Design of an fMRI Compatible System to Explore Neural Mechanisms Subserving VR Therapies

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Abstract— **Since most functional activities of daily living, involving the upper-extremity, are bilateral in nature, a rehabilitation system with functionally integrated activities could result in stronger training effects on the sensorimotor abilities of patients. The virtual reality piano trainer, described here, incorporates bilateral and multi-joint movements to exercise the hands, wrists and forearms. In an effort to better describe the underlying mechanisms that may be driving improvement from virtual reality therapies, and to more effectively develop such activities, a pilot fMRI study exploring simple VR tasks and preliminary data are introduced in this paper.**

I. INTRODUCTION

GUIDED by the understanding of the plasticity of the nervous system and the relationship of that plasticity to motor learning principles regarding frequency of use, task specificity, skill development and practice parameters, a computerized virtual reality exercise system was developed to provide intensive motor re-education and skill reacquisition in the hemiplegic hand of patients post-stroke [1,2,3]. Because of the complex sensorimotor control required for grasping and manipulating objects, even mild to moderate deficits in upper extremity control can impair most activities of daily living, especially when there is a loss or diminution of hand function. This is an important but difficult and challenging aspect of rehabilitation. Utilizing this system, patients post-stroke improved and retained gains made in range of motion, speed and isolated use of the fingers after training with this system [2]. These changes translated to improvements in real-world outcome measures.

When developing the activities for the original upper extremity VR studies, exercises were selected that involved discrete movements designed to train a single movement parameter at a time (e.g., range of motion). We assume that more functionally integrated activities could result in stronger training effects on the sensorimotor abilities of patients. The system was designed to train manipulative functions of the hand; however, because of the interdependence between the transport and object manipulation phases of prehension [4], training the upper extremity as a unit may lead to improved outcomes. Additionally, although treatment benefits have been reported with unilateral robotic-assisted training [5] and training in a VR environment [3,6], most functional activities involving the upper extremities are bilateral in nature. Bernstein [7] believed that the upper extremities are centrally linked and function as a coordinative structure. Since there is this tendency for synchronization and coupling between limb movements, specifically a coupling between the kinematic attributes of frequency, direction and amplitude, it has been suggested that facilitation of this inherent interlimb coordination might improve functional therapeutic outcomes [8]. Several researchers have used bilateral training to harness these spatial and temporal interactions [9,10,11,12].

However, none of these utilized virtual reality to provide engaging, motivating and adaptable training algorithms. A new system, described here, provides a bilateral, functional interface to exercise the hand, wrist and forearm as an integrated unit, or to train each pivot independently.

There are an ever increasing number of studies using virtual environments for motor rehabilitation. It is therefore timely to consider what underlying mechanisms may be driving these improvements. Many animal and human studies have shown activation of the motor cortex while observing the motor actions of others, in the absence of overt motor activity [13,14,15]. It is possible that this proposed “mirror neuron system”, thought to involve a complex network formed by various areas including the ventral premotor area, the inferior parietal area and the superior temporal area, may underlie many of the effects that we are getting in VR-based rehabilitation. It is reasonable to assume that use-related neural plasticity is not necessarily limited to reorganization of the primary sensorimotor cortex but would also include other higher level areas related to sensorimotor processing and control. However, it is not clear whether observation in a virtual environment will affect neural processing in a similar manner to observing real hand actions. Some studies have proposed that they do not [16], though it is important to consider whether one is just watching an action, even a realistic natural movement, or whether one attributes the

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observed action to oneself. For the purposes of using virtual environments for motor re-education it is important to understand the underlying neural mechanisms subserving VR therapies.

We will describe the development of a VR exercise system to incorporate bilateral and multi-joint movements. We also hypothesize that, over time, training in VR will generate a sense of being causally involved, inducing a feeling of ownership of the virtual hand. A second aim is to present preliminary results using fMRI to investigate this hypothesis.

II. METHODS

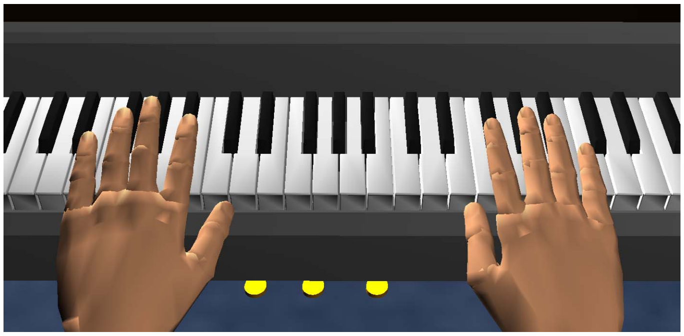
A. *Description of Training System*

In response to the need for a system that integrates a range of bimanual activities, the VR Piano Trainer was developed (Figure 1). This consists of a complete virtual piano which will play the appropriate notes as they are pressed by the virtual fingers. The position and orientation of both hands as well as the flexion and abduction of each of the fingers are recorded in real time and translated into movement in their three dimensional counterparts. The virtual environment was developed using Virtools [17] with the VRPack plugin which communicates with the open source VRPN (Virtual Reality Peripheral Network) [18]. The VRPN Server was modified to allow for additional devices which are not currently in the supported library. The game architecture was designed so that various inputs can seamlessly be used to track the hands as well as retrieve the finger angles. Currently it supports the use of a pair of Immersion Cybergloves [19] with the Ascension Flock of Birds [20]. The 5DT fMRI compatible glove [21], which uses fiber optic sensors to avoid interference with the magnet, has also been implemented for use in appropriate studies. The game may be used with or without hand tracking and we are investigating the use of MRI compatible tracking devices.

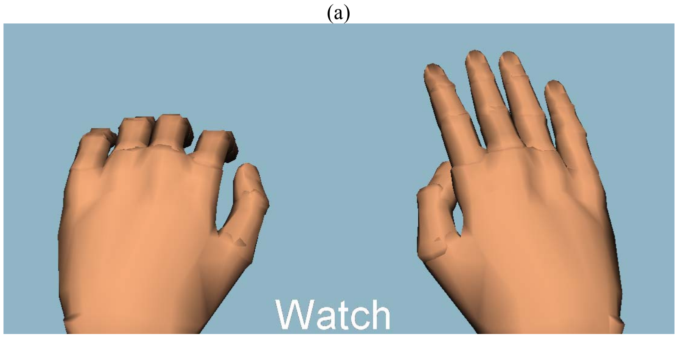
Fig. 1. Virtual Reality Piano Trainer

B. *Description of the fMRI experimental system*

To investigate the underlying role of VR in facilitating movement, a task-based virtual reality simulation was developed for use in an fMRI. Specifically, the fundamental elements of the training system, the VR representations of the user's hands, are shown to replicate the visual feedback during training activities (Figure 2). This virtual environment, also developed with Virtools utilizing the VRPN, presents various tasks to the user while displaying the scene. The subject wears a 5DT fMRI compatible data glove while inside the magnet. With the 5DT glove, finger articulation was measured during the task and used to translate into the hand movement within the simulation. Finger angles are stored for correlation with brain activation.



(a)



(b)

Fig 2. a) Subject View during Training Exercise
b) Subject View during fMRI Experiment.

The subjects perform specific manual tasks moving in response to the images and word commands. Figure 2b shows a typical display consisting of two virtual hands and a command. During the **WATCH** task, the subject is to remain still while watching an animation of a hand opening and closing. The **MOVE** task required that the user copy the open and close movement with their right hand. During this task, the subject would either see hands moving in response to their movements or would see only non-anthromorphic shapes. Finally, a **REST** task was implemented where there would be no change in visual stimulation and the subject was to keep their hands still.

C. *Protocol*

The fMRI compatible data glove was worn by the subject in the magnet and was plugged into a PC in the control room which ran the simulation. The simulation was displayed through a projector behind the magnet. While inside the MRI, subjects could view the simulation through a mirror placed above their eyes. The data glove was calibrated by verbally cueing the subject to open and close their hands. Only visual commands were used once the trial began.

During each trial, the subject was presented with a sequential set of tasks as specified above. These tasks were timed deliberately so they could be identified within the data (Figure 3). While the glove would only translate the finger movement into visual movement during specific tasks, the data were recorded during the course of the entire trial. These data were then used to verify how a subject was moving, or not moving, during specific tasks throughout a trial.

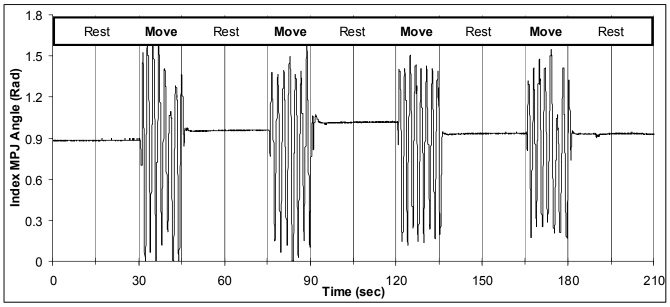


Fig. 3. Index MPJ Kinematics Data During fMRI Trial

In this pilot study, the control subject was presented with a task to perform in the MRI environment, and in the analysis, changes relative to a control state were mapped. Eight experimental runs were conducted each consisting of four fifteen second test tasks alternating with 30 second rest periods (Figure 3). Thirty-second rest periods assure brain activation settles to baseline while all task conditions are of equal duration. During the baseline rest condition, the subject was looking at motionless VR hands. The following are the three task conditions:

1) Watching the movement of the VR hands with the intention to imitate that movement

2) Subject moving hand while watching VR hands move in relation to their movement.

3) Subject moving hand while watching non-anthropomorphic shapes on the screen.

For this study, Trials #1 and #8 were run with **Condition 1**; Trials #2 and #3 were run with **Condition 2**; Trials #4 and #5 were run with **Condition 3**. (A fourth condition, tested in trials #6 and #7, is not covered in this paper) Aside from the placement of **Condition 1** trials, the order of conditions will be counterbalanced across subjects.

Images were obtained using a 3T Siemens Allegra imaging system. Single shot gradient echo (GE) axial EPI images (64×64, TR=1s, TE=27 ms, FOV= 22cm x 22 cm, slice thickness = 4 mm, 32 slices) were acquired over 105 data points (210 seconds). Each trials started with 30 seconds of baseline condition followed by 15 seconds of task condition and was done four times.

D. Data Analysis

Data were processed using the AFNI software package. The presence of any head motion induced signal changes was detected using image registration algorithm. Because the data collected especially from naive subjects are susceptible to head motion, all data used in this study was analyzed for the presence of motion-induced artifacts. In our experience, foam padding considerably reduces head motion and allows only small motions. While a large number of algorithms exist for the detection (and correction) of mis-registered images, a contour-based cross-correlation algorithm [22] was used for detecting the presence of any head motion. It is believed that this method is an improvement over earlier registration algorithms used in FMRI. A contour image of the first image in each data set was used as a reference and the motion estimated for every other image in the data sets. The estimated motion was tabulated as a function of time for each subject and for each data set. The statistical significance of differences in estimated head motion comparing each scan for every subject was calculated. An alternative automated image registration (AIR) technique developed by Woods et al, [23] that uses an iterative procedure to minimize the variance in voxel intensity was also used. Because this study involves small signal changes, data sets that exhibit head motion were corrected for motion prior to further analysis and any data set with motion of more than 2 pixels was discarded.

Task-induced signal changes were analyzed by cross-correlation, assuming that neuronal activity and FMRI task-induced signals change proportionally with the stimulus paradigm. In this method, the number of activated pixels is calculated for each activation correlation coefficient threshold. A synthesized box-car waveform corresponding to the stimulus presentation is cross-correlated with all pixel time courses on a pixel-by-pixel basis to identify regions activated by the task. The statistical significance p is calculated using a semi-empirical method that was described in an earlier paper [22] and is summarized here. The ideal reference waveform used for cross correlation FMRI analysis of filtered task-activation pixel time courses is applied to all filtered pixel time courses in the resting-state data set. The standard deviation of the distribution of the resting-state correlation coefficients is typically somewhat less than 0.1. A threshold of 0.5, five times the standard deviation, would lead to $p<0.0001$ rigorously if the resting-state data exhibited a normal distribution and both the resting-state and task-activation time courses were filtered in the same way. The histogram of the correlation coefficient values obtained when the ideal reference waveform is cross-correlated with filtered resting-state pixel time courses appears to be normal, which is the justification for the semi-empirical approach. All pixels that pass the threshold in the data set are considered activated and their locations noted.

A finite impulse response (FIR) low-pass filter with a cut-off frequency at 0.1 Hz has been designed to attenuate the fundamental respiratory and other high frequency noise components. Although the respiration frequency can be reliably filtered, the heart rate (which is typically in the range of 57-63 cycles/minute) will be aliased for FMRI data sets with longer TR times. Although the effects of aliasing is a concern, no significant problems have been detected in our work.

III. INITIAL RESULTS

Figure 4 shows the brain related activity for the three different conditions relative to the baseline rest condition. To test whether the subjects developed a sense of agency [24] with the VR hands and became causally involved we compared **Condition 1**, "watching the movement of the VR hands with the intention to imitate that movement (OTI)" pre and post training. During pre-training (Trial 1, OTI: Fig. 4a) there was minimal activation relative to the baseline. In post-training, activation can be seen in the insular cortex (Trial 8, OTI: Fig.4d). Figures 4b and 4c compare the differences in activation between the patient moving while watching the VR hands move and moving while watching non-anthropomorphic shapes. There is greater activation in the insula during the VR hand simulation (Fig. 4b) when compared to the minimal activation during the non-anthropomorphic shape simulation (Fig. 4c).

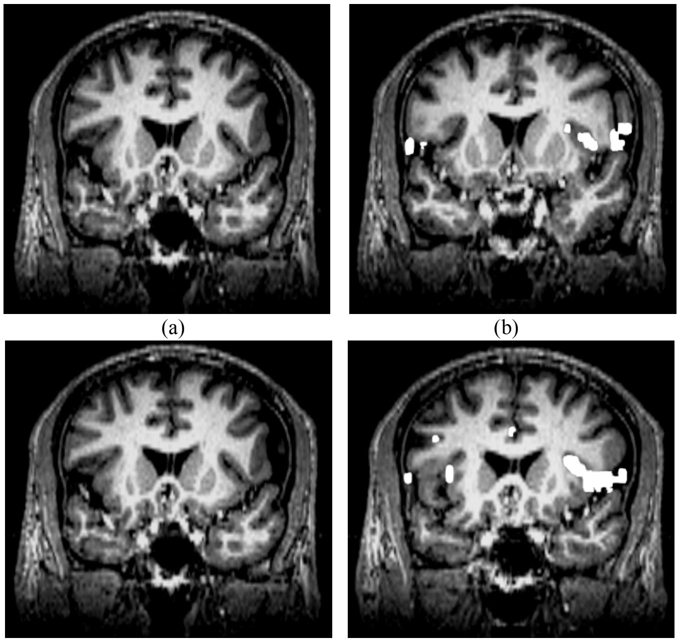


Fig. 4. Four coronal sections$^+$ showing activity associated with: **a)** Observation of moving VR hands with intention to imitate that movement, Pre Training; **b)** Right hand movement and observation of VR hands moving in relation to hand movement; **c)** Right hand movement and observation of non-anthropomorphic shapes; **d)** Observation of moving VR hands with intention to imitate that movement, Post Training; Sections in B and D show increased activity above the baseline in the insular cortex (highlighted in white). Right side of the brain is shown on the right.

IV. DISCUSSION

The goal of this initial work was to develop a bilateral system to be used in the rehabilitation of patients post stroke. The piano provides a realistic bilateral functional activity where both the proximal and distal components of the upper extremity can be trained either as an integrated unit or as individual components. Rehabilitation training in a virtual environment can provide an appropriate interactive, challenging and encouraging environment where a subject can practice repetitively, execute tasks and be guided and rewarded through systematic feedback. During the past few years, virtual environments have been used experimentally for rehabilitation. This piano simulation will provide an environment in which the patient can learn a new skill. This is a realistic simulation in that one feels the sense of immersion, is rewarded with real world auditory feedback through appropriate piano sounds and visual feedback through movement of the keys. Finger, hand and arm movement can be trained using this simulation. Additionally adaptive algorithms will drive the patient to perform at increasing higher levels while kinematic measures will provide important performance outcomes.

In a recent study involving stroke patients, a shift from primary to secondary motor networks was observed corresponding to the level of impairment of the corticospinal system. Both hemispheres were engaged in the generation of motor output. Secondary motor systems including bilateral premotor cortex, supplementary motor area, intraparietal sulcus, as well as dorsolateral prefrontal cortex and contralesional superior cingulate sulcus, are important for effective motor output when there is impaired function of the corticospinal system [25]. We are interested in whether skill, developed during training in a VR environment, will activate these secondary areas. This could be a potentially facilitory mechanism for training induced recovery of motor function. However, we hypothesize that for VR systems to be able to activate these secondary motor areas it has to first induce a sense of agency of the virtual limb model. This sense of agency, the feeling of being involved in an action and of attributing that action to ourselves, appears to be related to the degree of concordance between the intent of the movement and the sensory feedback related to actual movement; in other words to the feeling of control of the action [24]. This is thought to be a continuous mechanism, the greater the sense of agency the greater the activation in the right posterior insula. It is not known whether observation of VR hand models can induce this sense of agency. We have shown in this preliminary fMRI study that after training in a virtual environment the insular cortex showed greater activation than before training. This was evident when the subjects were moving while watching the VR hands (Trial 2, Figure 4b) but not when they were moving while watching non-anthropomorphic shapes (Trial 4, Figure 4c) and by the end of training (Trial 8, Figure 4d) even when they were watching the VR hands with only the intent to imitate. These results suggest that the increased activation in Trial 2 is not simply a result of movement and that the insular activation in Trial 8 is perhaps a result of the subject's development of a feeling of association with, or control of, the movement of the VR hands.

V. CONCLUSION AND FUTURE WORK

This preliminary study suggests that when provided with concordant feedback, VR has the potential to induce a sense of control of the virtual movements. In future work we will further investigate whether this finding is consistent and whether secondary motor areas are activated through training in a VR environment.

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