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ORIGINAL RESEARCH

Motor learning in hemi-Parkinson using VR-manipulated sensory feedback

Ori Ossmy[a,b], Lihi Mansano[c], Silvi Frenkel-Toledo[d], Evgeny Kagan[a], Shiri Koren[b], Roee Gilron[a,b], Daniel Reznik[a,b], Nachum Soroker[c,e] and Roy Mukamel[a,b]

[a]Sagol School of Neuroscience, Tel-Aviv University, Tel-Aviv, Israel; [b]School of Psychological Sciences, Tel-Aviv University, Tel-Aviv, Israel; [c]Department of Neurological Rehabilitation, Loewenstein Hospital, Ra'anana, Israel; [d]Department of Physiotherapy, Faculty of Health Sciences, Ariel University, Ariel, Israel; [e]Sackler Faculty of Medicine, Tel-Aviv University, Tel Aviv, Israel

ABSTRACT

Aims: Modalities for rehabilitation of the neurologically affected upper-limb (UL) are generally of limited benefit. The majority of patients seriously affected by UL paresis remain with severe motor disability, despite all rehabilitation efforts. Consequently, extensive clinical research is dedicated to develop novel strategies aimed to improve the functional outcome of the affected UL. We have developed a novel virtual-reality training tool that exploits the voluntary control of one hand and provides real-time movement-based manipulated sensory feedback as if the other hand is the one that moves. The aim of this study was to expand our previous results, obtained in healthy subjects, to examine the utility of this training setup in the context of neuro-rehabilitation.

Methods: We tested the training setup in patient LA, a young man with significant unilateral UL dysfunction stemming from hemi-parkinsonism. LA underwent daily intervention in which he intensively trained the non-affected upper limb, while receiving online sensory feedback that created an illusory perception of control over the affected limb. Neural changes were assessed using functional magnetic resonance imaging (fMRI) scans before and after training.

Results: Training-induced behavioral gains were accompanied by enhanced activation in the pre-frontal cortex and a widespread increase in resting-state functional connectivity.

Discussion: Our combination of cutting edge technologies, insights gained from basic motor neuroscience in healthy subjects and well-known clinical treatments, hold promise for the pursuit of finding novel and more efficient rehabilitation schemes for patients suffering from hemiplegia.

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Cross-education; upper-limb hemiparesis; mirror sensory feedback; proprioceptive feedback

➤ IMPLICATIONS FOR REHABILITATION

- Assistive devices used in hospitals to support patients with hemiparesis require expensive equipment and trained personnel – constraining the amount of training that a given patient can receive.
- The setup we describe is simple and can be easily used at home with the assistance of an untrained caregiver/family member.
- Once installed at the patient's home, the setup is lightweight, mobile, and can be used with minimal maintenance .
- Building on advances in machine learning, our software can be adapted to personal use at homes.
- Our findings can be translated into practice with relatively few adjustments, and our experimental design may be used as an important adjuvant to standard clinical care for upper limb hemiparesis.

Introduction

Unilateral impairment of upper-limb (UL) motor function can emerge from various aetiologies including stroke and hemi-Parkinson's disease and reflect damage to distinct components of the motor control network [1–4]. Patients may exhibit unilateral deficits in muscle tone and force regulation, correctness of movement and speed of sequence execution [5–7]. Rehabilitation therapy is usually delivered as a series of challenging but achievable activities with specific goals for the patient. However, finding an optimal training regime to achieve these goals has been elusive [8–10]. Previous research examined the utility of constraint-induced movement therapy (CIMT) [11–13] – an approach in which the patients' non-affected UL is artificially and temporarily restrained in order to force them to use their affected UL. Although this approach has well established effects on patients' performance, it is very challenging in cases where the basic motor capability of the affected hand is limited [14]. To bypass this problem, other studies examined various indirect training approaches.

One indirect approach to facilitate the performance of the affected UL is to use visual input which provides a rich source of information supporting motor behaviour. It is now well established that performance level on a motor task can increase following passive observation of someone else performing a similar task [15,16]. The physiological mechanism that underlies this phenomenon is believed to rely on activation of mirror neurons in regions

CONTACT R. Mukamel rmukamel@tau.ac.il School of Psychological Sciences & Sagol School of Neuroscience, Tel-Aviv University, Tel-Aviv 69978, Israel
Supplemental data for this article can be accessed here.

within the fronto-parietal cortex of the observer [17–19]. We have recently demonstrated in healthy participants that the activity in the superior parietal lobule (SPL) during passive action observation may play an important role in such a learning process [16]. The effectiveness of visual feedback and training by observation as an additional rehabilitation tool has been also examined with patients. One such tool is mirror visual feedback (MVF), where movement of the non-affected UL is viewed in a mid-sagittal mirror, creating an illusory percept of movement in the affected UL. MVF has been shown to alleviate phantom limb pain, a condition sometimes seen following limb amputation, which is thought to emerge as a result of maladaptive brain plasticity [20].

Using sensory input to improve motor performance is not limited to vision. Another indirect approach to improve performance is passive movement of the affected limb. In such training, the affected limb is typically strapped to a device that is controlled either by a computer [21,22] or by the subject's other limb [23]. In either case, the affected limb passively moves, and the subject receives proprioceptive input similar to what he would have received during voluntary movement. Most importantly, the volitional aspect of limb control in such training is lacking. Proprioceptive training, in which the limb is passively moved, was shown to improve performance level in the passively moved effector [21,23–25] and facilitate rehabilitation of hemiparetic patients [26–28] in various tasks including reaching forward, picking up balls and various fine motor skills. Recently, Picelli et al. used a robotic device to passively move arms of patients with Parkinson's disease. They demonstrated how practice in which the forearm and wrist of one limb are passively yoked to the other limb, enhances the function of the passively moved upper limb (UL) [29]. Together, these lines of research provide strong evidence for the important role of perception and proprioception in motor control and rehabilitation.

Finally, it is known for over a century, and corroborated by recent research, that physical training with one limb can result in substantial performance gains also in the untrained limb – a phenomenon known as cross-education (CE) [30–32]. This phenomenon was used in the clinical realm mainly in the context of immobilization therapy. During immobilization of a limb, following bone fracture for example, there is significant loss of muscle mass. Physical training of the contralateral (free) limb has been shown to prevent, or slow down this process, resulting in reduced loss of muscle volume in the immobilized arm [33,34]. Training based on CE was shown also to improve grip precision learning and force in the hemiparetic UL [35–38].

We have recently developed a unique virtual reality (VR) setup combining CE with manipulated visual and proprioceptive feedback creating an illusory perception of voluntary control over movement in the non-trained UL. Healthy subjects trained with this setup showed high performance outcomes in the hand that was not under voluntary control [23]. It is hoped that in the clinical context of neuro-rehabilitation, this can offer a new treatment strategy where standard exercises with the affected UL are of limited applicability due to severe spasticity, very limited voluntary control, or rapid fatigue. Here, we tested the feasibility of translating our findings in healthy subjects to the realm of clinical practice. Specifically, we examined in a highly motivated young man whose right hand (RH) was severely affected by hemi-Parkinson's disease, the effectiveness of training with his non-affected left hand (LH). Additionally, by using whole-brain functional magnetic resonance imaging (fMRI) we probed potential neural mechanisms underlying the effects of training.

Materials and methods

Patient

LA is a 46-years old right handed male with 18 years of formal schooling, working as a manager of energy projects. He is married, father of three and has no family history of neurological disorders. Three years prior to this study, he started to experience difficulties using his dominant RH during execution of fine motor skills, with a noticed change in handwriting. His neurological examination at that time and an MRI scan done somewhat later did not reveal any pathology. However, a scan detecting dopamine transporters (DaT Scan) showed depletion of striatal dopaminergic neurons suggestive of Parkinson's disease. Treatment with Amantadine, Rasagiline and Pramipexole did not ameliorate the hand function and eventually these medications were discontinued. Currently, LA shows serious slowness and rapid fatigue in repetitive movement of the RH with slight focal hypertonicity. In addition, he suffers from a restless right leg during intense activity calming at rest, for which treatment with Biperiden has been tried. LA keeps a daily aerobic exercise routine and receives two physiotherapy sessions per week. He also performs regularly at home a set of daily exercises aimed to improve control of fine movement in the affected RH. The exercises included a writing task, finger tapping task, drawing a star contour next to a sample star viewed in a mirror, and drawing a line from the starting point of a maze to its end point without touching the outline. The protocol was approved by the Ethics Committee of Tel-Aviv University and the Helsinki committee at Loewenstein Hospital.

Training setup

The training setup designed for LA is based on our earlier research with healthy subjects in which we demonstrated enhanced performance gains following sensory manipulations, and in the absence of voluntary movement of the trained hand [23]. The patient trained while sitting on a chair with the two ULs in a forward position and the palms of the hands positioned in a specialized motion control apparatus (Rehabit-Tec System). The device consists of a forearm and wrist rest, and the fingers of each hand are individually strapped to the device with palms facing down (see Figure 1(a)). Each finger in the non-affected LH is connected to a piston that moves a plunger on a potentiometer in accord with the amplitude of finger flexion. A control module reads the location of every potentiometer on each finger of the LH and powers motors that push/pull the corresponding RH finger to equalize the potentiometer's position. Each finger channel is independent and acts as a stand-alone control circuit. The device restricts voluntary movement of the RH fingers and only LH finger movements activate the motors. Thus, when the hands are strapped to the device, voluntary LH (non-affected hand) finger movement results in passive yoking of the corresponding RH (affected hand) fingers. In addition, the patient wore a VR headset (Oculus VR 1 used for 3D gaming) that prevented visual input of his real hands and the device and provided visual feedback of virtual hands instead. The patient also wore motion-sensing MR-compatible gloves (5DT Data Glove Ultra) that allow online monitoring of individual finger flexion in each hand. The training setup contained a head-mounted specialized 3D camera (PLAYSTATION Eye digital camera device) to provide online visual feedback of the real environment. Together, these devices allowed detection of the patient's real hand movements and translating them by customized software to virtual hand movements presented on the headset screen. The virtual hands were embedded in a specific location in

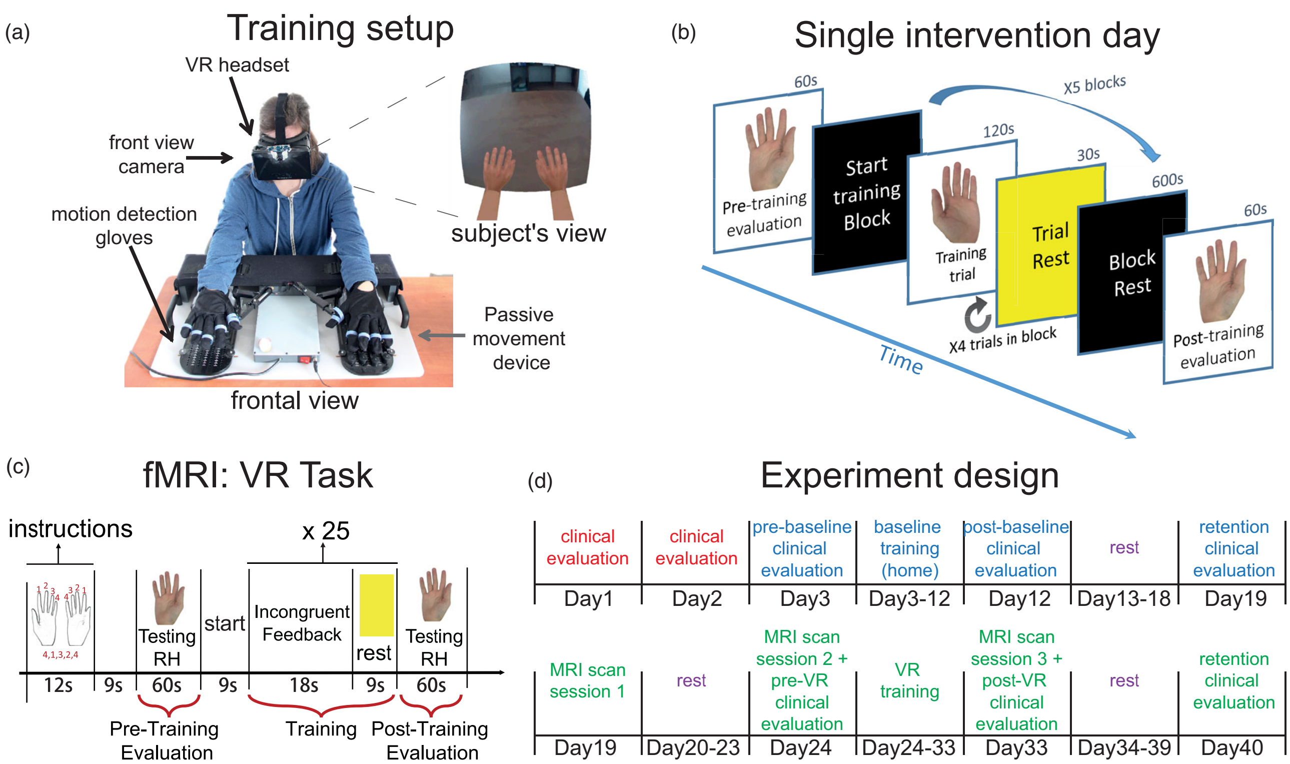

Figure 1. Experiment design. (a) Experiment setup illustration. The patient wore motion sensitive gloves and a headset through which he received visual feedback of virtual hands. The VR devices allowed manipulation of online visual feedback. A camera mounted on the headset allowed embedding the virtual hands inside a natural environment viewed by the camera. The passive-movement device was used with the virtual reality setup to produce yoked movement of the affected hand. (b) Schematic illustration of a single training day during the intervention period. (c) Schematic illustration of the VR task inside the MRI scanner. LA practiced with his left hand while receiving visual feedback of right virtual hand movement. (d) Schematic illustration of the experiment's design. The experiment had two main parts – baseline (first two weeks) and intervention (last two weeks). During the intervention, the patient was trained in our special setup.

space (captured by the camera) and were presented only when the patient looked down towards the natural position of his hands.

Main study: experimental design

Our main study started with two consecutive days in which the patient's manual function was evaluated using a battery of clinical tests. This was followed by two parts – a *baseline* part (10 days in which he continued doing his daily exercises), and an *intervention* part (nine days of training with the experimental setup), with an intervening period of six days in which he did not practice. During the baseline period, the patient conducted his regular daily exercises (see section "Materials and methods"/patient above) at 8 AM, five days per week, during two consecutive weeks. In the first and last day of the baseline period, the patient underwent clinical performance evaluation (see section "Behaviour: standardized clinical tests"). A week after the baseline period ended, the patient underwent another clinical evaluation to examine retention levels.

During the intervention period, the patient trained to execute rapid sequences of finger movements using our novel setup on a daily basis. Figure 1(b) demonstrates the timeline of a single intervention day. In an initial pre-training evaluation stage, the patient was instructed to perform a unimanual five-digit finger sequence movement: 3-1-4-2-3, repeatedly as accurately and rapidly as possible with the affected hand while wearing the motion sensitive gloves and receiving congruent visual feedback of hand movement. Sequence numbers correspond to fingers with 1 representing index and 4 representing the little finger. Performance level was measured as the number of correct sequences performed in 60 s. Following the pre-training evaluation stage, the patient's hands were strapped to a passive-movement device. A "Start" sound was played for 2 s cueing the patient to the upcoming training stage in which he performed the sequence of finger movements with his non-affected hand in the special training setup in a self-paced manner (see training setup). Importantly, during the training stage, patient's left hand finger movements were translated to right virtual hand finger movements on the screen (i.e. incongruent visual feedback). Training blocks lasted 10 min and were followed by 10 min of rest. Each block consisted of four trials and each trial consisted of 2-min training, followed by 30 s of a yellow blank screen to serve as a cue for resting period. The training stage consisted of five such training blocks (with overall training duration = 90 min). After the training stage, LA's hands were removed from the hand device and his performance level in the affected hand was re-evaluated as previously for 60 s. During both pre- and post-training evaluation stages, the patient was instructed to repeatedly execute the sequence as fast and as accurately as possible. An identical battery of clinical tests was performed in the first and last day of the intervention. During the 9th day of the intervention, we encountered technical problems (computer motherboard failure) that precluded training during that day. The problem was resolved for the 10th day of training. Similar to the baseline period, the patient underwent another set of clinical tests a week after the last day of the intervention to evaluate retention level. In addition, the patient completed three sessions of fMRI scans (see design of single fMRI session in Figure 1(c)) in three different days: four days before the intervention period, the first day of intervention and the last day of intervention (see Figure 1(d)).

Feasibility study

Three months before the main study, we conducted a feasibility study to verify LA's capability to perform the experiment's tasks on a daily basis. The feasibility tests lasted one month and comprised of two parts – a baseline part (two weeks) and an intervention part (two weeks). During the baseline period, the patient conducted daily exercises adjusted for his needs, which included a motion imagery exercise of the paretic hand, a star-drawing exercise using a mirror, copying a paragraph, trying to click as many times as possible on a specific key during 1 min and trying to draw a straight line between two horizontal or vertical lines. The patient performed these actions each day at 8 AM. In the first and last day of each week during the baseline period, the patient went through 90-s performance evaluation on the finger sequence task in a similar manner as described in the experimental design of the main study. Additionally, a battery of unimanual clinical tests was performed in the first and the last day of each week (see section "Main study: experimental design"). During the intervention period (the last two weeks), the patient conducted the aforementioned activities, and also performed our novel training regime on a daily basis.

Behaviour: motor sequence learning

We evaluated changes in task performance of the affected hand following training. Evaluation of performance (*p*) was based on the number of correctly performed complete five-digit sequence within 60 s in the evaluation stages. The same sequence (3-1-4-2-3) was used throughout the entire study (see Figure 1(c) for the mapping between digits and fingers). Performance gains were evaluated using Equation (1):

$$G = \frac{p_{\mathrm{post_{training}}} - p_{\mathrm{pre_{training}}}}{p_{\mathrm{post_{training}}} + p_{\mathrm{pre_{training}}}} \tag{1}$$

where $p_{\mathrm{post\_training}}/p_{\mathrm{pre\_training}}$ corresponds to the subject's performance (*p*) in the post/pre training evaluation stages. Therefore, a positive G index reflects improvement in performance. These gains were evaluated for each training day throughout the intervention period.

Behaviour: standardized clinical tests

Since our strategy is to train the non-affected hand as a proxy to improve performance of the affected hand, the clinical outcome measurements included a battery of commonly used standardized tests that focus on the speed and functional quality of unimanual movement. Performance of both left and RHs was measured using the Fugl-Meyer test [3], the Jebsen–Taylor test [39] and the Box and Blocks test [40].

Neuroimaging: VR task and stimuli

To explore putative brain regions underlying behavioural effects following intervention, the patient completed three sessions of fMRI scans (two before and one after the intervention period; see experiment design and Figure 1(d)). All three sessions were identical and consisted of six functional runs: performing the sequence task with the LH while receiving incongruent (right virtual hand) feedback, RH fist clenching with glove, RH fist clenching without glove, LH fist clenching with glove, LH fist clenching without glove, and resting-state.

During the incongruent-feedback training, the patient lied supine with his arms to the side of his body and palms facing up. He could not see his hands during the scans. We recorded the finger movements using the same MR compatible gloves used during the intervention period that allowed yoking the movements of virtual hands presented on a screen to real hand movements. Two virtual hands were presented on a screen with black background. In the scanner, the patient viewed the screen through a tilted mirror mounted in front of his eyes. In the beginning of the fMRI session (see design of single session in Figure 1(c)), the patient was presented with a similar instructions-slide as during the intervention period. Following the instructions, the patient performed an evaluation test – that is, performing the sequence as accurately and rapidly as possible using his affected RH. Next, he physically performed the sequence using his non-affected LH while receiving real-time corresponding visual feedback of right ("affected") virtual hand movement (as in the training part in the intervention period). Finally, he performed another evaluation test with his RH. This functional run lasted 825 s.

During the fist-clenching runs, the patient was asked to perform fist clenching following a simple auditory cue (once every 12 s). The patient performed four 4-min runs. In each run, the patient performed the clenches in the following conditions: (1) right hand fists with glove – the patient clenched his RH to a fist while wearing the MR compatible glove; (2) right hand fists without wearing the glove; (3) left hand fists with glove; (4) left hand fists without glove. Finally, during the resting-state run, the patient was instructed to relax with his eyes closed for 387 s while whole-brain functional data were collected.

Neuroimaging: fMRI data acquisition and processing

Blood oxygenation level dependent (BOLD) contrast was obtained on a 3 T Siemens Prisma scanner with an eight channel head coil located at the Strauss Computational Neuroimaging Center at Tel-Aviv University, Tel-Aviv, Israel. An echo-planar imaging sequence was used to obtain the functional data (39 ascending interleaved axial slices, 4 mm thickness, slice gaps = 0; TR = 3000 ms; flip angle = 90°; TE = 30 ms; in-plane resolution = 1.72×1.72 mm; matrix size = 128×128). In addition, anatomical reference was obtained by T1-weighted scan (voxel size = $1 \times 1 \times 1$ mm).

All fMRI data were processed using the BrainVoyager QX software (version 2.6, Brain Innovation, Maastricht, Netherlands; http://www.brainvoyager.com). Prior to statistical analysis, a preprocessing procedure was performed on all functional images that included cubic spline slice-time correction, trilinear 3D motion correction and high-pass filtering (above 0.006 Hz). In addition, we assessed head movements and verified no scans contained head movement exceeding 2 mm in either direction. The 2D functional images were co-registered to the anatomical images. Functional data were spatially smoothed (Gaussian filter, FWHM 6 mm) prior to statistical analysis.

Neuroimaging: resting-state analysis

To examine differences in functional connectivity between the pre- and post-intervention scans, we carried out whole-brain functional connectivity analysis during rest. For each scan, we parcelled the brain to 111 cortical and sub-cortical regions according to the Oxford-Harvard atlas [41]. The functional time courses (129 volumes) were averaged across all voxels within each region. Pearson's correlation was used to determine the connectivity strength between each pair of regions, yielding two 111×111 symmetrical connectivity matrices (one for each pre/post fMRI session). The significance of the correlations between pairs of regions

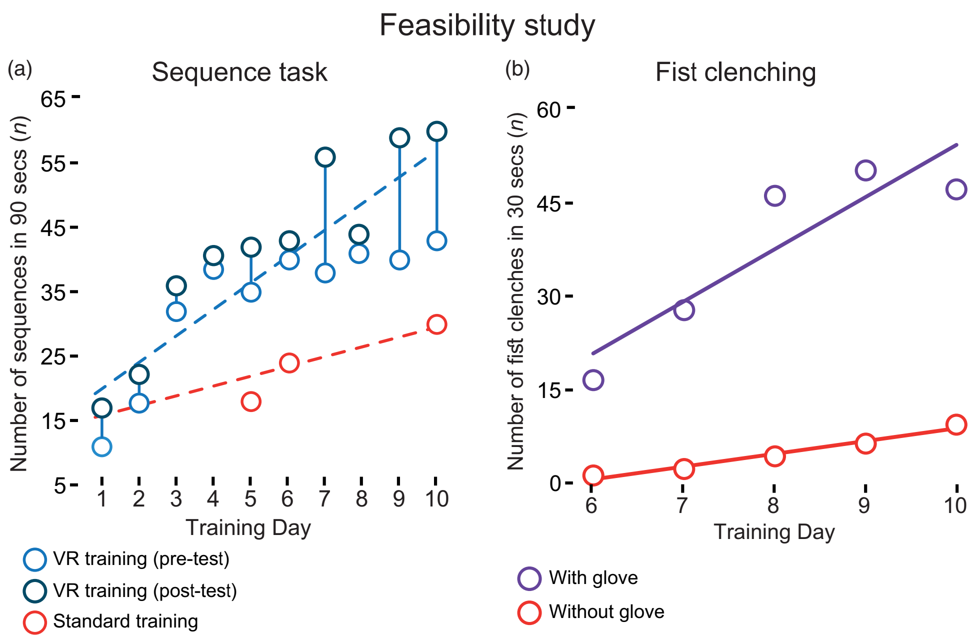

Figure 2. Feasibility study results. (a) training with the experiment setup during the intervention in the feasibility study (blue markers; both pre and post evaluations are included from day 1 to day 10) yielded significant increase in the number of accurate sequences performed with the affected hand during the evaluation stages (90 s; see *Materials and methods*) compared to standard training (red markers; 4 evaluations are presented – days 1, 5, 6 and 10; see *Materials and methods*). (b) Repeated testing of LA's fist clenching during the 2nd week of the feasibility study (see *Materials and methods*) shows a significantly higher number of right hand fist clenches during 30 s and a steeper increment in performance over time with glove (red) compared to without glove (purple).

was Bonferroni's corrected for multiple comparisons using a threshold of $p<(0.05/111)$.

Neuroimaging: VR task analysis

To detect regions exhibiting functional changes following training on the VR task, we performed a general linear model (GLM) analysis on the fMRI data obtained during the VR task stage by contrasting: $\text{training}_{\text{session3}} > \text{training}_{\text{session1}}$ and $\text{training}_{\text{session3}} > \text{training}_{\text{session2}}$. $\text{Training}_{\text{session\_x}}$ is the contrast activity during the task blocks in session x vs. rest. The resulting maps were corrected by controlling the false discovery rate [42] and thresholded at $q(\text{FDR})<0.05$, with a minimum cluster size of 50 voxels.

Results

Behaviour: feasibility study

In the early feasibility study (see section "Materials and methods"), LA improved from performing 17 accurate sequences during 90 s in the first day to 63 accurate sequences in the last day (Figure 2(a); slope of linear regression $=2.24$; $p<10^{-6}$; Pearson's correlation). The improvement observed during the baseline part of the feasibility study was smaller (from 16 accurate sequences in the first day of baseline to 27 in the last day), yielding an insignificant positive slope across training days (slope $=0.71$; $p=.08$; Pearson's correlation).

After five days of training in the feasibility study, LA noticed that he can move his affected RH more freely and quickly (e.g., during repetitive fist-clenching) when wearing the glove used for the training. He demonstrated the improvement by performing fast fist clenching while wearing the gloves. Intriguingly, when the patient took off the glove, the fist clenching was much slower (see supplementary movie 1). We assumed that this could reflect a case of context sensitivity acquired through the use of the VR motion-sensitive gloves in the training sessions (similar to other forms of context sensitivity known to affect motor performance in Parkinson's disease). Therefore, we added measurements of fist-clenching capabilities to the last week of the feasibility study and to the entire main study. We quantified the effect by comparing the number of fist clenching movements performed during 30 s without and afterward with the glove. Figure 2(b) demonstrates the changes in the number of fist clenches performed during the last week of the feasibility study. We found a highly significant improvement in the number of fist clenches when the patient wore the glove (mean ± SD number of movements in 30 s with glove across days $=39\pm12.48$, without the glove $=5.77\pm2.19$; $p=2.5\times10^{-5}$). Moreover, he showed a consistent improvement across time (slope of the linear regression $=4.1$) which was not observed without the glove (slope $=0.66$). The effect was not specific to the motion-detection gloves used during training and was observed also using regular cloth gloves.

Behaviour: main study

In the main study, the affected RH revealed a steady improvement in performance of the motor sequence task during the intervention period in which the patient practiced using the non-affected hand (see Figure 1(a) and section "Materials and methods"). A constant improvement is seen across the different days of intervention (Figure 3(a); slope of the linear regression$=2.17$; $p=10^{-5}$ Pearson's correlation $r=0.93$). The patient exhibited also a significant increase in the number of accurate sequences performed within training days (before/after training; average *G* index across days $=0.09$; $p=6.6\times10^{-5}$ two-tailed unequal variance *t*-test compare to zero). These results corroborate the findings obtained during the feasibility study (note that the evaluation stage in the main study lasted 60 s and not 90 s as in the feasibility study).

We re-examined the fist-clenching effect that appeared in the feasibility study at five time points during the intervention period of the main study. This re-examination yielded similar results (Figure 3(b)). The number of fist clenching during 60 s while wearing the

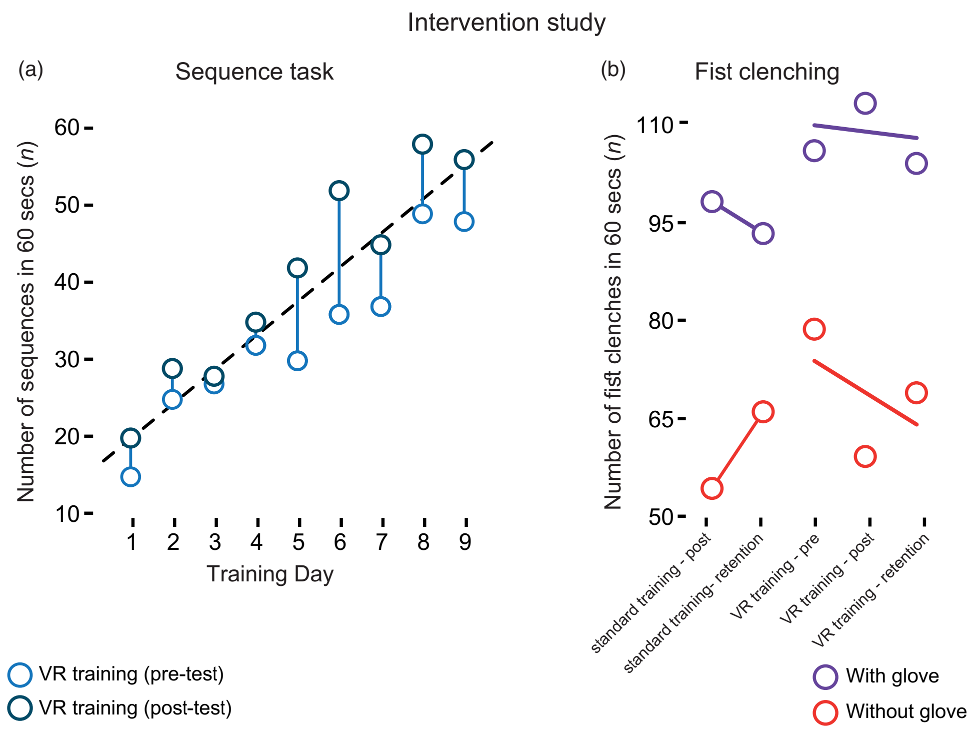

Figure 3. Main study results. (a) Training with the experimental setup during the intervention period yielded significant increase in the number of correct sequences performed with the affected hand during the evaluation stages. The light blue marker in each day represents the performance in the pre-training evaluation stage and the dark blue marker represents the performance in the post-training evaluation (each evaluation stage lasted 60 s; see Figure 1(b)). (b) The effect of wearing the glove re-examined during the main study showing an advantage for fist clenching with the glove (here during 60 s).

glove was significantly higher than without it (105.6 and 66.4, respectively, $p=.002$; two-tailed paired t-test).

Behaviour: standardized clinical tests in main study

The Fugl-Meyer test score for the right UL did not change following training and the score remained 53 out of 66. In the Jebsen–Taylor test, the patient exhibited differences in RH functioning (measured as time to complete the task) between the three evaluation time-points (pre-training, post-training and retention tests) both in the baseline and the intervention periods (see Figure 4 and section "Materials and methods"). However, these differences were not consistent across tests. LA had high performance gains in four tests, with higher gains during the intervention period compared to the standard training (where the patient just continued with his daily exercises) – stacking chekers (regression slope$=-0.42$ vs. -0.08; Figure 4(a)), moving full cans (–0.04 vs. 0.01; see Figure 4(b)), writing (–1.45 vs. -0.58; Figure 4(c)) and picking up beans with spoon (–0.88 vs. -0.55 respectively; see Figure 4(d)). Moreover, LA significantly improved in the Box and Blocks test where he exhibited high and consistent improvement during both the intervention and the baseline periods (regression slope $= 2.5$ vs. 4 for intervention and baseline respectively; Figure 4(e)). Nonetheless, on the flipping cards (–0.5 vs. 0.04 respectively; Figure 4(f)) and flipping coins (–0.25 vs. 0.01; Figure 4(h)) tasks, performance gains were higher following standard training vs. intervention. The patient's progress in the "moving empty cans" task was poor during both baseline and intervention (0.35 and 0.31; Figure 4(g)).

In a previous study with healthy subjects, we showed that training with incongruent visual feedback can impede improvement in the physically trained hand. Therefore, we examined LA's performance also with the trained, non-affected (left) hand. We did not find a significant change in the performance of the non-affected hand during intervention period (see Figure 5(a–g); $ps>.1$). In one clinical test – flipping coins – the patient was significantly worse following intervention ($p<.05$)

Neuroimaging: resting state

The brain was parcelled to 111 regions based on the Oxford-Harvard atlas and functional connectivity between all pairs of regions was assessed (see section "Materials and methods"). Resting-state functional connectivity reveals a global increase in the number of significantly connected regions in the post-intervention scan compared with the pre-intervention scans (560 and 239 pairs, respectively; see Figure 6(a)). We also specifically examined connections in a network that corresponds to the control of RH movements [23,43,44]. This network includes left and right SPL, left supplementary motor area, left precentral gyrus, left pallidum and motor-related areas in the left frontal lobe (e.g., premotor region). Similar to the whole-brain analysis, the number of significant connections within this network increased following training (from 16 to 38; see Figure 6(b)). These results suggest that 10-days of intervention in which learning by observation, CE and passive movement are combined, are sufficient to significantly strengthen the functional connectivity within the network of regions controlling movement of the affected limb.

Neuroimaging: VR task

During the fMRI scans, LA performed the VR task – finger sequence task with his non-affected LH while receiving incongruent visual feedback of corresponding right virtual hand movement. Figure 7(a) depicts the activation contrast map of post-intervention scan (session 3) vs. pre-intervention scans (sessions 1 and 2) during training blocks (see "Materials and methods"). GLM analysis of the data reveals several clusters in the pre-frontal

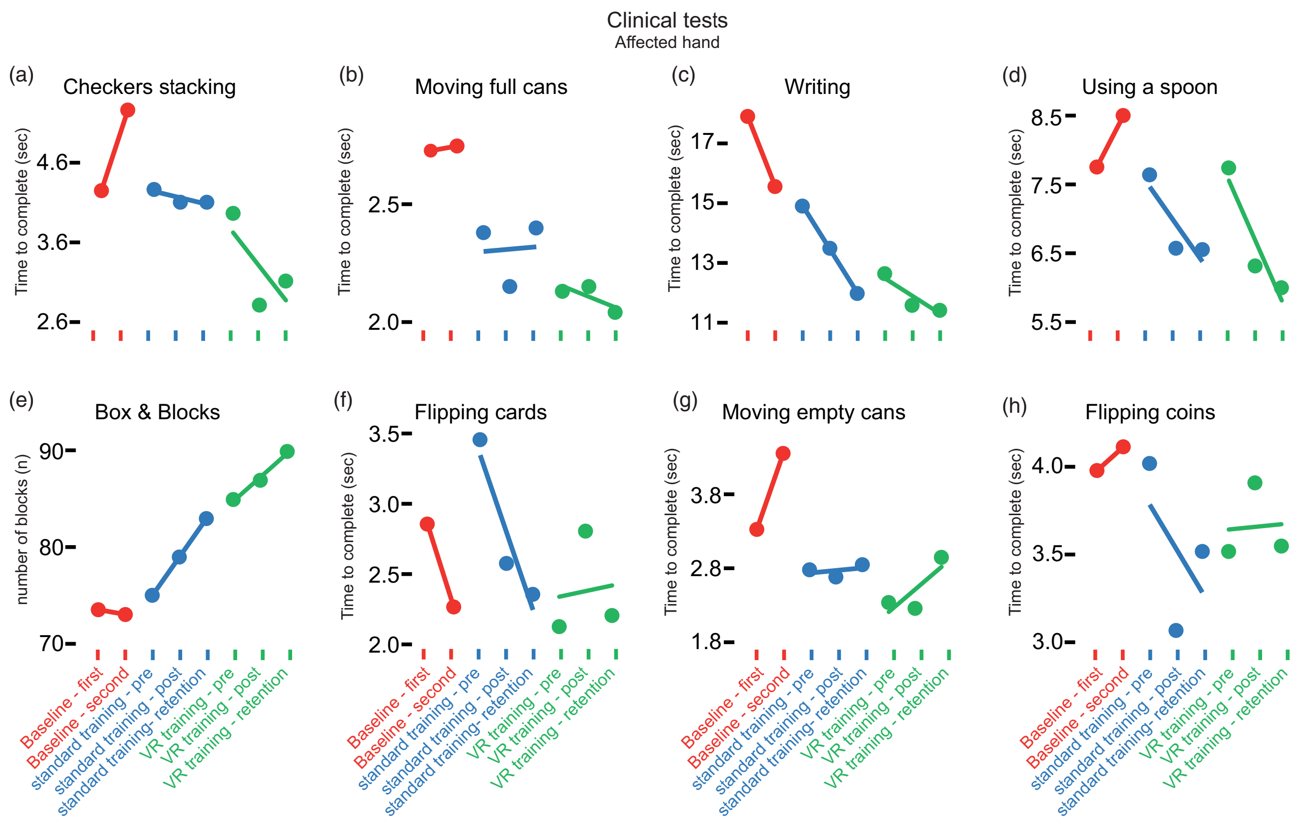

Figure 4. Main study – clinical tests with affected hand. (a–d) Jebsen and Taylor functional test results with a clear trend of improvement throughout the experiment. Patient exhibits clear improvement both in the standard training (blue) and Intervention (green) periods. (e) Box and Blocks test results. The patient consistently improved during the experiment in both the standard training and the VR training. (f–h) Jebsen and Taylor functional tests with inconclusive improvement after intervention.

cortex that are more active after the intervention compared to before. These clusters are located mainly in the superior and medial frontal gyri. A cluster in the medial occipital cortex, near the calcarine sulcus, was also obtained in this contrast. Additionally, a small cluster located in the right primary motor and primary somato-sensory cortices (contra-lateral to the moving hand, and ipsilateral to the affected hand) was more activated during the post-intervention session. In contrast, activation was higher during the pre-intervention scan in several regions that are key parts of the visual dorsal stream including SPLs, inferior parietal lobules (IPLs) and the lateral occipital gyri in both right and left hemispheres. These results imply that after a two-week training intervention with our novel setup, the frontal cortex is more engaged during performance of the VR task (incongruent visual feedback), at the expense of the visual dorsal stream.

Neuroimaging: fist clenching

During the fMRI scans, we also examined the glove effect on fist clenching. GLM analysis during the 3rd fMRI session (after intervention), contrasting brain activations during fist clenching with the affected RH with and without the glove, showed pre-frontal clusters in the superior and medial frontal gyri (Figure 7(b)), overlapping the clusters obtained during the incongruent-feedback training (80% overlap). Identical contrast in the two pre-intervention fMRI sessions yielded empty maps. Similarly, GLM analysis contrasting LH fists (non-affected hand), with and without gloves, yielded empty maps in all three fMRI sessions. These neuroimaging results suggest that the functional differences in the affected hand with and without gloves following training are mediated through processing conveyed by the pre-frontal cortex.

Discussion

The aim of the current study was to assess the clinical applicability of a novel training setup combining two principles: (a) cross-education – obtaining performance gain in the affected UL indirectly, by intensive training of the non-affected UL; (b) perceptual mirroring in two sensory systems – visual and proprioceptive – creating a manipulated perception of voluntary control over movement in the neurologically affected UL. In a previous study, proof of concept was obtained when 18 healthy subjects trained with a similar setup showed high performance outcomes in the UL that was not physically trained [23]. Before embarking on a large-scale RCT type clinical study, we decided to perform a detailed examination of the behavioural and brain activation dynamics related to training with the setup in a single-case design. Patient LA was selected for that because his marked unilateral bradykinesia and rapid fatigue prevented intensive direct training of the affected UL. Given the likelihood of motor-learning dysfunction in his condition (having hemi Parkinson's disease with DaT Scan showing depletion of striatal dopaminergic neurons), the finger sequence learning task used in the setup could have an added value, beyond an expected benefit from simple repetitive activation of the fingers (i.e., without the motor learning component).

Patient LA revealed a clear learning curve in repeated performance of the motor sequence task by the affected right UL during the intervention period. Importantly, he practiced using the non-

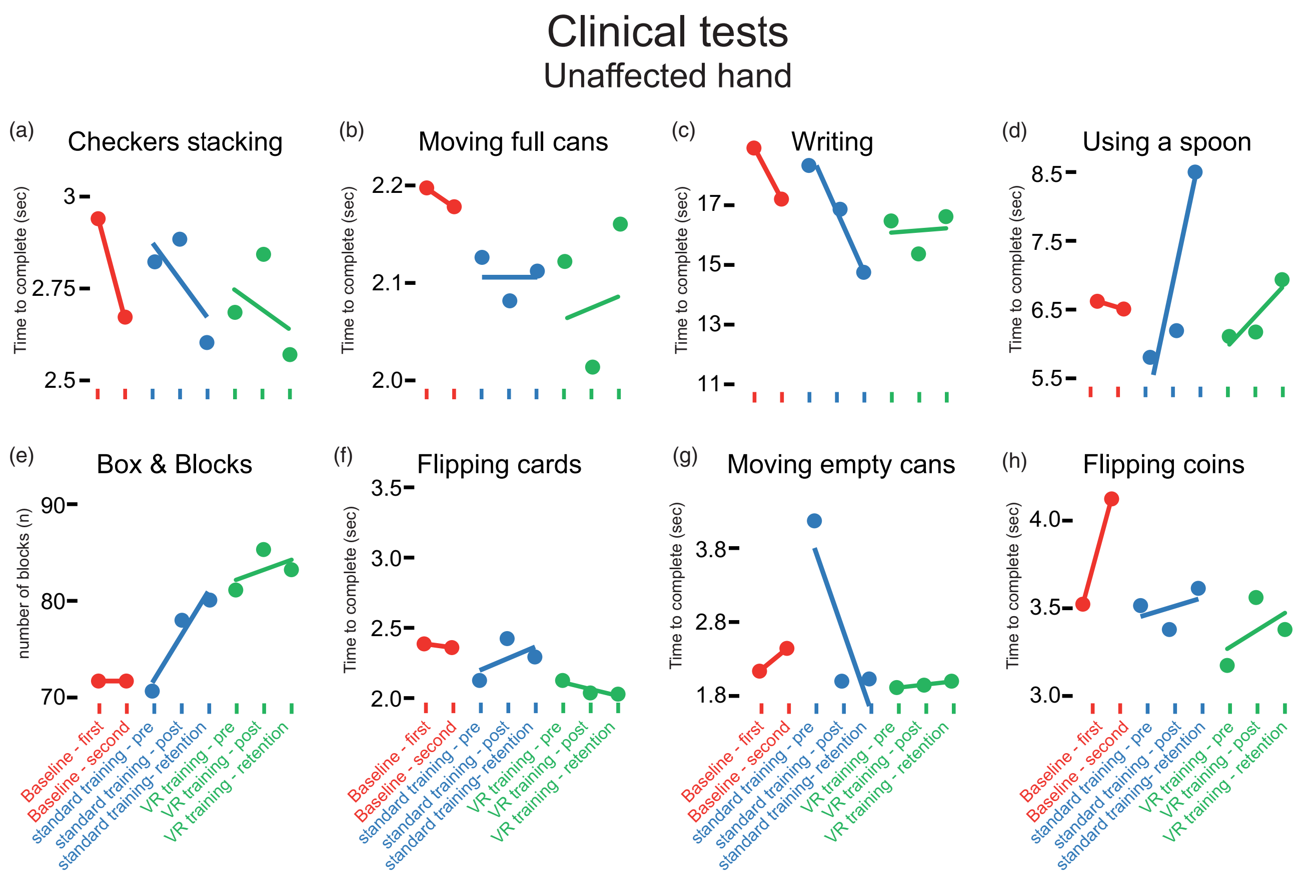

Figure 5. Main study – clinical tests with non-affected hand. (a–d) The Jebsen and Taylor functional tests that had clear trend of improvement in the affected hand, did not show a clear trend in the unaffected hand. Moreover, in some tasks (e.g., using a spoon), LA did worse with the non-affected hand after standard and VR training. (e) Box and Blocks test results. The patient consistently improved during the experiment even with the unaffected hand. (f–h) Jebsen and Taylor functional tests with inconclusive improvement in the affected hand had almost no effect on the unaffected hand.

affected left UL, thus showing clearly the possibility of inter-manual CE using the experimental setup. These results point to stable and significant performance gains with the affected UL in the absence of its voluntary physical training.

The improvement shown in sequence learning did not have a clear correlate in the clinical tests. In the Fugl-Meyer test, the total score before and after the intervention period remained the same (53/66). In the Jebsen–Taylor battery, three of the seven functional subtests (*picking beans with spoon*, *stacking checkers*, *moving full cans*) showed bigger performance gains during the intervention period compared to the baseline period (where he continued with daily exercising of the affected right UL). Conversely, performance gains were higher following baseline training in the *flipping cards* and *flipping coins* tasks. No change was observed in the *moving empty cans* task during both baseline and intervention training. In the Box and Blocks test, the patient exhibited high and consistent improvement during both baseline and intervention periods.

Although much of the clinical research on rehabilitation of unilateral UL paresis focuses on voluntary physical practice with the affected UL [11–13], this kind of movement-based intervention is usually limited by the amount of volitional motion the patient can actually produce [14,45,46]. Therefore, it is particularly important to examine alternative approaches, especially for the more severe cases in which direct training of the affected UL is not suitable. The experimental intervention employed in the current study is such an alternative approach, motivated by knowledge gained from recent motor learning research in healthy subjects [16,23]. The behavioural part of the study shows that this approach can have a useful clinical application in neuro-rehabilitation. It incorporates principles derived from MVF research showing the benefits of mirror therapy in a variety of clinical conditions [20,47–50]. In mirror therapy, movement of the non-affected UL is the source of visual feedback which is simultaneous and incongruent. We have recently reported two distinct electrophysiological counterparts of MVF implying (a) recruitment of mirror neurons and (b) attenuation of hemispheric asymmetry when the mirror reflection of the moving hand creates an illusory perception of movement in the other hand [51]. Here, we extended the standard MVF approach by using visual feedback in a VR environment, which allows feedback to be controlled by software. Virtual reality allows introducing various perturbations (in time and space, e.g., temporal delays or size changes in virtual hands [52]) that can facilitate finding the optimal parameters for efficient training. Another advantage of our VR setup lies in the combined application of visual and proprioceptive mirroring, which we found in healthy subjects to yield bigger performance gains in the non-trained UL compared to MVF training alone [23].

VR training has been reported to support release from gait akinesia in Parkinsonian patients [53], facilitate rehabilitation of people with stroke-related UL motor dysfunction [54–57] and improve spatial awareness in children with cerebral palsy [58]. Holden et al. indicated that patients are able to transfer performance gains from VR training to real-world tasks [59]. Recent work on the effect of VR intervention in patients with Parkinson's

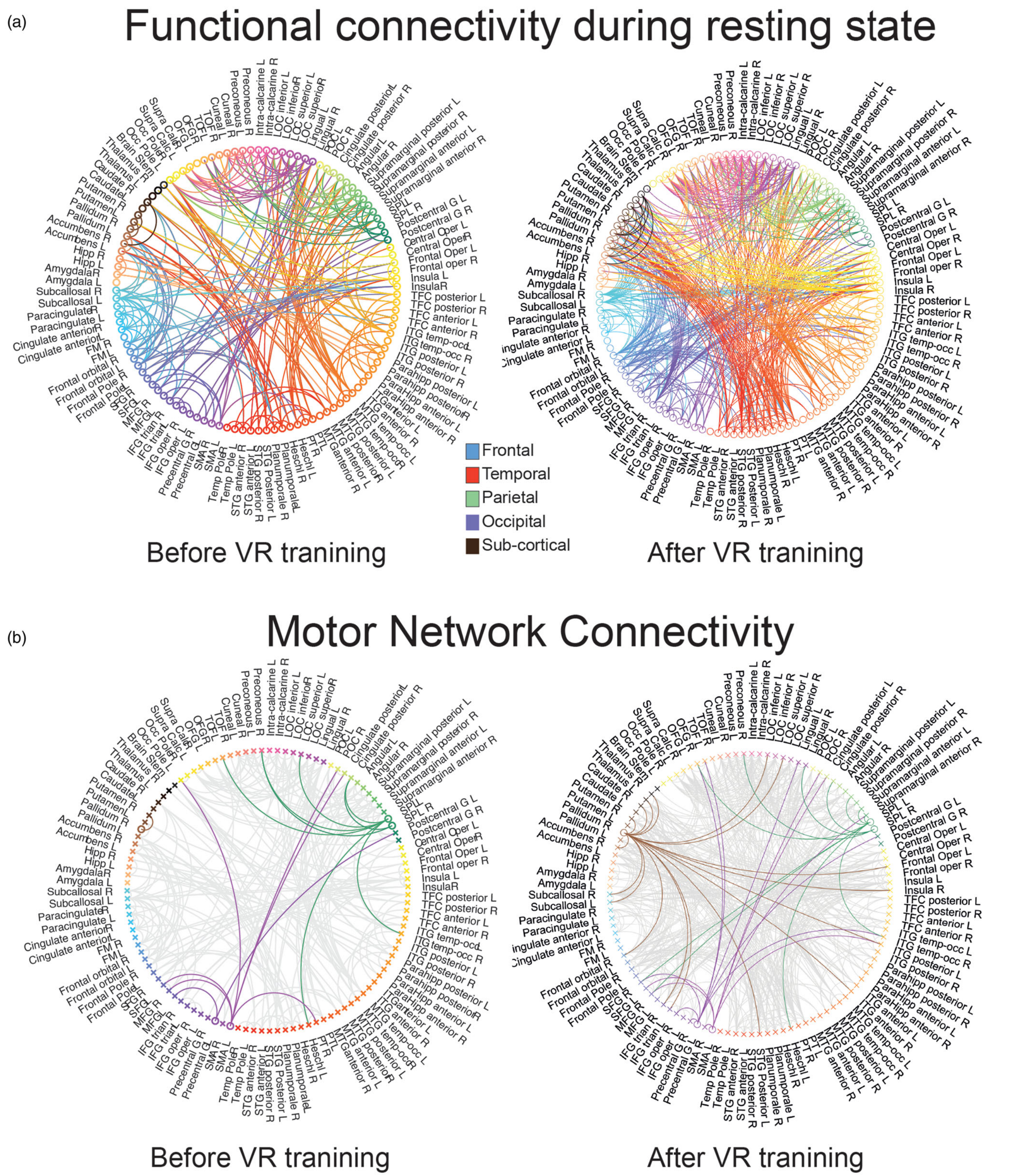

Figure 6. Functional connectivity during resting-state. (a) Network connections illustrated on a circular representation of cortical and sub-cortical regions – before and after the experimental training. Lines connecting the regions represent significant correlation between their averaged time-courses during resting-state scan (see *Materials and methods*). The regions (colour coded according to lobes) were defined by the Oxford-Harvard atlas. (b) Functional connectivity in regions that are associated with right hand movement – left SPL, right SPL, left SMA, left primary motor cortex and left pallidum (defined by the Harvard-Oxford atlas; see *Materials and methods*).

disease showed that using VR during training enhances motor imitation capacity which contributes to amelioration of movement deficits [60]. The current case-study is the first to demonstrate that combined use of manipulated visual and proprioceptive feedback in VR environment has the potential to boost motor rehabilitation in patients with UL dysfunction.

Assistive devices used in hospitals to support patients with hemiparesis (e.g., treadmills and robotic exoskeletons) require

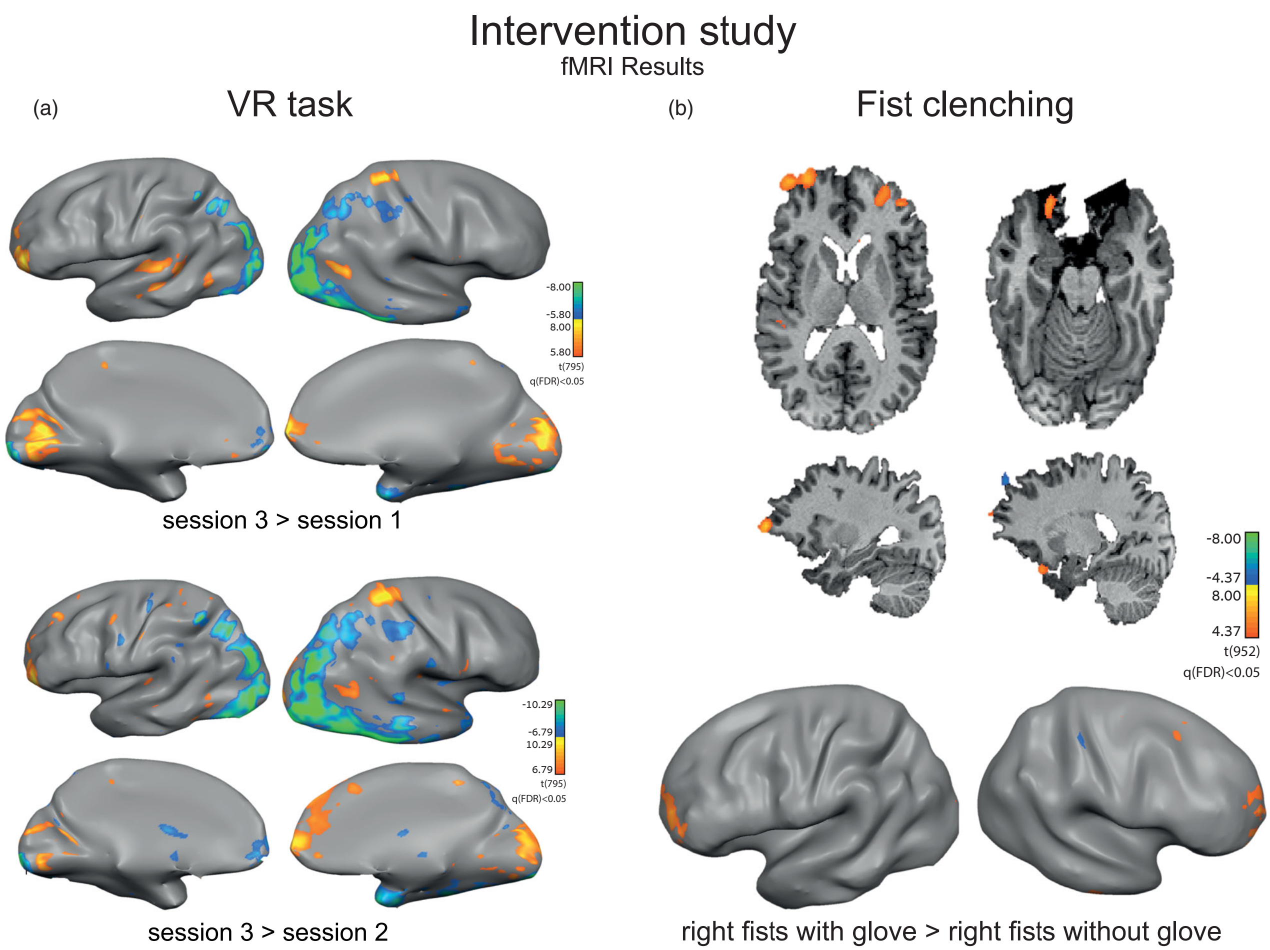

Figure 7. fMRI results. (a) GLM results in VR task. Activation maps displaying significant regions obtained from the GLM contrasts (q(FDR)$<$0.05) during the VR task. Bottom panel – session 3 (end of experimental intervention)$>$session 2 (beginning of experimental intervention); top panel – session 3 (end of experimental intervention)$>$session 1 (5 days before the starting day of the experimental intervention). (b) GLM results in fist-clenching task. The activation map displays significant regions obtained from the GLM contrast (q(FDR)$<$0.05): right hand fists with glove $>$ right hand fists without glove during the 3rd fMRI session (end of experimental intervention period).

expensive equipment and trained personnel – constraining the amount of training that a given patient can receive. The setup we describe is simple and can be easily used at home with the assistance of an untrained caregiver/family member [61]. Once installed at the patient's home, the setup can be used with minimal maintenance (the VR headset and motion sensitive gloves are commercially available at relatively low prices). Building on advances in machine learning [62], our software can be adapted to personal use at homes. The combination of VR headset and hand device is lightweight and mobile (does not require more than one person to move from one place to another). The procedure for strapping the patient's hands to the device at the beginning of training, requires the assistance of another person but this does not require special training. Taken together, we propose that our findings can be translated into practice with relatively few adjustments, and that our experimental design may be used as an important adjuvant to standard clinical care for UL hemiparesis.

Yet, because this is a single-case study, the implications of the current results should be treated with caution and further study is needed. Hemiparesis presents various symptoms in different stages of the hemi-Parkinson disease [1,2]. Therefore, the results obtained in a case of unilateral UL dysfunction secondary to hemi-Parkinson's disease might not replicate with types of unilateral UL dysfunction involving mainly the pyramidal system. Specifically, the remarkable impact of glove wearing on the fist-clenching ability of LA's affected RH. This phenomenon, shown after a short period of using the motion-sensitive gloves in the training sessions, is consistent with clinical observations suggesting that activation of a desired motor behaviour in Parkinsonian patients is sensitive to contextual cues such as a line on the floor, marching music or timing cues [63–66]. Moreover, external sensory cueing has been mentioned repeatedly as a good strategy to facilitate continuous motor performance in Parkinson's disease [67–69]. This kind of context sensitivity is seen much less often in patients with UL dysfunction secondary to stroke, except for cases where hemiparesis is accompanied by apraxia, in whom activation of a desired motor behaviour is facilitated by having it done in the natural context [70].

At the neural level, we found that after the intervention period, regions in the pre-frontal cortex are more engaged during training, while the visual dorsal stream is less engaged relative to the pre-intervention period. The dorsal stream processes visual information needed for directed actions in space [71], and plays a significant role in the action–observation interaction [72]. In contrast, pre-frontal regions are engaged in action selection and reinforcement learning [73,74]. Pre-frontal regions have been found crucial in linking memory representations to goal-directed motor behaviour and optimizing selection between competing responses [75]. Thus, our results suggest that the intervention induces a processing shift during mirror training from the parietal-occipital network engaged in spatial processing to more frontal cognitive circuits.

Over the past decade, several studies have applied fMRI resting-state analyses to investigate functional neural network characteristics of Parkinsonian patients [76–81]. A common finding of these studies is the reduced connectivity between motor-related areas in patients compared to connectivity patterns shown by healthy subjects. In the current study, we show that 10 days of intervention comprised of CE employing mirrored sensory feedback strengthens interconnections in the motor-related network. We did not find a similar difference in interconnections when we compared the functional connectivity in the first pre-intervention session to the second pre-intervention session. This finding suggests that the increase in strength between the regions was specific to the intervention. Yet, as the level of resting-state connectivity increased in a widespread manner after the intervention, further research with a higher number of patients and healthy controls is needed to clarify whether the intervention strengthens connections in the motor system in a specific manner.

In summary, in rehabilitation, there is a need for approaches that take into account developments in basic research in the field of motor neuroscience and transfer ideas and concepts to clinical practice. The strategy we adopted in the current study combines cutting edge technologies, insights gained from basic motor neuroscience in healthy subjects and well-known clinical treatments in the goal of developing a novel training regime for rehabilitation of patients with hemiplegia. Although our results constitute a single-case study, they hold promise for future studies examining the effectiveness of this line of research in more subjects and additional clinical populations in the pursuit of finding novel and more efficient rehabilitation schemes for patients suffering from hemiplegia.

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Disclosure statement

The authors declare that no competing interests exist.

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ORCID

Ori Ossmy http://orcid.org/0000-0002-7675-0890
Roy Mukamel http://orcid.org/0000-0001-9359-8950

References

[1] Buchman AS, Goetz CG, Klawans HL. Hemiparkinsonism with hemiatrophy. Neurology. 1988;38(4):527.

[2] Giladi N, Burke RE, Kostic V, et al. Hemiparkinsonism-hemiatrophy syndrome: clinical and neuroradiologic features. Neurology. 1990;40(11):1731.

[3] Fugl-Meyer AR, Jääskö L, Leyman I, et al. The post-stroke hemiplegic patient. 1. A method for evaluation of physical performance. Scand J Rehabil Med. 1974;7:13–31.

[4] Hsu A-L, Tang P-F, Jan M-H. Analysis of impairments influencing gait velocity and asymmetry of hemiplegic patients after mild to moderate stroke. Arch Phys Med Rehabil. 2003;84(8):1185–1193.

[5] Badke MB, Duncan PW. Patterns of rapid motor responses during postural adjustments when standing in healthy subjects and hemiplegic patients. Phys Ther. 1983;63(1):13–20.

[6] Sabari JS. Motor learning concepts applied to activity-based intervention with adults with hemiplegia. Am J Occup Ther. 1991;45(6):523–530.

[7] Bobath B. Adult hemiplegia: evaluation and treatment. 3rd ed. Oxford (England): Butterworth-Heinemann; 1990.

[8] Cifu DX, Stewart DG. Factors affecting functional outcome after stroke: a critical review of rehabilitation interventions. Arch Phys Med Rehabil. 1999;80(5 Suppl. 1):S35–S39.

[9] Ernst E. A review of stroke rehabilitation and physiotherapy. Stroke. 1990;21(7):1081–1085.

[10] Teasell RW, Foley NC, Bhogal SK, et al. An evidence-based review of stroke rehabilitation. Top Stroke Rehabil. 2003; 10(1):1–7.

[11] Grotta JC, Noser EA, Ro T, et al. Constraint-induced movement therapy. Stroke. 2004;35(11 Suppl. 1):2699–2701.

[12] Taub E, Uswatte G, Pidikiti R. Constraint-induced movement therapy: a new family of techniques with broad application to physical rehabilitation – a clinical review. J Rehabil Res Dev. 1999;36(3):237–251.

[13] Wolf SL, Winstein CJ, Miller JP, et al. Effect of constraint-induced movement therapy on upper extremity function 3 to 9 months after stroke: the EXCITE randomized clinical trial. JAMA. 2006;296(17):2095–2104.

[14] Hoare BJ, Wasiak J, Imms C, et al. Constraint-induced movement therapy in the treatment of the upper limb in children with hemiplegic cerebral palsy:a Cochrane systematic review. Clin Rehabil. 2007;21(8):675-685.

[15] Mattar AA, Gribble PL. Motor learning by observing. Neuron. 2005;46(1):153–160.

[16] Ossmy O, Mukamel R. Activity in superior parietal cortex during training by observation predicts asymmetric learning levels across hands. Sci Rep. 2016;6:32133.

[17] Rizzolatti G, Fogassi L, Gallese V. Neurophysiological mechanisms underlying the understanding and imitation of action. Nat Rev Neurosci. 2001;2(9):661–670.

[18] Mukamel R, Ekstrom AD, Kaplan J, et al. Single-neuron responses in humans during execution and observation of actions. Curr Biol. 2010;20(8):750–756.

[19] Rizzolatti G, Fabbri-Destro M, Cattaneo L. Mirror neurons and their clinical relevance. Nat Clin Pract Neurol. 2009; 5(1):24–34.

[20] Ramachandran VS, Altschuler EL. The use of visual feedback, in particular mirror visual feedback, in restoring brain function. Brain. 2009;132(Pt 7):1693–1710.

[21] Wong JD, Kistemaker DA, Chin A, et al. Can proprioceptive training improve motor learning? J Neurophysiol. 2012; 108(12):3313–3321.

[22] Lotze M, Braun C, Birbaumer N, et al. Motor learning elicited by voluntary drive. Brain. 2003;126(Pt 4):866–872.
[23] Ossmy O, Mukamel R. Neural network underlying intermanual skill transfer in humans. Cell Rep. 2016;17(11): 2891–2900.
[24] Darainy M, Vahdat S, Ostry DJ. Perceptual learning in sensorimotor adaptation. J Neurophysiol. 2013;110(9): 2152–2162.
[25] Vahdat S, Darainy M, Ostry DJ. Structure of plasticity in human sensory and motor networks due to perceptual learning. J Neurosci. 2014;34(7):2451–2463.
[26] Hesse S, Schulte-Tigges G, Konrad M, et al. Robot-assisted arm trainer for the passive and active practice of bilateral forearm and wrist movements in hemiparetic subjects. Arch Phys Med Rehabil. 2003;84(6):915–920.
[27] Lindberg P, Schmitz C, Forssberg H, et al. Effects of passive-active movement training on upper limb motor function and cortical activation in chronic patients with stroke: a pilot study. J Rehabil Med. 2004;36(3):117–123.
[28] Volpe BT, Krebs HI, Hogan N. Is robot-aided sensorimotor training in stroke rehabilitation a realistic option? Curr Opin Neurol. 2001;14(6):745–752.
[29] Picelli A, Tamburin S, Passuello M, et al. Robot-assisted arm training in patients with Parkinson's disease: a pilot study. J Neuroeng Rehabil. 2014;11(1):28.
[30] Scripture E, Smith TL, Brown EM. On the education of muscular control and power. Stud Yale Psychol Lab. 1894;2: 114–119.
[31] Sainburg RL, Wang J. Interlimb transfer of visuomotor rotations: independence of direction and final position information. Exp Brain Res. 2002;145(4):437–447.
[32] Anguera JA, Russell CA, Noll DC, et al. Neural correlates associated with intermanual transfer of sensorimotor adaptation. Brain Res. 2007;1185:136–151.
[33] Hendy AM, Spittle M, Kidgell DJ. Cross education and immobilisation: mechanisms and implications for injury rehabilitation. J Sci Med Sport. 2012;15(2):94–101.
[34] Farthing JP. Cross-education of strength depends on limb dominance: implications for theory and application. Exerc Sport Sci Rev. 2009;37(4):179–187.
[35] Raghavan P, Krakauer JW, Gordon AM. Impaired anticipatory control of fingertip forces in patients with a pure motor or sensorimotor lacunar syndrome. Brain. 2006; 129(Pt 6):1415–1425.
[36] Urbin M, Harris-Love ML, Carter AR, et al. High-intensity, unilateral resistance training of a non-paretic muscle group increases active range of motion in a severely paretic upper extremity muscle group after stroke. Front Neurol. 2015;6:119.
[37] Ruddy KL, Carson RG. Neural pathways mediating cross education of motor function. Front Hum Neurosci. 2013;7: 397.
[38] Howatson G, Zult T, Farthing JP, et al. Mirror training to augment cross-education during resistance training: a hypothesis. Front Hum Neurosci. 2013;7:396.
[39] Jebsen RH, Taylor N, Trieschmann R, et al. An objective and standardized test of hand function. Arch Phys Med Rehabil. 1969;50(6):311–319.
[40] Mathiowetz V, Volland G, Kashman N, et al. Adult norms for the Box and Block Test of manual dexterity. Am J Occup Ther. 1985;39(6):386–391.
[41] Smith SM, Jenkinson M, Woolrich MW, et al. Advances in functional and structural MR image analysis and implementation as FSL. NeuroImage. 2004;23:S208–S219.
[42] Benjamini Y, Hochberg Y. Controlling the false discovery rate – a practical and powerful approach to multiple testing. J R Stat Soc B Met. 1995;57(1):289–300.
[43] Grillner S, Hellgren J, Menard A, et al. Mechanisms for selection of basic motor programs—roles for the striatum and pallidum. Trends Neurosci. 2005;28(7):364–370.
[44] Wing AM, Haggard P, Flanagan JR. Hand and brain: the neurophysiology and psychology of hand movements. San Diego: Academic Press; 1996.
[45] Bard G, Hirschberg G. Recovery of voluntary motion in upper extremity following hemiplegia. Arch Phys Med Rehabil. 1965;46:567–572.
[46] Skilbeck CE, Wade DT, Hewer RL, et al. Recovery after stroke. J Neurol Neurosurg Psychiatry. 1983;46(1):5–8.
[47] Rosén B, Lundborg G. Training with a mirror in rehabilitation of the hand. Scand J Plast Reconstr Surg Hand Surg. 2005;39(2):104–108.
[48] Bagce HF, Saleh S, Adamovich SV, et al. Visuomotor discordance in virtual reality: effects on online motor control. 2011 Annual International Conference of the IEEE Engineering in Medicine and Biology Society; 2011; Boston, MA. p. 7262–7265.
[49] Sathian K, Greenspan AI, Wolf SL. Doing it with mirrors: a case study of a novel approach to neurorehabilitation. Neurorehabil Neural Repair. 2000;14(1):73–76.
[50] Selles RW, Schreuders TA, Stam HJ. Mirror therapy in patients with causalgia (complex regional pain syndrome type II) following peripheral nerve injury: two cases. J Rehabil Med. 2008;40(4):312–314.
[51] Bartur G, Pratt H, Dickstein R, et al. Electrophysiological manifestations of mirror visual feedback during manual movement. Brain Res. 2015;1606:113–124.
[52] Ossmy O, Mukamel R. Short term motor-skill acquisition improves with size of self-controlled virtual hands. PLoS One. 2017;12(1):e0168520.
[53] Weghorst S. Augmented reality and Parkinson's disease. Commun ACM. 1997;40(8):47–48.
[54] Broeren J, Rydmark M, Sunnerhagen KS. Virtual reality and haptics as a training device for movement rehabilitation after stroke: a single-case study. Arch Phys Med Rehabil. 2004;85(8):1247–1250.
[55] Merians AS, Jack D, Boian R, et al. Virtual reality-augmented rehabilitation for patients following stroke. Phys Ther. 2002; 82(9):898–915.
[56] Viau A, Feldman AG, McFadyen BJ, et al. Reaching in reality and virtual reality: a comparison of movement kinematics in healthy subjects and in adults with hemiparesis. J NeuroEng Rehabil. 2004;1(1):11.
[57] You SH, Jang SH, Kim Y-H, et al. Virtual reality-induced cortical reorganization and associated locomotor recovery in chronic stroke: an experimenter-blind randomized study. Stroke. 2005;36(6):1166–1171.
[58] Foreman N, Wilson P, Stanton D. VR and spatial awareness in disabled children. Commun ACM. 1997;40(8):76–77.
[59] Holden M, Todorov E, Callahan J, et al. Virtual environment training improves motor performance in two patients with stroke: case report. J Neurol Phys Ther. 1999;23(2):57–67.
[60] Robles-García V, Corral-Bergantiños Y, Espinosa N, et al. Effects of movement imitation training in Parkinson's

disease: a virtual reality pilot study. Parkinsonism Relat Disord. 2016;26:17–23.
[61] Ossmy O, Mukamel R. Using virtual reality to transfer motor skill knowledge from one hand to another. JoVE. 2017; 127(127):e55965.
[62] Yang Q, Banovic N, Zimmerman J. Mapping machine learning advances from HCI research to reveal starting places for design innovation. Proceedings of the 2018 CHI Conference on Human Factors in Computing Systems. New York (NY): ACM; 2018. p. 1–11.
[63] Freeman J, Cody F, Schady W. The influence of external timing cues upon the rhythm of voluntary movements in Parkinson's disease. J Neurol Neurosurg Psychiatry. 1993; 56(10):1078–1084.
[64] Howe TE, Lövgreen B, Cody F, et al. Auditory cues can modify the gait of persons with early-stage Parkinson's disease: a method for enhancing Parkinsonian walking performance. Clin Rehabil. 2003;17(4):363–367.
[65] Jiang Y, Norman KE. Effects of visual and auditory cues on gait initiation in people with Parkinson's disease. Clin Rehabil. 2006;20(1):36–45.
[66] Martin JP. The basal ganglia and posture. London: Pitman Medical; 1967.
[67] McIntosh GC, Brown SH, Rice RR, et al. Rhythmic auditory-motor facilitation of gait patterns in patients with Parkinson's disease. J Neurol Neurosurg Psychiatry. 1997; 62(1):22–26.
[68] Morris ME, Iansek R, Matyas TA, et al. Ability to modulate walking cadence remains intact in Parkinson's disease. J Neurol Neurosurg Psychiatry. 1994;57(12):1532–1534.
[69] Thaut MH, McIntosh GC, Rice RR, et al. Rhythmic auditory stimulation in gait training for Parkinson's disease patients. Mov Disord. 1996;11(2):193–200.
[70] Frenkel-Toledo S, Bentin S, Perry A, et al. Dynamics of the EEG power in the frequency and spatial domains during observation and execution of manual movements. Brain Res. 2013;1509:43–57.
[71] Goodale MA, Milner AD. Separate visual pathways for perception and action. Trends Neurosci. 1992;15(1):20–25.
[72] Lee J-H, van Donkelaar P. Dorsal and ventral visual stream contributions to perception-action interactions during pointing. Exp Brain Res. 2002;143(4):440–446.
[73] Ridderinkhof KR, Van Den Wildenberg WP, Segalowitz SJ, et al. Neurocognitive mechanisms of cognitive control: the role of prefrontal cortex in action selection, response inhibition, performance monitoring, and reward-based learning. Brain Cogn. 2004;56(2):129–140.
[74] Rowe JB, Toni I, Josephs O, et al. The prefrontal cortex: response selection or maintenance within working memory? Science. 2000;288(5471):1656–1660.
[75] Hadland K, Rushworth M, Passingham R, et al. Interference with performance of a response selection task that has no working memory component: an rTMS comparison of the dorsolateral prefrontal and medial frontal cortex. J Cogn Neurosci. 2001;13(8):1097–1108.
[76] Wu T, Long X, Wang L, et al. Functional connectivity of cortical motor areas in the resting state in Parkinson's disease. Hum Brain Mapp. 2011;32(9):1443–1457.
[77] Baudrexel S, Witte T, Seifried C, et al. Resting state fMRI reveals increased subthalamic nucleus-motor cortex connectivity in Parkinson's disease. NeuroImage. 2011;55(4): 1728–1738.
[78] Hacker C, Perlmutter J, Criswell S, et al. Resting state functional connectivity of the striatum in Parkinson's disease. Brain. 2012;135(12):3699–3711.
[79] Helmich RC, Derikx LC, Bakker M, et al. Spatial remapping of cortico-striatal connectivity in Parkinson's disease. Cereb Cortex. 2010;20(5):1175–1186.
[80] Kwak Y, Peltier S, Bohnen NI, et al. Altered resting state cortico-striatal connectivity in mild to moderate stage Parkinson's disease. Front Syst Neurosci. 2010;4:143.
[81] Luo C, Song W, Chen Q, et al. Reduced functional connectivity in early-stage drug-naive Parkinson's disease: a resting-state fMRI study. Neurobiol Aging. 2014;35(2):431–441.