four experimental conditions were: OS/PED; VS/PED; OS/Game; VS/Game. The four conditions were exactly the same during their pre-adaptation and de-adaptation phases and consisted of performing 30 reaching movements to targets within the PED program and did not involve any OS or VS. Each participant had 2 visits that lasted 30-60 minutes each, depending on individual speed of performance. The order of the experimental conditions was the same for all subjects (Day 1: OS/PED followed by VS/PED; Day 2: OS/Game followed by VS/Game). During each session, participants completed approximately 320 reaches. Because visual feedback of the arm and hand during the reaching movement may reduce VMA induction [89, 90], the initial portion of the reaching movement was hidden from the participant’s view. This was achieved by obscuring the lower third of the prism goggles or clear goggles with painter’s tape. A similar effect was achieved with regard to the appearance of the hand cursor on the screen by preventing its appearance on the monitor until the distance the participant had moved their hand exceeded a minimum threshold. To prevent fatigue, sessions were scheduled over the course of two days. Because the adaptation phase of the intervention was followed by a de-adaptation phase that washed out the induced effect, participants were able to complete 2 of the 4 experimental conditions within the same visit. The 30 reaches performed during the pre-adaptation phase of each also contributed to the washout and to ensuring a more consistent baseline. Visits were scheduled over sequential days and the order of sessions was not randomized. Two occupational therapy graduate students who had been trained in appropriate research and intervention methods carried out the interventions at the Human Performance Lab from January to April 2016.

2.3. Setting and Equipment

This study was completed at the Human Performance Laboratory within the Occupational Therapy Program at Washington University in St. Louis. Visual stimuli and games were presented on a 48-inch flatscreen monitor via a laptop computer. The computer interfaced with the Microsoft Kinect v2 (Microsoft, Redmund, WA) using a USB 3.0 connection and the latest version of the Microsoft Kinect SDK (v2.0). The computer had access to the Internet (to use free online games) and met all recommended hardware specifications for the required software including Matlab (The Mathworks Inc., Natick, MA), the Flexible Action and Articulated Skeleton Toolkit (FAAST) [91], and the Pointing Error Detection (PED) program.

FAAST (http://projects.ict.usc.edu/mxr/faast/) is a middleware program that translates movements in physical space into keystrokes or mouse clicks on the computer to illicit a virtual action. These movements can be specified by type (e.g. right shoulder flexion) and magnitude of body movement (e.g. range of motion in cm). Movements can be selected from a virtual library of preset actions, or the clinician can specify the parameters of the movement and the resulting keyboard output. FAAST uses a Virtual Reality Peripheral Network (VRPN) algorithm to track the position and orientation of the skeletal markers recognized by the Kinect v2. For the purposes of this study, a custom Matlab program was used to create FAAST configurations that convert right arm movement into mouse movement and a forward reach with the right arm into a mouse click to mimic the procedure for PA therapy.

In order to record information from the Kinect skeleton, another custom Matlab program was developed to collect data. This program had real-time access to VRPN information that the Kinect server used. Designated skeletal positions were recorded as the individual interacted with the virtual environment. The study used 11 markers of interest (hand, wrist, elbow, shoulder, neck, head, and torso) to track during study sessions. The x- and y-coordinates, in pixels, of the mouse in the coordinate system of the screen were also collected to identify reaching errors (VMA) and to measure de-adaptation.

The Microsoft Kinect version 2 is a motion sensor that is typically paired with the Xbox One (http://www.xbox.com/en-us/xbox-one) video game console. For the purposes of this study, the Kinect was paired directly with a computer, and no Xbox console was needed. The Kinect allows the player to interact with a game by moving their body to produce a desired computer action. The Kinect uses a color camera, depth sensor, and complex algorithms that are able to subtract background objects. This creates a three dimensional skeleton that is overlaid on the player’s body to track the real-time position and orientation of up to 23 joints as the player moves.

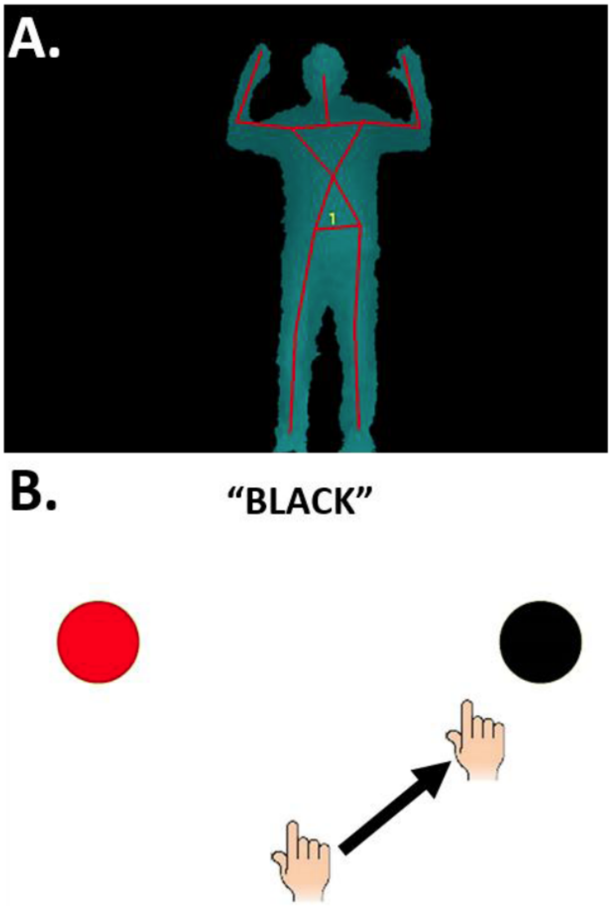

Figure 1: A. Screenshot of the skeletal tracking from the Kinect v2 motion sensor. **B**. Screenshot of the Pointing Error Detection program. On each reaching trial, the red dot and the black dot appear in their fixed location. In the example shown in **B**, the word "Black" appeared instructing the subject they had to move the hand cursor from the starting position onto the black dot. The horizontal distance from the position of the hand-shaped cursor at the end of the reaching movement to the center of the target is recorded and used as a measure of horizontal reaching error.

The PED program was developed to assess visuomotor adaptation. The PED was designed to simulate PA therapy in a virtual environment. The program utilizes the same principal components as traditional PA therapy, and was either paired with prism glasses or a virtual shift in hand cursor location. The PED program (Figure **1**) requires players to use a ballistic reaching movement to hit one of the two targets on the screen with the cursor with a cursor simulating the participant's hand. Participants were visually cued to reach for either the red or black target when the word "RED" or "BLACK" appeared on the screen in between the targets in a randomly generated order. The hand would not move on screen until the player's right hand passed a certain distance in front of their shoulder. This distance was the threshold that defined a successful reaching motion for the purposes of this study (40cm from right shoulder to right hand). Once the target was hit, positive visual and auditory feedback was presented to let the player know they hit the target. There was also a time delay between reaching movements to encourage a ballistic action rather than searching for the target after passing the threshold.

The PED was combined with custom FAAST configurations developed in Matlab as previously described. Two different versions of these configurations were designed: aligned or virtually shifted. The aligned configurations were predictable in nature and developed such that the reaching space and screen space were aligned (e.g. a reaching movement aimed at a target would move the cursor directly to the target). The virtually shifted configuration was designed to mimic the twelve degree visual deviation created by the prism glasses in PA therapy by shifting the coordinates on the screen to the right, thus requiring individuals to reach further to the left in order to hit both targets (e.g. a reach directly to the target would actually miss the target by approximately 300 pixels to the right). This virtually shifted configuration was applied during the two Virtual Shift experimental conditions (see below).

Finally, free online games provided alternative VR environments to the PED program. Participants could choose to play either "Darts" or "Whack-a-Mole." These games were chosen because they require the participants to aim at targets on screen and require only one click to play, which mimics the procedure for PA therapy and the PED program.

2.4. Measures

The main outcome measure in this study was the horizontal reaching error during the pre-adaptation, adaptation and de-adaptation phases. It is important to underscore that participants' performance on first trials of the de-adaptation phase can be considered as an index of the VMA that has taken place. Given the direction of the OS and VS during the adaptation phase (rightward deviation), it was predicted that the induction of VMA would manifest as the appearance of leftward reaching errors during the initial portion of the de-adaptation phase (after-effect). Reaching errors were assessed with the PED recording program and were reported as the horizontal distance in centimeters from where the cursor appeared on the screen at the end of a reach to the center of the intended target presented by the PED program. The quantification of reaching errors was used to infer the induction of VMA as well as its magnitude and duration. Trajectory data was also obtained for each reach trial.

2.5. Data Analysis

To determine if the baseline states were comparable prior to the adaptation phase of each of the four experimental conditions an ANOVA on the mean of the last 5 trials [92], or trials 26-30, from the preadaptation phase for each of the four conditions was performed. One subject had only 27 pre-adaptation reach trials hence trials 23-27 were averaged. To determine if VMA was induced a repeated measures 2x2 factorial ANOVA (factor 1=time: reach # 30 in Pre-adaptation, reach # 1 in De-adaptation; factor 2=condition: PED, Game) was performed for the OS conditions and for the VS conditions. Subsequently a paired t-test was performed comparing the mean of the last 5 reaches of the Pre-adaptation phase with the mean of the first 5 reaches of the De-adaptation phase was carried out to perform the appropriate post-hoc analyses. This analysis was repeated for each of the four experimental conditions. No statistical tests were performed to directly compare the means across OS and VS conditions because we could not calibrate the magnitude of the OS and VS shifts to be the exactly same and because they may not engage exactly the same neural systems.

3. RESULTS

Participant demographics are shown in Table **1**.

Table 1: Participant Demographics

	Number	Mean (SD)
Age		
23	3	
24	2	24.1 (1.5)
25	1	
27	1	
Gender		
Male	1	
Female	6	
Hand Dominance	6	
Right	1	
Left		
Education Completed		
16 years	2	16.7 (0.5)
17 years	5	
Race		
White	6	
African American	1	

Mean trial-by-trial horizontal pointing errors across the three phases in the four experimental conditions for all 7 participants are shown in Figure **2A**. Pointing errors could not be determined for the adaptation phase of the OS/Game and VS/Game conditions because during the game, targets appear in random locations, precluding a calculation of the hand cursor-to-target distance.

A repeated measures ANOVA was performed on the average of 5 reaching trials at the end of the Pre-adaptation phase to determine if there was any difference in pointing error in the four experimental conditions prior to inducing visuomotor adaptation. With a Greenhouse-Geisser correction for non-sphericity, the mean scores for pointing error were not statistically significantly different ($F(1.698, 3.395) = 8.307$, $p = 0.05$).

Using a Greenhouse-Geisser correction, since sphericity could not be assumed, a two-way repeated measures ANOVA was conducted on the influence of two independent variables (treatment, time) on the pointing error measured during the PED task, under the *optical* shift training condition. Treatment type included 2 levels (PED, Game) and time consisted of two levels (Pre-adaptation, De-adaptation). Only the effect for time was significant, F(1,2) = 19.935, p = 0.047, indicating a significant difference in the pointing error in the Pre-adaptation phase and the De-adaptation phase. The main effect for treatment (PED or Game) was not significant, F(1,2) = 0.264, p = 0.659. The interaction effect was not significant, F(1,2) = 0.004, p = 0.955.

Also, using a Greenhouse-Geisser correction, since sphericity could not be assumed, a two-way repeated measures ANOVA was conducted on the influence of two independent variables (treatment, time) on the pointing error measured during the PED task, under the *virtual* shift training condition. Treatment type included 2 levels (PED, Game) and time consisted of two levels (Pre-adaptation, De-adaptation). Only the effect for time was significant, F(1,2) = 1048.936, p = 0.001, indicating a significant difference in the pointing error in the Pre-adaptation phase and the De-adaptation phase. The main effect for treatment (PED or Game) was not significant, F(1,2) = 0.025, p = 0.888. The interaction effect was not significant, F(1,2) = 1.119, p = 0.401.

Using paired t-tests, we determined that in the OS/PED condition there was a significant difference in

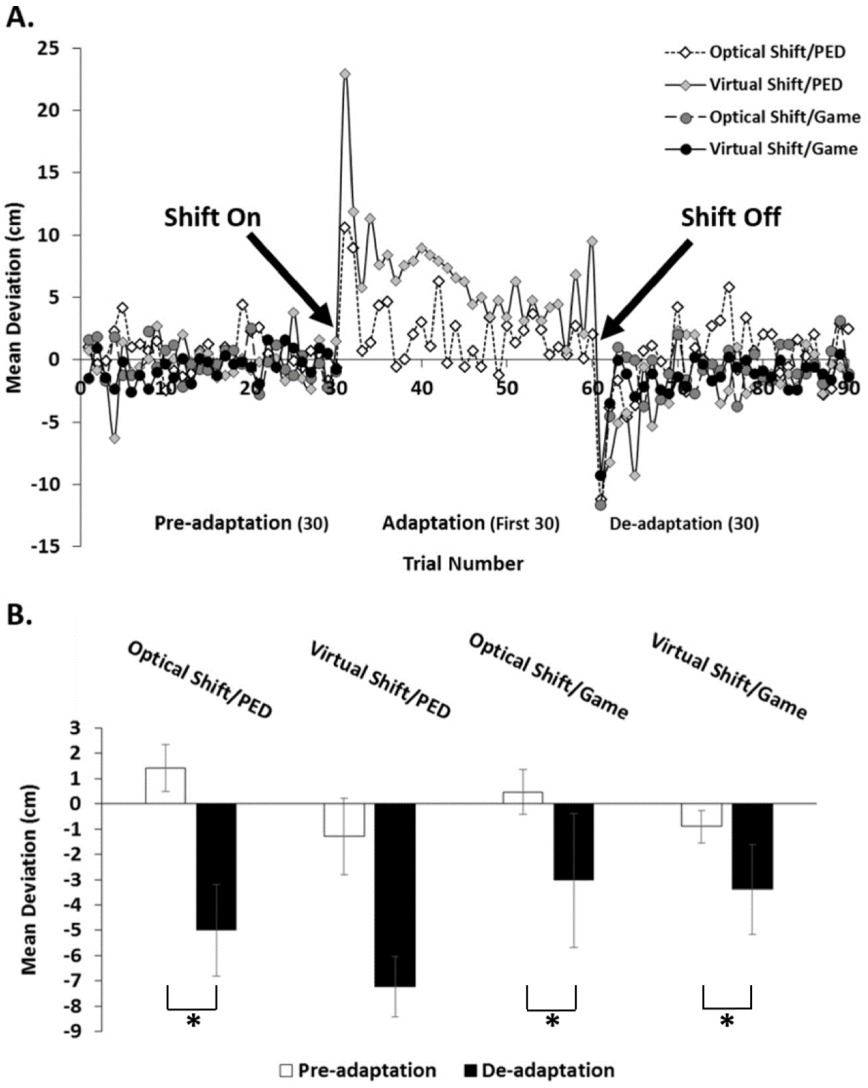

Figure 2: A. Mean trial-by-trial pointing error on horizontal axis (in cm) in the 4 experimental conditions, through the three phases of a session (30 reaches in pre-adaptation, first 30 out of 100 reaches in adaptation, 30 reaches in de-adaptation). Positive and negative numbers correspond to rightward and leftward pointing errors, respectively. **B**. Mean pointing error on horizontal axis (in cm) binned by groups of 5 reaches for the last 5 reaches of the pre-adaptation phase, and the 5 reaches of the de-adaptation phase for the 4 experimental conditions. Error bars indicate standard deviation of the mean. * = p < 0.05.

the pointing error for pre-adaptation (M=1.41, SD=2.64) and de-adaptation (M=-4.82, SD=1.47) phases; t(4)=4.61, p=0.01, Cohen's d = 2.92. In the VS/PED condition the difference in the pointing error for pre-adaptation (M=-1.65, SD=1.03) and de-adaptation (M=-7.23, SD=4.94) phases did not achieve significance, t(4)=2.48, p=0.068, Cohen's d = 1.56. In the OS/Game condition there was a significant difference in the pointing error for pre-adaptation (M=0.78, SD=1.26) and de-adaptation (M=-3.02, SD=2.45) phases; t(4)=3.11, p=0.04, Cohen's d = 1.95. In the VS/Game condition there was a significant difference in the pointing error for pre-adaptation (M=-1.07, SD=2.28) and de-adaptation (M=-3.39, SD=2.14) phases; t(4)=3.84, p=0.02, Cohen's d = 1.05 (Figure **2B**).

Visual inspection of the pointing error across the three phases of training (Figure **2A**) shows that during the pre-adaptation phase, pointing errors are small and distributed around zero. At the beginning of the adaptation phase, the application of an OS or VS leads to rightward pointing errors. As adaptation takes place, pointing errors diminish to near zero with successive reaches. At the beginning of the de-adaptation phase, the OS or VS is removed, and now pointing errors are in the opposite direction, to the left, indicating that VMA had been induced. The effect of the three phases on pointing trajectory can be seen at the level of individual subjects and individual trials (Figure **3**). The first trial in the adaptation phase is to the right of the last trial of the pre-adaptation phase and the first trial in the de-

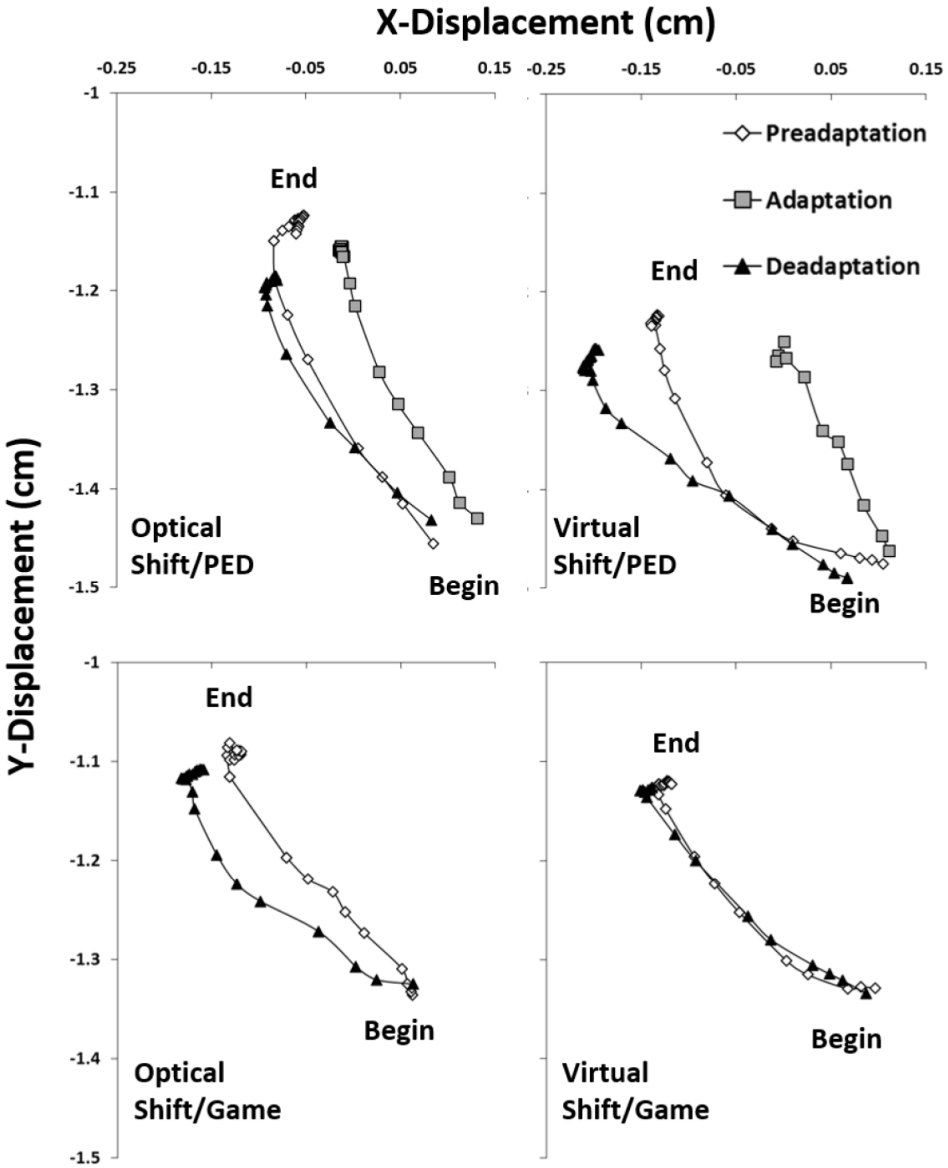

Figure 3: Reaching trajectories plotted in the x,y plane as seen from above, in selected subject demonstrating effect of VMA in the 4 experimental conditions measured in the PED program. Last leftward trial in the pre-adaptation phase, first leftward trial in the adaptation phase, and first leftward trial in the de-adaptation phase are shown. Pointing error during the adaptation phase could be calculated only for the Optical Shift/PED and Virtual Shift/PED conditions where target position was known.

adaptation phase is to the left of the last trial of the pre-adaptation phase.

4. DISCUSSION

The purpose of this proof-of-principle study was to determine if a VMA could be induced in neurologically intact individuals while they played a VR game where the relationship between motor output and visual input was distorted virtually. First, we showed that practicing reaching to fixed targets in a VR environment where the relationship between motor output and visual input is disturbed by the introduction of a right-ward displacing OS with prisms leads to a left-ward pointing error when prisms are removed. Second, we showed that a similar effect is obtained if the relationship between motor output and visual input is disturbed by the introduction of a right-ward displacing VS that shifts the position of the hand-cursor to the right of the actual hand position. Third, we showed that this effect can also be obtained (whether under OS or VS conditions) by playing engaging computer games that require reaching to targets that appear in random locations. These results suggest that VMA was induced in three of four conditions. Although significance was not achieved in the VS/PED condition due to large standard deviations, the mean change in pointing error was in the direction predicted by VMA (leftward overshoot after removal of prisms) and would likely be significant with a larger sample size. The results also suggest that a virtual shift affecting perceived hand position may be as effective as an optical shift affecting perceived target location in generating the after-effect. Accordingly, the amplitude of the after-effect and the shape of its decay during the de-adaptation phase had temporal characteristics similar to the after-effect produce by PA therapy (leftward overshoot, with gradual de-adaptation over time). Very importantly, VMA was induced in the VS/Game experimental condition, as this is the scenario that may have the most implications for the rehabilitation of stroke patients with USN. These results demonstrate that a simple, low-cost, low-immersion VR environment using commercially available components like the Kinect v2 motion sensor and a simple pointing program were sufficient to perform and assess VMA induced by prism adaptation or virtual adaptation.

Mechanisms of VMA

A number of studies have explored the neural correlates of prism adaptation in healthy subjects using fMRI and positron emission tomography (PET). Task-based studies have reported activations in the contralateral posterior parietal cortex and intraparietal sulcus [93] (studied with PET), left anterior cingulate, anterior intraparietal region and right cerebellum [94], left parieto-occipital sulcus and left anterior intraparietal sulcus, right intraparietal cortex, lobules IV and V in the right cerebellum, bilateral superior temporal sulcus, superior temporal gyrus [95], right cerebellum and inferior parietal lobe [96]. A recent fMRI study showed bilateral increases in middle frontal gyrus and superior parietal activation immediately after just one session of prism adaptation [97]. Lesions studies have implicated the cerebellum whose damage appears to interfere with adaptation first shown by Baizer *et al.* [98] and Weiner *et al.* [99] and subsequently confirmed by others [27, 100]. The effect of parietal lesions is less clear. In PA therapy, the mismatch between visual input and motor output is due to prism-induced distortion of the visual input. Whether similar regions are implicated when a virtual shift is applied as opposed to an optical shift is not known. In this study, a rightward deviation was imposed on the movement of the virtual arm, a scenario that may be similar to when a force field is applied to study human motor adaptation and learning using center-out tasks [23, 101, 102]. Those studies have generally implicated the cerebellum [100, 103, 104], the parietal cortex [105, 106] as well as the right inferior frontal gyrus, primary motor cortex, inferior temporal gyrus [107, 108], cingulate motor area [109] basal ganglia [110] and right dorsolateral prefrontal cortex [105]. Exactly which areas are crucial may depend on the details of the training task such as whether the arm movement requires simply joy stick manipulation, versus moving a mouse on a 2-D surface, versus reaching out into 3-D space. Beyond simply compiling a list of regions involved in visuomotor adaptation, there is a growing recognition that our models must also account for the broader cognitive effects that likely underlie the functional improvements reported in some studies on visuo-motor adaptation post stroke [43].

Optimizing VMA

It is currently not known whether an input-output mismatch due to forced deviation of the motor output relative to visual input would cause a lesser or greater level of VMA than PA. The after-effect can be characterized by both its amplitude as well as its persistence. Our study was not designed to perform a direct comparison of the after-effect between experimental conditions. However, on the very first reach in the de-adaptation phase, the mean pointing error is similar for the four conditions (Figure **2A**). In all four conditions, the after-effect decays with subsequent reaching trials. It is interesting to note that the decay back to a stable baseline seems more rapid in the OS/PED and OS/Game conditions. By contrast, the decay was slower in the VS/PED and VS/Game conditions. Given our small sample size, it is not possible to conclude that a virtual shift is more effective than an optical shift, in part because we did not calibrate the magnitude of the shifts to each other but rather optimized the virtual shift for our laboratory environment and the equipment being used. Future studies could investigate the importance of these determinants. Based on our results, we are also unable to infer anything about the participant’s level of engagement in the different experimental scenarios. However, we hypothesize that higher levels on engagement will lead to better outcomes because patients will be likely to perform more repetitions of the training task which has been shown to lead to a longer lasting after-effect [26, 63]. It is also possible that higher levels of engagement have beneficial effects on rehabilitation through attentional mechanisms that directly modulate levels of brain activity and activity-dependent synaptic plasticity [111, 112]. Demonstrating that the experimental conditions used here are successful in inducing VMA is crucial first step in translating this research into new interventions for individuals with neglect. Additional studies will be required to determine the parameters that will give the greatest effect, similar to the call for studies to optimize the delivery of PA therapy [64].

Application to Patients with USN

The protocol described in this study is scalable, sustainable and directly transferrable to stroke patients with USN. Sustainability features include its low operational costs, high safety, low supervision requirement and its potential adaptability for evaluating and treating patients with USN. Additionally, the proposed Kinect-FAAST-based VR environment may in the future be adapted for the investigation and rehabilitation of other deficits including hemiparesis as well as impairment of memory and executive function. Benefits to patients include the opportunity to supplement their standard outpatient therapy regimen which is generally woefully underdosed [113, 114] with hundreds more repetitions needed to drive the mechanism of activity-dependent plasticity to promote better stroke recovery. In addition, interacting with a VR environment of the patient's choosing activates reward mechanisms and is likely to encourage more of the activity. Finally, the overall simplicity of the apparatus and near ubiquitous availability of its components opens the door to using VR at home [115-118], increasing the likelihood that they will get more exposure to the therapy. However, it is likely that some stroke patients with USN will be more responsive to VR based VMA, due to multiple factors including overall stroke severity, lesion location, and level of attention impairment. Specifically, patients with cerebellar lesions [32] or left parietal lesions [106] may benefit less. One solution to this problem lies in the unique property that VMA is a type of neuronal plasticity that can be induced quickly during a single session. Hence its presence or absence could serve as a screening biomarker for the appropriateness of the therapy in any given patient [119, 120].

LIMITATIONS

Limitations of the study include its small sample size and the fact that few subjects had a complete data set across all conditions. However, the magnitude of the effect size suggests that the effect is robust. The order of the experimental conditions was not randomized and was the same for all subjects. However, the absence of a difference between the pointing error during pre-adaptation phases of each treatment condition suggests that sufficient deadaptation was achieved to return subjects back to baseline. The OS and the VS were not calibrated to be of equal magnitude and may rely on different neural mechanisms making direct comparison difficult. The sensitivity and accuracy of the Kinect 2 sensory was not validated against a gold standard reference, but it is likely to continue to improve with successive generations due to market demands. Finally, because of the random location of targets in the adaptation phase when playing a game, pointing errors could not be calculated.

5. CONCLUSION

We have shown that with a lost-cost, low-immersion VR environment, it is possible to induce and detect VMA using prisms to create an optical shift or using a virtual shift of the hand cursor in the VR setting. In addition, this VMA can be induced with the participant playing free online games from the internet that require a ballistic reaching movement. To the best of our knowledge this is the first time that a VR environment was used in humans where, instead of distorting the perception of the visual input, the perception of the motor output was distorted to drive brain plasticity without the use of a joystick, mouse, or other robotic manipulandum. This innovative use of VR technology will allow us to investigate how distortion of the perceived reaching movement can be used to retrain desired reaching strategies and facilitate exploration of the left side of space in stroke patients recovering from USN.

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