An MR-Compatible Virtual Reality System for Assessing Neuronal Plasticity of Sensorimotor Neurons and Mirror Neurons

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Abstract. Virtual reality (VR) assisted rehabilitation system is being used more commonly in supplementing upper extremities (UE) functional rehabilitation. Mirror therapy (MT) is reportedly a useful training in encouraging motor functional recovery. However, the majority of current systems are not compatible with magnetic resonance (MR) environments. Resting-state functional magnetic resonance imaging (rs-fMRI) data, for measuring neuronal recovery status, can only be collected by these systems after the participants have been done with the VR therapy. As a result, real-time observation of the brain in working status remains unattainable. To address this challenge, we developed a novel MR-compatible VR system for Assessment of UE motor functions (MR.VRA). Three different modes are provided adapting to a participant's appropriate levels of sensorimotor cortex impairment, including a unilateral-contralateral mode, a unilateral-ipsilateral mode, and a unilateral-bilateral mode. Twenty healthy subjects were recruited to validate MR.VRA for UE function rehabilitation and assessment in three fMRI tasks. The results showed that MR.VRA succeeded in conducting the fMRI tasks in the MR scanner bore while stimulating the sensorimotor neurons and mirror neurons using its embedded therapies. The findings suggested that MR.VRA may be a promising alternative for assessing neurorehabilitation of stroke patients with UE motor function impairment in MR environment, which allows inspection of direct imaging evidence of activities of neurons in the cortices related to UE motor functions.

Keywords: virtual reality, MR-compatible, mirror neurons, mirror therapy, sensorimotor neurons.

1 Introduction

In the past decade, virtual reality (VR)-based rehabilitation systems were already used in neurological rehabilitation. Its impressive immersion and interestingness stimulated neurologically impaired patients to finish robotically-facilitated repetitive functional practice [1]. Meanwhile, many VR-based rehabilitation systems have been proven to be effective and safe for the improvement of upper extremities (UE) motor functionalities [2-7]. Past studies revealed that stroke patients statistically showed better improvement using VR-based rehabilitation therapies compared with using occupational therapies and physical therapies [8-11]. Mraz et al. are pioneers in combining VR systems with magnetic resonance imaging (MRI) to measure brain activities [12]. Subsequent studies, also evident in functional neuroimaging research, have shown that VR-based rehabilitation systems are effective in boosting neuronal rehabilitation [13-15].

These VR-based rehabilitation therapies often integrate with the traditional physical therapies, motivating patients to actively engage in rehabilitation through immersive scenarios. Specifically, mirror therapy (MT) is a traditional rehabilitation therapy inspired by the mirror neuron (MN) theory [16]. MT was proposed to augment movement training in poststroke rehabilitation by showing patients the reflection of their unimpaired arm in a mirror setting [17], while the impaired limb not moving. VR-based MT not only retains the advantages of traditional MT but also overcomes its limitations. Conventional mirror therapies typically place a flat mirror in the median sagittal plane to induce visual feedback by a left-right reflection, patients need to physically lean their body to watch the reflection of their unaffected extremity in the mirror and imagine the movement of their affected extremity [18, 19], which is quite inconvenient. However, our previous studies, which combined VR with MT for the rehabilitation of UE motor function in post-stroke patients, effectively addressed this limitation [14]. In the immersive virtual environment, patients observe their affected extremity move just like the unaffected extremity does in reality during rehabilitation training. The findings based on longitudinal rs-fMRI data before and after using the VR-based MT suggest that the neuroscientifically grounded VR system benefits motor function rehabilitation in patients with motor nerve injury.

Nevertheless, none of these aforementioned rehabilitation systems was MR-compatible for use inside an MR scanner to evaluate the neuronal conditions of neurologically impaired patients on-the-fly when they were receiving the VR-based MT. To closely observe neuronal activities during the mirrored therapeutic training, we now have upgraded the VR-based MT into a newer VR system for UE motor functional assessment (MR.VRA) that incorporates MT and is compatible with an MR environment, so that real-time neuroimaging data including fMRI data during execution of a task can be collected. Three different task modes are provided adaptive to a participant's appropriate levels of sensorimotor cortex impairment, including a unilateral-contralateral mode, a unilateral-ipsilateral mode, and a unilateral-bilateral mode. Its design incorporated MT and provided participants game-based training and assessing tasks so that activations of sensorimotor neurons (SMN) and MN in a task-fMRI setting may be imaged in real time for follow-up investigations. Twenty healthy subjects were recruited to test whether the MR.VRA system may truly stimulate SMN and MN. We expected that the MR.VRA system may be well suited in an MR scanner setting and subsequently hypothesized that the activation of SMN and MN could be effectively observed during the VR-based MT tasks.

2 Materials and Methods

2.1 MR.VRA Hardware Design

The framework of the hardware system of MR.VRA (Fig.1) consists of the following components: (1) An MR-compatible liquid crystal display (LCD, http://www.sinorad.com); (2) An MR-compatible button box; (3) A signal-response controller (S/R controller); (4) A head coil mirror; (5) A high-performance computer. During operation, the VR scene is transmitted from the computer using fiber optics and displayed on the LCD placed behind the MR scanner bore. The S/R controller is used for signal communication between the MR scanner and the software running on the computer outside of the MR scanner room. It also ensures precise synchronization of data acquired from the scanner and the execution of the VR paradigm. Meanwhile, the MR-compatible button box relays any participant-initiated button actions to the computer via the S/R controller. This smooth and prompt exchange of information ensures real-time interactivity between the participant and the VR environment during the rehabilitation task. Throughout the entire process, the head coil mirror offers the participant a comfortable viewing angle of the MR-compatible LCD as the participant lies in the supine position.

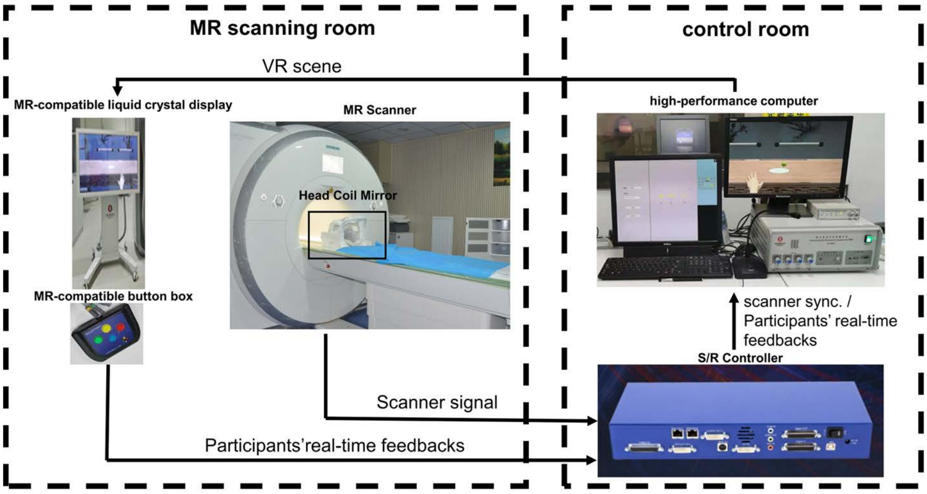


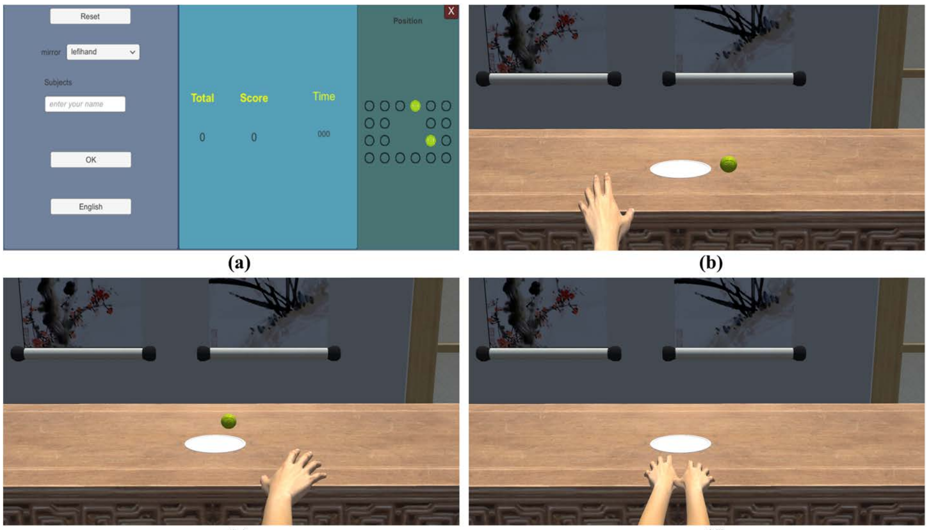
Fig. 1. An overview of the MR.VRA system's hardware logic. The arrows indicate the transmission direction of signal and data flows.

2.2 MR.VRA Software Design

Considering the cross-platform capability and flexibility of programming, we chose C# as the program language, Microsoft Visual Studio 2019 as the integrated development environment (IDE), and Unity-3D game engine (http://www.unity3d.com) as the graphics toolkit for developing the MR.VRA software system. MR.VRA was programmed to immerse the participant in a virtual room. Entering the virtual room, the participant would see a table in the front against a wall with a white basket atop it. During the VR tasks, a ball will show up for each trial at a particular location on the table, as designated ahead of the task by an investigator administering the VR task. The participant is required to control the virtual limb to grab the ball and put it into the white basket by operating the MR-compatible button box, using either the healthy arm or the impaired arm, if possible.

Three different modes are provided, tailored to accommodate each participant's appropriate levels of sensorimotor cortex impairment, including a unilateral-contralateral mode, a unilateral-ipsilateral mode, and a unilateral-bilateral mode. In the unilateral-contralateral mode (Fig.2(b), supposing the left-arm is healthy), a participant uses the healthy-side arm (unilateral) to control the opposite virtual arm (contralateral), which is in the contralateral side of the unaffected arm. This unilateral-contralateral mode is consistent with the previous version of VR-based MT that participants received in the rehabilitation hospital [14], and we now aim to examine using fMRI the activation of SMN and MN when participants are receiving the VR-based MT. The unilateral-ipsilateral mode (Fig.2(c)) was similar to the unilateral-contralateral mode, except that a participant uses the affected arm (only when basic motor functions have been more or less regained) to control ipsilateral virtual arm so that motor neurons in the injured cortices may be stimulated, activated and thereby seen in fMRI data. In the unilateral-bilateral mode (Fig.2(d)), a participant uses the healthy-side arm to control both virtual arms, which is an effective MT paradigm to help hemiplegia participants relearn bimanual cooperation [20]. This unilateral-bilateral mode seeks to help reestablish the functional connectivity across the two hemispheres between the bilateral motor cortices.

The user interface (Fig.2(a)) on the console allows a task administrator to set up the VR tasks with initial parameters, including choosing the task modes, designating locations where balls will pop up, and setting up the duration of the tasks. The console will also provide information for monitoring the execution of the tasks, such as elapsed time, task progresses and success rate.



(a) (b)

(c) (d)

Fig. 2. The interface and scenario of the MR.VRA software system. (a) The console user interface; (b) the unilateral-contralateral mode; (c) the unilateral-ipsilateral mode; (d) the unilateral-bilateral mode. These modes suppose the right-side arm unaffected. The virtual arms will be left-right exchanged when the unaffected arm is to the left side.

2.3 fMRI Experiments

Participants. Healthy volunteers were recruited through posters at the online Zhejiang University forum. The participants met the following inclusion criteria: (1) right-handed; (2) negative history of neurological or psychiatric disorder; (3) no medication history in the last 6 weeks; (4) adult (age 18 years and older); (5) normal or corrected to normal vision; (6) no contraindications to MRI scanning. The study was approved by the ethics committee of the Zhejiang Province People's Hospital. All participants were informed about the experimental procedure. A written informed consent was signed and obtained from every participant before enrolment into the study. In addition, standard MRI safety screening was performed before scanning for each participant.

Functional MRI Experiment Design. At least twenty healthy participants were to be recruited to ensure adequate statistical power for evaluating the usefulness of the MR.VRA system. We used healthy participants for observing activations of the neurons in the related brain regions because healthy brains may exclude bias that may possibly be introduced by diseased brains such as those of stroke participants. As stroke typically happens in one hemisphere, we chose the unilateral-ipsilateral and the unilateral-contralateral modes in the MR.VRA with a block-design. The first task employed the unilateral-ipsilateral task and the second task employed the unilateral-contralateral task, so that contrast of the activation pattern of SMN during the VR-based MT and MN potentially activated by observation only may be identified based on these two tasks.

The two tasks were arranged as the active blocks each followed by a black screen as resting blocks. One complete task lasted 900 seconds in total, including five 124-second active blocks alternated with four 70-second intervals of resting blocks. During the active blocks, a participant should finish three actions each time a ball popped up: reaching for the ball on the desk, grasping the ball and moving the ball to the white basket. While in the resting blocks, the MR-compatible display would show a black screen and the participant should keep arms relaxed and motionless.

Data preprocessing and analysis. A 3T MRI scanner (SIEMENS MAGNETOM Prisma, Erlangen, Germany) was used to acquire MRI data. High-resolution T1-weighted MRI data were prescribed using a 3-D FLASH sequence with the following parameters for the purpose of anatomical overlay and spatial registration: repetition time (TR) = 2300ms, echo time (TE) = 2.32ms, matrix = 256 × 256, field of view (FOV) = 240 mm × 240 mm, flip angle (FA) = 8º, slice thickness = 0.9 mm, voxel size = 0.9 mm × 0.9 mm × 0.9 mm voxel size. A T2∗ weight single-shot gradient-recalled echo planar imaging (EPI) sequence was adopted to obtain fMRI data: Number of volumes=900, TR=1,000ms, TE=34.00ms, matrix=64×64, FOV = 230 mm × 230 mm, FA = 50 º, slice thickness = 2.5 mm, voxel size= 2.5mm× 2.5 mm × 2.5 mm. Total scanning time = 33 min 12 sec.

Contrast regarding in blood oxygenated level dependency (BOLD) in fMRI data associated with the performance of the tasks were assessed on a pixel-by-pixel basis, using the general linear model and the theory of Gaussian field [21]. The imaging data were processed using SPM12 (Statistical Parametric Mapping, Wellcome Department of Imaging Neuroscience, UCL, London, United Kingdom). Firstly, gradient-echo echo-planar imaging (EPI) scans were spatially aligned to the first scan to correct head motion. Subsequently, all images were spatially normalized to the Montreal Neurological Institute (MNI) standard brain space and then smoothed using an isotropic Gaussian filter with a 7 mm full-width-at-half-maximum (FWHM) kernel. An fMRI dataset was retained for subsequent statistical analysis if the maximum translation detected in the images were less than 3.0 mm in any of the x, y, and z directions and the maximum rotation was less than 3 degrees along any of the axis.

Data analysis included two stages, a first level of single subject analysis and a second level of multi-subject analysis. In the first-level analysis, a standard hemodynamic response function was applied to analyze fMRI BOLD signal differences, implemented with general linear model (GLM) in SPM12. Contrasting the data of active blocks with those of the resting blocks, a T-map was obtained for each participant, highlighting the brain activations or deactivations in the related task. Whole-brain activation maps were thresholded at $P < 0.05$, family wise error (FWE) corrected. In the second-level analysis, the beta coefficients based on the linear regression in the first-level analysis were converted to P-values using one-sample t-test to observe the significant level, thresholded at $P < 0.05$ FWE corrected and minimum cluster size = 50 voxels. Brain regions were identified using the Brainnetome atlas [22] and the peak activations were reported in the MNI coordinates.

3 Results and Discussion

This study finally recruited twenty healthy volunteers (11 males and 9 females, aged 21-28). Participants' task-fMRI outcomes are depicted in Fig.3. One participant was excluded because of her intolerance of the scanner noise and consequently incompleteness of her dataset. Therefore, data from nineteen participants (11 males and 8 females, age = 24.5±2.07years) entered the final statistical analysis.

During the unilateral-ipsilateral task, we observed significantly increased fMRI activation in key brain regions(Fig.3): the precentral gyrus (PreCG), with peak activation at MNI coordinates (-40, -18, 61) and t-value= 17.23; the postcentral gyrus (PoCG), with peak activation at MNI coordinates (-35, -29, 55) and t-value= 16.62; the supplementary motor area (SMA), at MNI coordinates (-9, 1, 54), t-value= 13.96; the inferior parietal lobule (IPL), at MNI coordinates (-37, -40, 43), t-value= 12.32; and the superior parietal lobule (SPL), at MNI coordinates (-27, -54, 65), t-value= 15.81. Similarly, in the unilateral-contralateral task, we noted significant activation in the PreCG, at MNI coordinates (38, -19, 54), t-value= 16.35; the PoCG, at MNI coordinates (43, -24, 40), t-value= 16.71; the SMA, at MNI coordinates (-7, 0, 54), t-value= 11.94; the IPL, at MNI coordinates (-45, -32, 40), t-value= 9.64; and the SPL, at MNI coordinates (-20, -56, 64),t-value= 13.76.

These sensorimotor areas have been proven to play a pivotal role in somatosensory and motor recovery post-stroke [23], with variable activation levels discerned based on stroke participants' recovery stages. The results infer with confidence that MR.VRA will be able to effectively assess UE motor function in patients with sensorimotor cortex impairment.

Additionally, the 19 usable fMRI datasets showed that MN were activated effectively by executing the unilateral-ipsilateral and unilateral-contralateral tasks, indicating normal MN functionalities in these healthy subjects. While the test involved only healthy subjects, no significant difference in the neuronal activation pattern was seen between the data of their unilateral-ipsilateral and unilateral-contralateral tasks. Although some activations with relatively low t-scores were visible in the brain of unilateral-ipsilateral task, they were not seen in the unilateral-contralateral task. Therefore, we reasonably expect to see neuronal activation deficits in the brain regions of participants with impairment of UE motor functions, compared with those of the health participants. This supposition is fortified by our previous rs-fMRI studies' results that acquired longitudinal data before and after training the stroke patients using our past version of VR paradigm [14, 15], without MRI-compatibility.

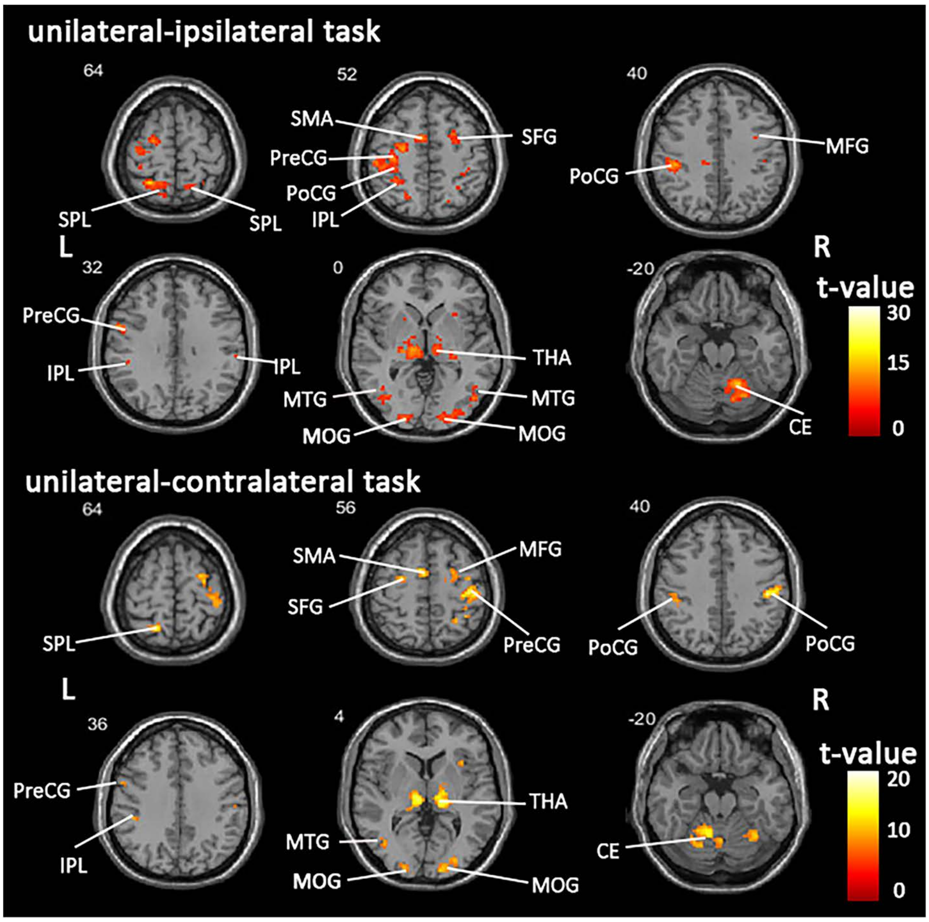


Fig. 3. Clusters of voxels with statistical significance resulted from the data of the unilateral-ipsilateral task (MNI coordinates are Z = 64, 52, 40, 32, 0, -20) and the unilateral-contralateral task (MNI coordinates are Z = 64, 56, 40, 36, 4, -20). The color spectrum from red to yellow represents the increasing levels of t-value ($P < 0.05$ FWE corrected, cluster ≥50 voxels). SMA:Supplementary Motor Area; preCG: Precentral Gyrus; poCG: Postcentral Gyrus; MOG: Middle Occipital Gyrus; MFG: Middle Frontal Gyrus; SFG: Superior Frontal Gyrus IPL: Inferior Parietal Lobule; MTG: Middle Temporal Gyrus SPL: Superior Parietal Lobule; THA: Thalamus; CE: Cerebellum; FWE: family wise error.

4 Conclusion

In this study, we developed a novel MR-compatible system, MR.VRA, incorporated with MT for UE motor function assessment and rehabilitation level evaluation. Preliminary experiments using a group of healthy volunteers have shown that the system indeed may help monitor the neuronal activities in SMN and MN in a task imaging procedure. We therefore expect that MR.VRA may become an effective alternative for investigators to study neuro-mechanisms of UE motor function rehabilitation, particularly in participants who recently experienced stroke, cerebral palsy, multiple sclerosis, or spinal cord injury.

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Disclosure of Interests. The authors declare that there are no conflicts of interest regarding the publication of this paper.

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