Neuroscience 549 (2024) 92–100

Contents lists available at ScienceDirect

Neuroscience

journal homepage: www.elsevier.com/locate/nsc

Research Article

Virtual Reality Action Observation and Motor Imagery to Enhance Neuroplastic Capacity in the Human Motor Cortex: A Pilot Double-blind, Randomized Cross-over Trial

Niamh Connelly [a], Ellana Welsby [a], Belinda Lange [b], Brenton Hordacre [a,*]

[a] Innovation, Implementation and Clinical Translation (IIMPACT) in Health, Allied Health and Human Performance, University of South Australia, Adelaide, Australia
[b] Caring Futures Institute, College of Nursing and Health Sciences, Flinders University, Adelaide, Australia

ARTICLE INFO

Key words:
motor imagery
virtual reality
non-invasive brain stimulation
transcranial magnetic stimulation
motor cortex
neuroplasticity

ABSTRACT

Neuroplasticity is important for learning, development and recovery from injury. Therapies that can upregulate neuroplasticity are therefore of interest across a range of fields. We developed a novel virtual reality action observation and motor imagery (VR-AOMI) intervention and evaluated whether it could enhance the efficacy of mechanisms of neuroplasticity in the human motor cortex of healthy adults. A secondary question was to explore predictors of the change in neuroplasticity following VR-AOMI. A pre-registered, pilot randomized controlled cross-over trial was performed. Twenty right-handed adults (13 females; mean age: 23.0 ± 4.53 years) completed two experimental conditions in separate sessions; VR-AOMI and control. We used intermittent theta burst stimulation (iTBS) to induce long term potentiation-like plasticity in the motor cortex and recorded motor evoked potentials at multiple timepoints as a measure of corticospinal excitability. The VR-AOMI task did not significantly increase the change in MEP amplitude following iTBS when compared to the control task (Group × Timepoint interaction $p = 0.17$). However, regression analysis identified the change in iTBS response following VR-AOMI was significantly predicted by the baseline iTBS response in the control task. Specifically, participants that did not exhibit the expected increase in MEP amplitude following iTBS in the control condition appear to have greater excitability following iTBS in the VR-AOMI condition ($r = -0.72$, $p < 0.001$). Engaging in VR-AOMI might enhance capacity for neuroplasticity in some people who typically do not respond to iTBS. VR-AOMI may prime the brain for enhanced neuroplasticity in this sub-group.

Introduction

Neuroplasticity is the ability of the central nervous system to change in structure or function in response to injury, environment, or behavior. This ability to remodel neural circuitry is available throughout life, facilitates learning, and appears to be temporarily enhanced during critical stages of human development or in response to injury (Nelson, 1999; Murphy and Corbett, 2009; Dayan and Cohen, 2011; Oberman and Pascual-Leone, 2013; Hordacre et al., 2021). Given the importance of neuroplasticity for human behavior, it is reasonable to explore novel therapies that might promote or enhance neuroplasticity in humans.

Motor imagery (also known as mental practice) involves the cognitive rehearsal of movements in the absence of an actual motor output (Decety, 1996). Motor imagery can modify brain activity and facilitate improved upper limb motor recovery following neurological injury, particularly when combined with traditional training (Decety, 1996; Pollock et al., 2014; Hatem et al., 2016; Barclay et al., 2020). Recent advances have explored the value of performing motor imagery during action observation (Taube et al., 2014; Bek et al., 2016). Typically, this entails imagining the sensation and kinesthetics of movement corresponding to congruent visual input (Eaves et al., 2016). As action observation and motor imagery do not require motor output, it is likely to be clinically feasible, even for people with severe motor

Abbreviations: EMG, Electromyography; FDI, First dorsal interosseous; GA, Grand average; iTBS, intermittent Theta Burst Stimulation; LTP, Long-term potentiation; MEP, Motor evoked potential; MSO, Maximal stimulator output; RMT, Resting motor threshold; SSQ, Simulator Sickness Questionnaire; SUS, System Usability Scale; VMIQ, Vividness of Movement Imagery Questionnaire; VR, Virtual reality; VR-AOMI, Virtual reality action observation and motor imagery.

* Corresponding author. Address: Innovation, IMPlementation and Clinical Translation (IIMPACT) in Health, University of South Australia, City East Campus, GPO Box 2471, Adelaide, South Australia 5001, Australia.
E-mail address: brenton.hordacre@unisa.edu.au (B. Hordacre).

https://doi.org/10.1016/j.neuroscience.2024.04.011
Received 22 November 2023; Accepted 25 April 2024
Available online 3 May 2024

impairments. Preliminary evidence indicates that synchronous action observation and motor imagery can enhance excitability of the sensorimotor cortex and lead to rapid behavioral improvement following stroke (Sun et al., 2016). Could it be that the therapeutic benefit of combined action observation and motor imagery are at least partly due to an enhancement of neuroplasticity? Motor imagery, action observation and physical practice seem to promote similar changes in neural activity in higher motor regions including the supplementary motor area and premotor cortex (Lotze et al., 1999; Page et al., 2009; Nedelko et al., 2012; Taube et al., 2015). However, there are inconsistent reports of primary motor cortex activity following action observation and motor imagery. Some studies suggest increased neural activity and corticospinal excitability, similar to what is observed with physical practice (Hashimoto and Rothwell, 1999; Lotze et al., 1999; Strafella and Paus, 2000), while others suggest motor cortex changes are absent or reduced (Roth et al., 1996; Gerardin et al., 2000; Avanzino et al., 2015; Taube et al., 2015). One possible explanation is that higher order motor regions, such as the supplementary and premotor areas, exert a facilitatory influence on the motor cortex (Abbruzzese et al., 1996). Increased excitability of neural inputs onto the motor cortex could modify capacity for synaptic plasticity of neurons in this region. As such, the efficiency and magnitude of these synaptic changes may explain the divergent results of motor cortex excitability in the literature. Furthermore, action observation and motor imagery appear to modify the excitation-inhibition balance within the motor cortex, leading to a cortical environment that is more favorable for neuroplasticity. For example, transcranial magnetic stimulation (TMS) studies have shown GABAergic inhibition is reduced during motor imagery (Abbruzzese et al., 1999; Meng et al., 2018), while action observation can lead to alterations in both excitation and inhibition (Strafella and Paus, 2000). Together, these characteristics might suggest that action observation and motor imagery have potential to modify neuroplasticity within the motor cortex.

Despite action observation and motor imagery holding therapeutic promise, clinical delivery can be uninteresting and monotonous. For example, during motor imagery, people are asked to close their eyes and repeatedly imagine opening and closing their affected hand or completing repetitive finger sequences (Roosink and Zijdewind, 2010; Avanzino et al., 2015). Unfortunately, reduced engagement with the task could impede induced neurophysiological changes. Alternative methods to deliver motor imagery may prove more engaging and lead to stronger brain changes. Virtual reality (VR) is a novel platform to deliver therapy that may be worthy of exploration. VR is highly customizable, can promote increased and sustained participant motivation, leading to stronger engagement and immersion within the task and environment (Laver et al., 2017; Bui et al., 2021). These attributes lend themselves well to a combined action observation and motor imagery task. In addition, VR has further benefits that may prove fruitful for future clinical applications of a combined action observation and motor imagery task. These include alignment with neurorehabilitation principles, such as providing an optimal challenge, feedback, and ability to design salient and highly interactive task-specific training that can be delivered within a safe environment (Levin et al., 2015; Maier et al., 2019; Tang et al., 2022). Furthermore, recent work has reported that VR is well tolerated, promotes behavioral improvements, and is considered an enjoyable therapy by people with stroke (Shin et al., 2016; Kiper et al., 2018; Bui et al., 2021; Fong et al., 2022). Considering the positive effects of action observation, motor imagery and VR based therapies, a limited number of studies exploring the use of virtual reality action observation and motor imagery (VR-AOMI) currently exist. One study delivered VR-AOMI that involved hand grasping movements and found greater oscillatory changes in neural signals from the sensorimotor cortex compared to viewing movements on a monitor display (Choi et al., 2020). Additionally, motor evoked potential (MEP) amplitude has been reported to increase following a game-based VR task involving wrist extension motor imagery while observing incongruent motor actions in both healthy and stroke participants (Im et al., 2016). As such, this novel approach for delivering motor imagery may be highly engaging and enhance subsequent brain changes.

The purpose of this pilot study was to investigate whether a novel VR-AOMI task could enhance the efficacy of mechanisms of neuroplasticity in the human motor cortex in healthy adults. To evaluate foundational mechanisms of neuroplasticity, we used a repetitive stimulation protocol known as intermittent theta burst stimulation (iTBS) which temporarily increases corticospinal excitability by strengthening the efficiency of synapses within the cortex for a brief period following stimulation (Huang et al., 2005). The increase in excitability can additionally be blocked by NMDA receptor antagonists suggesting that the after-effects of iTBS are likely due to short-term, LTP-like effects on synaptic connections (Huang et al., 2007). Furthermore, based on recordings of corticospinal volleys, it appears iTBS increases excitability of circuits generating late I-waves, suggesting the likely site of action is intrinsic circuits within the motor cortex (Di Lazzaro et al., 2008). As such, iTBS likely represents the foundational basis for an early form of long-term potentiation (LTP) synaptic plasticity. The effect of iTBS on synapses in the cortex can be approximated by assessing the change in corticospinal excitability. Specifically, with this model for assessing mechanisms of synaptic plasticity, we hypothesized that if the VR-AOMI task increased capacity for neuroplasticity, we would observe a change in iTBS response towards a greater increase in corticospinal excitability compared to the control condition. A secondary question was to explore predictors of the change in iTBS response following engagement in VR-AOMI.

Experimental procedures

Participants

Participants were recruited from May to September 2021 via convenience sampling with advertisements placed around the University of South Australia campus and on social media. Potential participants were eligible for inclusion if they were 18–40 years of age and right-handed (Edinburgh Handedness Short Form (Veale, 2014)). Participants were excluded if they had contraindications for non-invasive brain stimulation, such as metallic implants, history of seizures or were taking medications known to alter CNS excitability (Rossi et al., 2011). An upper age limit of 40 years was selected as there is some evidence that capacity for neuroplasticity induced by brain stimulation decreases with age (Di Lazzaro et al., 2008; Freitas et al., 2011; Opie et al., 2017). A power calculation was performed based on data extracted from a previous study of neuroplasticity and motor imagery. Here, the authors investigated the effect of kinesthetic motor imagery on response to a facilitatory brain stimulation protocol known as paired associative stimulation (Bonassi et al., 2017). Based on this data, a mean difference of 0.33 mV from baseline to post motor imagery and paired associative stimulation, and pooled standard deviation of 0.42, to achieve 80% power and $p < 0.05$, 16 participants were required. We conservatively adjusted this estimate to 20 participants to account for technical issues or participant drop-out. Ethical approval was granted by the University of South Australia Human Research Ethics Committee and all participants provided written informed consent prior to their participation.

Experimental design

A double-blind pilot randomized controlled crossover trial was conducted, where participants completed both VR-AOMI and control experiments, separated by at least seven days. A randomized crossover design was chosen as it is an efficient and rigorous method for evaluating effect of an intervention (Dwan et al., 2019). A crossover, as

opposed to parallel groups, is justified where treatment effects are reversible and short lived (Dwan et al., 2019). There is evidence that action observation and motor imagery briefly modulate corticospinal excitability, with aftereffects reversed within 20 min (Yasui et al., 2019). Similarly, iTBS aftereffects are temporary, typically persisting less than an hour (Wischnewski and Schutter, 2015; Hill et al., 2023).

This study was conducted and reported using the CONSORT extension for randomized pilot and feasibility studies (Eldridge et al., 2016). Data collection occurred at the University of South Australia Health and Medical Clinic from August to September 2021. Both participants and outcome assessors were blind to allocation. All neurophysiological procedures were performed by the same person throughout the experiment (NC) who was trained prior to data collection and supervised throughout by an expert (BH) with > 10 years' experience in human neurophysiology in both research and clinical application. Experimental order was randomized using a random number generator (allocation ratio 1:1) by an experimenter not involved in data collection, recruitment or analysis. The protocol for the sessions, which took approximately 90 min, is summarized in Fig. 1. The study was preregistered with Open Science Framework (DOI https://doi.org/10.17605/OSF.IO/BVRTM).

Transcranial Magnetic Stimulation

Single pulse TMS and surface electromyography (EMG) were used to record MEPs from the right first dorsal interosseous (FDI) muscle. Alcohol was used to prepare the skin overlying the FDI and disposable EMG electrodes were positioned in a belly-tendon montage (22 × 34 mm, FIAB, Florence, Italy). A ground strap was placed around the wrist. A figure-of-eight coil was placed over the left motor cortex, tangentially to the scalp with the handle positioned at 45° posterolateral (90 mm external wing diameter) (Brasil-Neto et al., 1992). The optimal position for evoking MEPs in the right FDI was determined by systematically moving the coil anterior/posterior, medial/lateral and rotating the handle in small increments. The coil position was then marked on the scalp with a water-soluble felt tip marker for consistent placement for the duration of the experimental procedures. Resting motor threshold (RMT) was determined by an automated algorithm that systematically identified the minimum stimulus intensity required to evoke a MEP in the relaxed FDI with a peak-to-peak amplitude larger than 50 μV in at least 5 out of 10 trials (pulse frequency 0.2 Hz) (Rossini et al., 1994; Groppa et al., 2012). Corticospinal excitability was quantified by recording MEPs and measuring peak-to-peak amplitudes (stimulus intensity 120% RMT). MEPs were recorded at six time points (before VR task, after VR Task, 0 min post iTBS, 5 min post iTBS, 10 min post iTBS, and 15 min post iTBS). The average MEP response from each time point was determined from 30 recorded responses to provide high within- and between-session reliability (Goldsworthy et al., 2016).

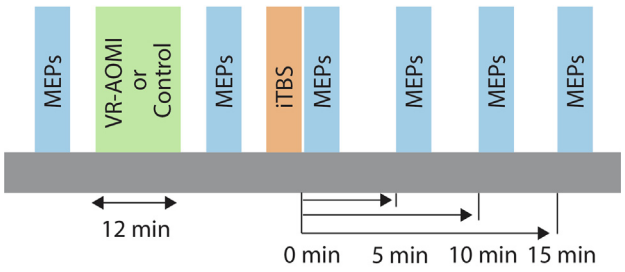

Fig. 1. Experimental Design: Each participant completed both the VR-AOMI and control experiments in a randomized order, separated by at least 7 days. Duration of VR-AOMI or the control task was 12 min. Abbreviations: iTBS, intermittent theta burst stimulation; MEP, Motor evoked potential; VM-AOMI, Virtual reality action observation and motor imagery.

Intermittent Theta Burst Stimulation (iTBS)

A figure-of-eight coil (external wing diameter 90 mm) was used to administer the iTBS protocol (Huang et al., 2005) to the left motor cortex hot-spot at 70% RMT. Stimulation was delivered at 70% RMT as it is approximately similar to the absolute stimulator intensity when determining 80% of active motor threshold, but yields more consistent after-effects while also avoiding muscle contraction required to determine active motor threshold (Fried et al., 2019). Theta burst stimulation delivers 3 pulses at 50 Hz, repeated every 200 ms (Huang et al., 2005). The intermittent protocol (iTBS) involves delivering a 2 s train of theta burst stimulation, repeated every 10 s for a total of 190 s (600 pulses total) (Huang et al., 2005).

VR-AOMI and Control Experiments

In both the VR-AOMI and control experiments, participants used an Oculus Quest 2 headset to view a video clip that was 12 min in duration. The hand-held controllers were not used within the virtual environment. The 12-minute duration was selected as it is within the suggested optimal length for motor imagery and because motion sickness with VR increases with session length (Driskell et al., 1994; Duzmanska et al., 2018).

An Insta Pro 2 camera with six lenses and four microphones was used to film the VR-AOMI video. The output of each lens was combined using stitching software. The resulting high-bitrate video was imported into Adobe Premiere to add text slides and converted into a 180-degree immersive video, suitable for the Oculus Quest 2 headset. In addition, the sound was edited in an ambisonic format, using Adobe Audition. This task involved a first-person perspective of an individual's arms completing a range of activities, following a story line that they were preparing for 'Charlie's Juggling Circus'. At the start of the task, participants were instructed to "imagine these are your arms and you are doing the tasks. Try to feel the weight of the objects you pick up. Imagine the sensation and texture of each item that you touch." The introduction was approximately 1 min in duration. The story line followed four key scenes: making breakfast (~4 min); completing warm-up hand exercises (~2 min); packing a bag (~3 min); and writing a plan on a whiteboard (~2 min; Fig. 2). Between each scene, participants were encouraged to rest, advised of the continuing story line, and reminded to complete action observation and motor imagery without physically moving their upper limbs. This was intended to support immersion into the story line and engagement in motor imagery. The actions completed within each scene were specifically developed to promote motor imagery of common hand grips used in activities of daily living (Kyberd et al., 2009; Vergara et al., 2014). These included an oblique palmar grasp when lifting the coffee plunger (making breakfast scene), a pinch grip while selecting marbles from a jar (packing bag scene) and a tripod grip while writing (writing plan scene) (Vergara et al., 2014). Additionally, standard hand and wrist range of motion exercises were included, with the participant imagining wrist flexion and extension, wrist rotation, and digit flexion and extension (warm-up exercises scene). All recorded tasks were completed with right hand dominance. Fig. 2 provides examples of tasks completed during each of the four scenes.

The control condition was a 12-minute wildlife documentary video that the participant viewed as if they were seated in a cinema. The documentary included wildlife and nature only and participants were instructed to simply sit and watch the video, with no mention of motor imagery.

Measures

Demographics and experimental characteristics including age, sex and time of session were recorded. The Vividness of Movement Imagery Questionnaire (VMIQ) was completed as a measure of

Fig. 2. Experimental Condition Video: The experimental condition video clip involved following a story line that included watching four scenes; 1) Making breakfast (top left), 2) Completing hand exercises (top right), 3) Packing a bag (bottom left), and 4) Writing a plan on a whiteboard (bottom right).

participants' perceived ability to perform visual and kinesthetic motor imagery (Isaac et al., 1986; Lequerica et al., 2002). The VMIQ is a reliable and valid measure that directs participants to rate their ability to perform visual and kinesthetic motor imagery for 24 items on a 5-point scale, with a rating of 1 being perfectly clear and vivid as normal vision and 5 being no image at all. The System Usability Scale (SUS) (Brooke, 1995) and the Simulator Sickness Questionnaire (SSQ) (Kennedy et al., 1993) were both administered at the end of each session. The SUS is a widely used, reliable and valid tool that was used to collect the participants' opinion of usability and engagement within the VR-AOMI and control experiments (Brooke, 1995; Bangor et al., 2008; Nguyen et al., 2023). The SUS contains 10 questions about the usability of the VR task that are scored on a 5-point scale, ranging from (1) strongly disagree to (5) strongly agree. A SUS score above 68 is considered above average (Lewis and Sauro, 2018). The SSQ identified adverse effects experienced by the participant while using the VR headset (Kennedy et al., 1993). Participants were directed to rate the degree to which they felt 16 listed symptoms as either none, slight, moderate, or severe. A total score was then calculated as well as subscores for nausea, disorientation, and oculomotor symptoms. Simulator sickness symptoms are considered minimal if the total score is less than 10.

Statistical analysis

All statistical analyses were performed in SPSS with level of significance set at $p < 0.05$. Normality of data was confirmed using the Kolmogorov-Smirnov test and all statistical assumptions for each analysis were checked. Participant demographics and characteristics were reported using descriptive statistics. RMT, baseline MEP amplitudes, SUS, SSQ total and each subscale (Nausea, Disorientation and Oculomotor) were compared between sessions with paired t-tests. A Bonferroni correction was applied to the repeated analysis of SSQ subscales. To confirm session order did not influence iTBS response following VR-AOMI, an independent *t*-test compared grand average (GA) iTBS response between people completing VR-AOMI first and second. The GA iTBS response was determined as the mean of the post iTBS MEPs divided by the mean of the baseline MEPs (>1 indicated an increase in MEP amplitude following iTBS).

Effect of VR-AOMI on iTBS response was analyzed using a linear mixed model with the dependent variable of raw MEP amplitudes and factors of Group (VR-AOMI, Control) and Timepoint (Baseline, Post VR, 0 min post iTBS, 5 min post iTBS, 10 min post iTBS, 15 min post iTBS). Independent predictors of the change in iTBS response following VR-AOMI were analyzed using linear regression. The change in iTBS response induced by VR-AOMI was considered as the difference in GA iTBS response between VR-AOMI and Control experiments. For the regression analysis, the dependent variable was the change in iTBS response following VR-AOMI. The independent variables were age, sex, session order, time of day sessions were performed, RMT at each session, baseline MEP amplitude at each session, MEP difference post VR-AOMI (difference in MEP amplitude pre to post VR-AOMI, prior to iTBS), the GA iTBS response in the control condition, VMIQ visual imagery items mean and VMIQ kinesthetic imagery items mean.

Results

Demographics and characteristics

Twenty healthy, right-handed participants aged 19 – 37 years (13 females; mean age: 23.0 ± 4.53 years) participated in the study. There were no participant withdrawals, and all experimental sessions and data were complete. A CONSORT flow diagram is provided in Fig. 3. Time between sessions ranged from 7 to 19 days, with an average of 8 days. Table 1 presents the mean RMT, baseline MEP amplitude, and scores for kinesthetic and visual VMIQ, SUS and SSQ for the VR-AOMI and control experiments. RMT and baseline MEP amplitude was not significantly different between conditions (RMT, $t_{(19)} = -0.29$, 95%CI; −3.71 – 2.81, $r = 0.07$, $p = 0.78$; Baseline MEP, $t_{(19)} = -0.16$, 95%CI; −0.28 – 0.24, $r = 0.04$, $p = 0.87$). No significant difference was found between VR-AOMI and control experiments for SUS ($t_{(19)} = -1.12$, 95%CI; −5.16 – 1.41, $r = 0.25$, $p = 0.25$), SSQ total ($t_{(19)} = 0.66$, 95%CI; −3.27 – 6.26, $r = 0.15$, $p = 0.52$) or the SSQ subscales of Nausea ($t_{(19)} = 2.03$, 95%CI; −0.07 – 4.84, $r = 0.42$, $p = 0.18$, Bonferroni corrected), Disorientation ($t_{(19)} = 0.33$, 95%CI; −5.77 – 7.92, $r = 0.08$, $p = 1.00$, Bonferroni corrected) and Oculomotor ($t_{(19)} = 0.18$, 95%CI; −5.90 – 7.04,

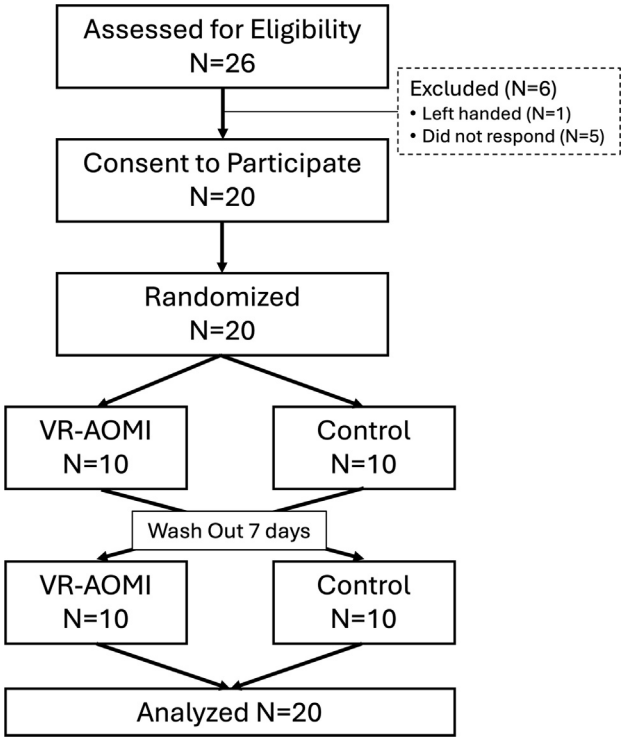

Fig. 3. CONSORT participant flow diagram.

Table 1
Neurophysiological and experimental characteristics: Values presented as means and standard deviations

	VR-AOMI (n = 20)	Control (n = 20)
RMT (%MSO)	42.00 ± 6.50	42.4 ± 6.80
MEP Baseline Amplitude (mV, 120% RMT)	0.62 ± 0.48	0.64 ± 0.51
VMIQ Visual	2.61 ± 1.04	–
VMIQ Kinesthetic	2.32 ± 0.98	–
SUS Score	80.13 ± 10.84	82.00 ± 12.29
SSQ Total Score	9.35 ± 10.04	7.85 ± 10.71
SSQ Nausea	6.68 ± 8.81	4.29 ± 7.24
SSQ Disorientation	5.25 ± 12.95	4.18 ± 7.95
SSQ Oculomotor	10.80 ± 11.49	10.23 ± 14.19

Abbreviations: MEP, motor evoked potential; MSO, maximal stimulator output; RMT, resting motor threshold; SSQ, Simulator Sickness Questionnaire; SUS, System Usability Scale; VMIQ, Vividness of Movement Imagery Questionnaire; VR-AOMI, Virtual reality action observation and motor imagery.

r = 0.04, p = 1.00, Bonferroni corrected). The GA iTBS response was not different for people who completed VR-AOMI first or second, suggesting no evidence of session order effects ($t_{(18)}$ = −0.23, 95%CI; −0.43 – 0.35, r = 0.05, p = 0.71).

Effect of VR-AOMI on iTBS response

Analysis of MEP amplitude found no effect of Group ($F_{(1,19.0)}$ = 0.02, p = 0.88), Timepoint ($F_{(5,16.1)}$ = 1.07, p = 0.41) or Group × Timepoint interaction ($F_{(5,16.6)}$ = 1.77, p = 0.17) of VR-AOMI on iTBS response. When controlling for age, sex, RMT and VMIQ, there remained no significant effect of Timepoint ($F_{(5,17.8)}$ = 1.03, p = 0.43) or Group × Timepoint interaction ($F_{(5,18.2)}$ = 1.74, p = 0.32). There was, however, a main effect of Group ($F_{(1,13.54)}$ = 9.72, p = 0.04), with further exploration revealing that MEPs were, on average, larger in the VR-AOMI Group ($t_{(1\,3\,9)}$ = 3.0, 95%CI; 1.10 – 4.90, r = 0.25, p = 0.01). However, these findings suggest that VR-AOMI did not enhance the response to iTBS, even when controlling for covariates (see Fig. 4).

Factors that predict change in iTBS response following VR-AOMI

The results of a linear regression with factors that might predict the change in iTBS response following VR-AOMI are shown in Table 2. When adjusting for all other variables, the only significant predictor was iTBS response in the control session. This analysis indicated for every 1 unit decrease in GA iTBS response in the control session, the change in iTBS response between sessions increased by 1.08 units.

The regression model findings appeared to be driven by a significant association between the change in iTBS response following VR-AOMI and the GA iTBS response for the control condition (r = −0.72, p < 0.001), see Fig. 5. Participants who did not have a MEP facilitation following iTBS in the control task predominantly changed their iTBS response toward a greater increase in MEP amplitude after the VR-AOMI experiment. This might suggest a stronger iTBS response following VR-AOMI in a subset of participants.

Discussion

The aim of this study was to explore whether a VR-AOMI task could enhance capacity for neuroplasticity in the human motor cortex in healthy adults. Our measure of neuroplasticity was the transient increase in MEP amplitude following iTBS, likely representing the foundational basis for an early form of LTP synaptic plasticity. At a group level, our findings do not suggest that VR-AOMI increased MEP amplitude following iTBS to a greater extent than that observed following a control condition. However, further analysis of factors that predict the change in iTBS response following VR-AOMI suggest this task might increase MEP amplitude in a subset of participants. Specifically, participants who did not increase in MEP amplitude in the control condition, appeared to change their response toward increased corticospinal excitability following iTBS in the VR-AOMI condition. This could prove beneficial for promoting neurological recovery.

Contrary to our hypothesis, we did not observe an enhanced capacity for neuroplasticity following the VR-AOMI task in all participants. However, our findings could be viewed as suggesting that the action observation and motor imagery task does modulate neuroplasticity, dependent on the participants iTBS response in the control condition. This finding is notable as iTBS produces relatively robust test–retest reliability of effects in young healthy adults, suggesting individual responses should be consistent from one session to the next (Hinder et al., 2014). That we may have observed an effect of VR-AOMI in changing the iTBS response is therefore of interest. For those that did not exhibit a MEP increase following iTBS, VR-AOMI appears to bias networks for a greater neuroplastic response as exhibited by an increase in excitability following iTBS. It is possible that for this group of people, VR-AOMI primed the brain for neuroplastic changes. However, our results could also suggest that VR-AOMI appeared to impede neuroplasticity in people who responded to iTBS in the control condition. If this is so, one explanation could be that the combined action observation and motor imagery task, delivered prior to iTBS, induced homeostatic plasticity which counteracted the LTP-like plasticity induced by iTBS. Specifically, VR-AOMI may have induced neural changes that then led to reversal of after-effects induced by iTBS. In support, there is some evidence from studies investigating non-invasive brain stimulation and motor practice, where homeostatic plasticity is thought to have occurred (Gentner et al., 2007; Ragert et al., 2009; Gamboa et al., 2010; Karabanov et al., 2015).

The results of the SUS and SSQ indicate that the VR-AOMI task developed for this study was usable and produced minimal simulator sickness symptoms (Stanney et al., 1997; Bangor et al., 2008). The

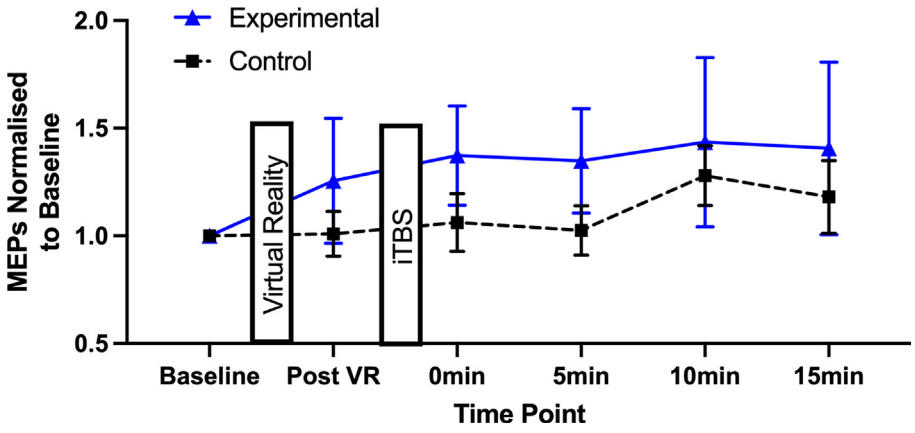

Fig. 4. Neurophysiological data: MEPs normalized to baseline MEP mean, demonstrating that MEPs were, on average, larger in the motor imagery condition than in the control condition. Abbreviations: iTBS, intermittent theta burst stimulation; MEP, Motor evoked potential. Error bars show standard deviation. Raw data is available in appendix 1.

Table 2
Results of linear regression: dependent variable was change in GA iTBS response and independent variables are grouped by headings of demographics, experimental and control factors. The statistically significant variable is shown in bold

	Unstandardized Coefficients		Standardized Coefficients	t	Sig.
	B	Std. Error	Beta		
(Constant)	3.49	2.04		1.71	0.15
Demographics					
Age	−0.05	0.05	−0.42	−1.14	0.31
Sex	0.29	0.57	0.25	0.51	0.63
Session order	0.11	0.47	0.10	0.23	0.83
VMIQ Visual Imagery Score	0.45	0.32	0.81	1.39	0.22
VMIQ Kinesthetic Imagery Score	−0.42	0.38	−0.71	−1.10	0.32
VR-AOMI experiment					
Time of session	−0.13	0.22	−0.26	−0.58	0.59
RMT	−0.02	0.04	−0.27	−0.55	0.61
MEP Baseline	−0.47	0.59	−0.39	−0.80	0.46
MEP difference post VR-AOMI	0.13	0.55	0.11	0.25	0.82
Control experiment					
Time of session	−0.10	0.34	−0.17	−0.29	0.79
RMT	0.00	0.02	−0.02	−0.08	0.94
MEP Baseline	0.25	0.35	0.22	0.71	0.51
MEP change from Baseline	0.43	0.72	0.21	0.60	0.58
Grand average iTBS response	**−1.08**	**0.32**	**−0.92**	**−3.42**	**0.02**

Abbreviations: VMIQ, Vividness of Motor Imagery Questionnaire; RMT, resting motor threshold; MEP, motor evoked potential; iTBS, intermittent theta burst stimulation; VR-AOMI, virtual reality action observation and motor imagery.

low SSQ scores may have been due to our VR tasks having the participants observe the movements in a static position. In many instances, the depiction of motion in a VR task can create a sense of actual self-motion, known as vection, which can cause strong feelings of disequilibrium and motion sickness (Hettinger et al., 2015; Chang et al., 2020). By having our participants complete the entire task from a static position, vection was most likely eliminated, contributing to low SSQ scores. However, we note that the total SSQ score, and all subscores, particularly nausea, were higher in the VR-AOMI task than in the control condition, though these differences were not statistically significant. This could be attributed to the need for participants to remain focused on completing action observation and motor imagery for a range of tasks, requiring ongoing concentration and some head movements required to track the virtual arms. On the other hand, when participants completed the control, they were not required to focus on a cognitively taxing task and did not need to move their head to track movements.

While few studies have investigated a VR based action observation and motor imagery task, there are some notable differences between that presented here and earlier work (Im et al., 2016; Choi et al., 2020). Im et al. found an increase in MEP after completing a game-based VR task involving wrist extension motor imagery while observing incongruent motor actions for both healthy adults and people with stroke (Im et al., 2016). The task used was imagined repetitive wrist extension, following an avatar that jumped over obstacles (Im et al., 2016). That the action observation (an avatar jumping) was incongruent with the motor imagery (wrist extension) might have led to differential effect on cortical activity as clinical studies indicate synchronous action observation and motor imagery may be highly effective (Sun et al., 2016). Choi, et al. (2020) used a VR-AOMI task consisting of avatar hands opening and closing into a fist. This research used electroencephalography to identify changes in the elicited neural signals of the sensorimotor cortex (Choi et al., 2020). The results of their study suggest that using the VR headset was more effective at improving event related desynchronization performance when compared to a monitor display. Furthermore, it is particularly noteworthy that the simple and repetitive movements undertaken in these two studies imitate those completed in studies of motor imagery without VR that find increases in corticospinal excitability (Avanzino et al., 2015; Bonassi et al., 2017; Meng et al., 2019). Thus, repetition of a specific move-

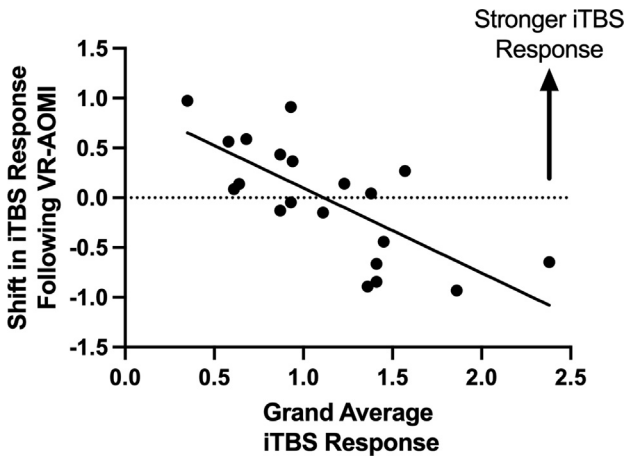

Fig. 5. Correlation between the change in iTBS response following VR action observation and motor imagery and the GA iTBS response for the control condition. Abbreviations: GA, Grand Average; iTBS, intermittent Theta Burst Stimulation; VR-AOMI, virtual reality action observation and motor imagery.

ment, while monotonous, may also prove an effective method to induce neural changes. Conversely, our VR-AOMI task took a task-orientated approach by having the participant imagine several different tasks. This approach allowed motor imagery to be performed for a range of functional grips and movements, though limited repetition of movements were performed. In support of our approach, there is some indication that task-oriented training may be a more effective therapeutic strategy following stroke when compared to repetitive training (Song, 2015). Of course, the behavioral relevance of performing repetitive specific movements as opposed to more salient task-specific activities of daily living during a combined action observation and motor imagery task, like those employed in our study, requires investigation.

The results of this preliminary work suggest that VR-AOMI might enhance capacity for neuroplasticity in some people, suggesting potential utility to prime the brain for greater neural changes during learning. However, prior to gaining any therapeutic benefit, we suggest future research should initially test the reliability of these results. More specifically, it would be valuable to test whether the change in neuroplasticity following VR-AOMI in participants who do not normally respond to iTBS can be reproduced. Furthermore, future studies should evaluate the importance of using virtual environments for this task. While we devised a novel task to be delivered through the Oculus Quest 2 headset in a virtual environment, it is unclear whether enhancement of neuroplasticity would be similar if delivered via a traditional monitor, such as a PC screen. Previous work has shown neural changes are less robust when delivered via a monitor (Choi et al., 2020), suggesting immersion in virtual environments could be critical. Further probing mode of delivery might provide insight to the mechanism by which VR-AOMI exerts its effect and would be valuable to inform optimal delivery platform in future studies. Similarly, to further tease apart effects of the VR-AOMI task on neuroplasticity, future studies should consider measuring both hemispheres. In the current study, we evaluated physiological effects on the left (dominant) hemisphere. However, the VR-AOMI task was bi-manual, and it is reasonable to hypothesize physiological effects extend to both hemispheres. Evaluating neuroplasticity from both dominant and non-dominant hemispheres could provide a more comprehensive understanding of VR-AOMI effects on the brain and might have clinical implications. Alternative physiological or imaging measures should also be considered to provide additional insight to the effect of VR-AOMI on brain activity. Potential candidates include paired-pulse TMS, TMS combined with electroencephalography, or various forms of neuroimaging (Kujirai et al., 1993; Komssi et al., 2002; Hordacre et al., 2019; Goldsworthy et al., 2021). Finally, clinical application of this task might provide therapeutic opportunity. Once VR-AOMI is refined and further understood, exploration in a patient population would appear appropriate. This would likely require longer treatment durations, delivered in a parallel group design, with the addition of behavioral measures to understand the clinical benefit of enhancing neuroplasticity for improved function and activities of daily living. We note, a clinical population will likely present additional challenges for engaging in the VR-AOMI task due to potential vestibular or visual impairments as a result of brain injury. This will require consideration in future studies.

A number of limitations of the study exist. First, while the sample size was calculated from a previous study of motor imagery, it is still a small sample. As such, the results of our study cannot be generalized to the whole population and need to be considered carefully. A post-hoc sample size was performed based on our data, indicating 88 participants would be required in an appropriately powered trial (allowable difference for grand average iTBS response between group of 0.26, population variance of 1.50, alpha 0.05 and 80% power). This analysis is of course specific to a study with healthy young adults. Effect sizes may differ in people with neurological conditions where VR-AOMI could have therapeutic potential. A second limitation of the study was that the development of the video resulted in minor warping of the virtual arms at some points during the VR-AOMI task. This was due to the proximity of the arms to the camera during recording, causing the stitching software to create some minor warping effects where the lenses overlapped. This warping could have reduced the participants' immersion with the task and consequently reduced engagement. However, this was not flagged in the feedback received through the SUS data.

Our findings suggest that engaging in a VR-AOMI task could modulate capacity for neuroplasticity as measured by response to an iTBS protocol. Corticospinal excitability was greater in the VR-AOMI group. In some participants, the VR-AOMI task appeared to change iTBS responses with evidence of increased corticospinal excitability compared to the control condition. This finding may suggest capacity for neuroplasticity was enhanced in this subgroup of participants. Future research is required to consolidate our findings, further understand VR-AOMI, and to explore application for clinical populations.

Funding

BH was supported by a National Health and Medical Research Council fellowship (1125054).

Conflict of interest statement

BH holds a paid consultancy role for Recovery VR and has a clinical partnership with Fourier Intelligence. The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Acknowledgments

The authors would like to acknowledge Steve Hall for contributing to the contents and producing the experimental VR-AOMI task.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.neuroscience.2024.04.011.

References

Abbruzzese, G., Trompetto, C., Schieppati, M., 1996. The excitability of the human motor cortex increases during execution and mental imagination of sequential but not repetitive finger movements. Exp. Brain Res. 111, 465–472.

Abbruzzese, G., Assini, A., Buccolieri, A., Marchese, R., Trompetto, C., 1999. Changes of intracortical inhibition during motor imagery in human subjects. Neurosci. Lett. 263, 113–116.

Avanzino, L., Gueugneau, N., Bisio, A., Ruggeri, P., Papaxanthis, C., Bove, M., 2015. Motor cortical plasticity induced by motor learning through mental practice. Front. Behav. Neurosci. 9, 105.

Bangor, A., Kortum, P.T., Miller, J.T., 2008. An empirical evaluation of the system usability scale. Int. J. Hum. Comput. Interact. 24, 574–594.

Barclay, R.E., Barclay, R.E., Stevenson, T.J., Poluha, W., Semenko, B., Schubert, J., 2020. Mental practice for treating upper extremity deficits in individuals with hemiparesis after stroke. Cochrane Database Syst. Rev.CD005950.

Bek, J., Poliakoff, E., Marshall, H., Trueman, S., Gowen, E., 2016. Enhancing voluntary imitation through attention and motor imagery. Exp. Brain Res. 234, 1819–1828.

Bonassi, G., Biggio, M., Bisio, A., Ruggeri, P., Bove, M., Avanzino, L., 2017. Provision of somatosensory inputs during motor imagery enhances learning-induced plasticity in human motor cortex. Sci. Rep. 7, 9300.

Brasil-Neto, J.P., Cohen, L.G., Panizza, M., Nilsson, J., Roth, B.J., Hallett, M., 1992. Optimal focal transcranial magnetic activation of the human motor cortex: effects of coil orientation, shape of the induced current pulse, and stimulus intensity. J. Clin. Neurophysiol. 9, 132–136.

Brooke, J., 1995. SUS: a quick and dirty usability scale. In: Jordan, P.W., Thomas, B., Weerdmeester, B., McClelland, A. (Eds.), Usability Evaluation in Industry. Taylor and Francis, London.

Bui, J., Luauté, J., Farnè, A., 2021. Enhancing upper limb rehabilitation of stroke patients with virtual reality: a mini review. Front. Virtual Real. 2.

Chang, E., Kim, H.T., Yoo, B., 2020. Virtual reality sickness: a review of causes and measurements. Int. J. Hum. Comput. Interact. 36, 1658–1682.

Choi, J.W., Kim, B.H., Huh, S., Jo, S., 2020. Observing actions through immersive virtual reality enhances motor imagery training. IEEE Trans. Neural Syst. Rehabil. Eng. 28, 1614–1622.

Dayan, E., Cohen, L.G., 2011. Neuroplasticity subserving motor skill learning. Neuron 72, 443–454.

Decety, J., 1996. The neurophysiological basis of motor imagery. Behav. Brain Res. 77, 45–52.

Di Lazzaro, V., Pilato, F., Dileone, M., Profice, P., Oliviero, A., Mazzone, P., Insola, A., Ranieri, F., et al, 2008. The physiological basis of the effects of intermittent theta burst stimulation of the human motor cortex. J. Physiol. 586, 3871–3879.

Driskell, J.E., Copper, C., Moran, A., 1994. Does mental practice enhance performance? J. Appl. Psychol. 79, 481–492.

Duzmanska, N., Strojny, P., Strojny, A., 2018. Can simulator sickness be avoided? A review on temporal aspects of simulator sickness. Front. Psychol. 9, 2132.

Dwan, K., Li, T., Altman, D.G., Elbourne, D., 2019. CONSORT 2010 statement: extension to randomised crossover trials. BMJ 366, l4378.

Eaves, D.L., Riach, M., Holmes, P.S., Wright, D.J., 2016. Motor imagery during action observation: a brief review of evidence, theory and future research opportunities. Front. Neurosci. 10, 514.

Eldridge, S.M., Chan, C.L., Campbell, M.J., Bond, C.M., Hopewell, S., Thabane, L., Lancaster, G.A., 2016. CONSORT 2010 statement: extension to randomised pilot and feasibility trials. BMJ 355, i5239.

Fong, K.N.K., Tang, Y.M., Sie, K., Yu, A.K.H., Lo, C.C.W., Ma, Y.W.T., 2022. Task-specific virtual reality training on hemiparetic upper extremity in patients with stroke. Virtual Reality 26, 453–464.

Freitas, C., Perez, J., Knobel, M., Tormos, J.M., Oberman, L., Eldaief, M., Bashir, S., Vernet, M., et al, 2011. Changes in cortical plasticity across the lifespan. Front. Aging Neurosci., 3.

Fried, P., Jannati, A., Morris, T., Buss, S., Santarnecchi, E., Shafi, M., Pascual-Leone, A., 2019. Relationship of active to resting motor threshold influences the aftereffects of theta-burst stimulation. Brain Stimul. 12, 465.

Gamboa, O.L., Antal, A., Moliadze, V., Paulus, W., 2010. Simply longer is not better: reversal of theta burst after-effect with prolonged stimulation. Exp. Brain Res. 204, 181–187.

Gentner, R., Wankerl, K., Reinsberger, C., Zeller, D., Classen, J., 2007. Depression of human corticospinal excitability induced by magnetic theta-burst stimulation: evidence of rapid polarity-reversing metaplasticity. Cereb. Cortex 18, 2046–2053.

Gerardin, E., Sirigu, A., Sp, L., Poline, J.-B., Gaymard, B., Marsault, C., Agid, Y., Le Bihan, D., 2000. Partially overlapping neural networks for real and imagined hand movements. Cereb. Cortex 10, 1093–1104.

Goldsworthy, M.R., Hordacre, B., Ridding, M.C., 2016. Minimum number of trials required for within- and between-session reliability of TMS measures of corticospinal excitability. Neuroscience 320, 205–209.

Goldsworthy, M.R., Hordacre, B., Rothwell, J.C., Ridding, M.C., 2021. Effects of rTMS on the brain: is there value in variability? Cortex 139, 43–59.

Groppa, S., Oliviero, A., Eisen, A., Quartarone, A., Cohen, L.G., Mall, V., Kaelin-Lang, A., Mima, T., et al, 2012. A practical guide to diagnostic transcranial magnetic stimulation: Report of an IFCN committee. Clin. Neurophysiol. 123, 858–882.

Hashimoto, R., Rothwell, J.C., 1999. Dynamic changes in corticospinal excitability during motor imagery. Exp. Brain Res. 125, 75–81.

Hatem, S.M., Saussez, G., della Faille, M., Prist, V., Zhang, X., Dispa, D., Bleyenheuft, Y., 2016. Rehabilitation of motor function after stroke: a multiple systematic review focused on techniques to stimulate upper extremity recovery. Front. Hum. Neurosci. 10, 442.

Hettinger, L.J., Schmidt-Daly, T.N., Jones, D.L., Keshavarz, B., 2015. Illusory self-motion in virtual environments. In: Handbook of Virtual Environments. CRC Press, pp. 435–459.

Hill, G., Johnson, F., Uy, J., Serrada, I., Benyamin, B., Van Den Berg, M., Hordacre, B., 2023. Moderate intensity aerobic exercise may enhance neuroplasticity of the contralesional hemisphere after stroke: a randomised controlled study. Sci. Rep. 13, 14440.

Hinder, M.R., Goss, E.L., Fujiyama, H., Canty, A.J., Garry, M.I., Rodger, J., Summers, J. J., 2014. Inter- and intra-individual variability following intermittent theta burst stimulation: implications for rehabilitation and recovery. Brain Stimul. 7, 365–371.

Hordacre, B., Ghosh, R., Goldsworthy, M.R., Ridding, M.C., 2019. Transcranial magnetic stimulation-EEG biomarkers of poststroke upper-limb motor function. J. Stroke Cerebrovasc. Dis., 104452.

Hordacre, B., Austin, D., Brown, K.E., Graetz, L., Pareés, I., De Trane, S., Vallence, A.-M., Koblar, S., et al, 2021. Evidence for a window of enhanced plasticity in the human motor cortex following ischemic stroke. Neurorehabil. Neural Repair 35, 307–320.

Huang, Y.-Z., Edwards, M.J., Rounis, E., Bhatia, K.P., Rothwell, J.C., 2005. Theta burst stimulation of the human motor cortex. Neuron 45, 201–206.

Huang, Y.-Z., Chen, R.-S., Rothwell, J.C., Wen, H.-Y., 2007. The after-effect of human theta burst stimulation is NMDA receptor dependent. Clin. Neurophysiol. 118, 1028–1032.

Im, H., Ku, J., Kim, H.J., Kang, Y.J., 2016. Virtual reality-guided motor imagery increases corticomotor excitability in healthy volunteers and stroke patients. Ann. Rehabil. Med. 40, 420–431.

Isaac, A., Marks, D.F., Russell, D.G., 1986. An instrument for assessing imagery of movement: The Vividness of Movement Imagery Questionnaire (VMIQ). J. Ment. Imag. 10, 23–30.

Karabanov, A., Ziemann, U., Hamada, M., George, M.S., Quartarone, A., Classen, J., Massimini, M., Rothwell, J., et al, 2015. Consensus paper: probing homeostatic plasticity of human cortex with non-invasive transcranial brain stimulation. Brain Stimul. 8, 442–454.

Kennedy, R.S., Lane, N.E., Berbaum, K.S., Lilienthal, M.G., 1993. Simulator sickness questionnaire: an enhanced method for quantifying simulator sickness. Int. J. Aviat. Psychol. 3, 203–220.

Kiper, P., Szczudlik, A., Agostini, M., Opara, J., Nowobilski, R., Ventura, L., Tonin, P., Turolla, A., 2018. Virtual reality for upper limb rehabilitation in subacute and chronic stroke: a randomized controlled trial. Arch. Phys. Med. Rehabil. 99, 834–842.e834.

Komssi, S., Aronen, H.J., Huttunen, J., Kesäniemi, M., Soinne, L., Nikouline, V.V., Ollikainen, M., Roine, R.O., et al, 2002. Ipsi- and contralateral EEG reactions to transcranial magnetic stimulation. Clin. Neurophysiol. 113, 175–184.

Kujirai, T., Caramia, M.D., Rothwell, J.C., Day, B.L., Thompson, P.D., Ferbert, A., Wroe, S., Asselman, P., et al, 1993. Corticocortical inhibition in human motor cortex. J. Physiol. 471, 501–519.

Kyberd, P.J., Murgia, A., Gasson, M., Tjerks, T., Metcalf, C., Chappell, P.H., Warwick, K., Lawson, S.E.M., et al, 2009. Case studies to demonstrate the range of applications of the Southampton Hand Assessment Procedure. Br. J. Occup. Ther. 72, 212–218.

Laver, K.E., Lange, B., George, S., Deutsch, J.E., Saposnik, G., Crotty, M., 2017. Virtual reality for stroke rehabilitation. Cochrane Database Syst. Rev..

Lequerica, A., Rapport, L., Axelrod, B.N., Telmet, K., Whitman, R.D., 2002. Subjective and objective assessment methods of mental imagery control: construct validation of self-report measures. J. Clin. Exp. Neuropsychol. 24, 1103–1116.

Levin, M.F., Weiss, P.L., Keshner, E.A., 2015. Emergence of virtual reality as a tool for upper limb rehabilitation: incorporation of motor control and motor learning principles. Phys. Ther. 95, 415–425.

Lewis, J., Sauro, J., 2018. Item Benchmarks for the System Usability Scale 13, 158–167.

Lotze, M., Montoya, P., Erb, M., Hülsmann, E., Flor, H., Klose, U., Birbaumer, N., Grodd, W., 1999. Activation of cortical and cerebellar motor areas during executed and imagined hand movements: an fMRI study. J. Cogn. Neurosci. 11, 491–501.

Maier, M., Rubio Ballester, B., Duff, A., Duarte Oller, E., Verschure, P.F.M.J., 2019. Effect of specific over nonspecific VR-based rehabilitation on poststroke motor recovery: a systematic meta-analysis. Neurorehabil. Neural Repair 33, 112–129.

Meng, H.J., Pi, Y.-L., Liu, K., Cao, N., Wang, Y.-Q., Wu, Y., Zhang, J., 2018. Differences between motor execution and motor imagery of grasping movements in the motor cortical excitatory circuit. PeerJ 2018, e5588.

Meng, H.J., Cao, N., Lin, Y.T., Liu, K., Zhang, J., Pi, Y.L., 2019. Motor learning enhanced by combined motor imagery and noninvasive brain stimulation is associated with reduced short-interval intracortical inhibition. Brain Behav. 9, e01252.

Murphy, T.H., Corbett, D., 2009. Plasticity during stroke recovery: from synapse to behaviour. Nat. Rev. Neurosci. 10, 861–872.

Nedelko, V., Hassa, T., Hamzei, F., Schoenfeld, M.A., Dettmers, C., 2012. Action imagery combined with action observation activates more corticomotor regions than action observation alone. J. Neurol. Phys. Ther. 36, 182–188.

Nelson, C.A., 1999. Neural Plasticity and Human Development. Curr. Dir. Psychol. Sci. 8, 42–45.

Nguyen, C.M., Uy, J., Serrada, I., Hordacre, B., 2023. Quantifying patient experiences with therapeutic neurorehabilitation technologies: a scoping review. Disabil. Rehabil., 1–11.

Oberman, L., Pascual-Leone, A., 2013. Chapter 4 – Changes in plasticity across the lifespan: cause of disease and target for intervention. In: Merzenich, M.M., Nahum, M., Van Vleet, T.M. (Eds.), Prog. Brain Res.. Elsevier, pp. 91–120.
Opie, G.M., Vosnakis, E., Ridding, M.C., Ziemann, U., Semmler, J.G., 2017. Priming theta burst stimulation enhances motor cortex plasticity in young but not old adults. Brain Stimul. 10, 298–304.
Page, S.J., Szaflarski, J.P., Eliassen, J.C., Pan, H., Cramer, S.C., 2009. Cortical plasticity following motor skill learning during mental practice in stroke. Neurorehabil. Neural Repair 23, 382–388.
Pollock, A., Farmer, S.E., Brady, M.C., Langhorne, P., Mead, G.E., Mehrholz, J., van Wijck, F., Pollock, A., 2014. Interventions for improving upper limb function after stroke. Cochrane Database Syst. Rev.CD010820.
Ragert, P., Camus, M., Vandermeeren, Y., Dimyan, M.A., Cohen, L.G., 2009. Modulation of effects of intermittent theta burst stimulation applied over primary motor cortex (M1) by conditioning stimulation of the opposite M1. J. Neurophysiol. 102, 766–773.
Roosink, M., Zijdewind, I., 2010. Corticospinal excitability during observation and imagery of simple and complex hand tasks: Implications for motor rehabilitation. Behav. Brain Res. 213, 35–41.
Rossi, S., Hallett, M., Rossini, P.M., Pascual-Leone, A., 2011. Screening questionnaire before TMS: an update. Clin. Neurophysiol. 122, 1686.
Rossini, P.M., Barker, A.T., Berardelli, A., Caramia, M.D., Caruso, G., Cracco, R.Q., Dimitrijevic, M.R., Hallett, M., et al, 1994. Non-invasive electrical and magnetic stimulation of the brain, spinal cord and roots: basic principles and procedures for routine clinical application. Report of an IFCN committee. Electroencephalogr. Clin. Neurophysiol. 91, 79–92.
Roth, M., Decety, J., Raybaudi, M., Massarelli, R., Delon-Martin, C., Segebarth, C., Morand, S., Gemignani, A., et al, 1996. Possible involvement of primary motor cortex in mentally simulated movement: a functional magnetic resonance imaging study. Neuroreport 7, 1280–1284.
Shin, J.-H., Kim, M.-Y., Lee, J.-Y., Jeon, Y.-J., Kim, S., Lee, S., Seo, B., Choi, Y., 2016. Effects of virtual reality-based rehabilitation on distal upper extremity function and health-related quality of life: a single-blinded, randomized controlled trial. J. Neuroeng. Rehabil. 13, 17.
Song, G.B., 2015. The effects of task-oriented versus repetitive bilateral arm training on upper limb function and activities of daily living in stroke patients. J. Phys. Ther. Sci. 27, 1353–1355.
Stanney, K.M., Kennedy, R.S., Drexler, J.M., 1997. Cybersickness is not simulator sickness. Proc. Human Factors Ergon. Soc. Annual Meet. 41, 1138–1142.
Strafella, A.P., Paus, T., 2000. Modulation of cortical excitability during action observation: a transcranial magnetic stimulation study. Neuroreport 11, 2289–2292.
Sun, Y., Wei, W., Luo, Z., Gan, H., Hu, X., 2016. Improving motor imagery practice with synchronous action observation in stroke patients. Top. Stroke Rehabil. 23, 245–253.
Tang, Y.M., Chau, K.Y., Kwok, A.P.K., Zhu, T., Ma, X., 2022. A systematic review of immersive technology applications for medical practice and education – trends, application areas, recipients, teaching contents, evaluation methods, and performance. Educ. Res. Rev. 35, 100429.
Taube, W., Lorch, M., Zeiter, S., Keller, M., 2014. Non-physical practice improves task performance in an unstable, perturbed environment: motor imagery and observational balance training. Front. Hum. Neurosci. 8, 972.
Taube, W., Mouthon, M., Leukel, C., Hoogewoud, H.-M., Annoni, J.-M., Keller, M., 2015. Brain activity during observation and motor imagery of different balance tasks: an fMRI study. Cortex 64, 102–114.
Veale, J.F., 2014. Edinburgh Handedness Inventory - Short form: a revised version based on confirmatory factor analysis. Laterality 19, 164–177.
Vergara, M., Sancho-Bru, J.L., Gracia-Ibáñez, V., Pérez-González, A., 2014. An introductory study of common grasps used by adults during performance of activities of daily living. J. Hand. Ther. 27, 225–233. quiz 234.
Wischnewski, M., Schutter, D.J.L.G., 2015. Efficacy and time course of theta burst stimulation in healthy humans. Brain Stimul. 8, 685–692.
Yasui, T., Yamaguchi, T., Tanabe, S., Tatemoto, T., Takahashi, Y., Kondo, K., Kawakami, M., 2019. Time course of changes in corticospinal excitability induced by motor imagery during action observation combined with peripheral nerve electrical stimulation. Exp. Brain Res. 237, 637–645.