ABSTRACT

SENSORIMOTOR EXPERIENCE IN VIRTUAL ENVIRONMENTS

by
Katherine Grace August

The goal of rehabilitation is to reduce impairment and provide functional improvements resulting in quality participation in activities of life. Plasticity and motor learning principles provide inspiration for therapeutic interventions including movement repetition in a virtual reality environment. The objective of this research work was to investigate functional specific measurements (kinematic, behavioral) and neural correlates of motor experience of hand gesture activities in virtual environments stimulating sensory experience (VE) using a hand agent model. The fMRI compatible Virtual Environment Sign Language Instruction (VESLI) System was designed and developed to provide a number of rehabilitation and measurement features, to identify optimal learning conditions for individuals and to track changes in performance over time. Therapies and measurements incorporated into VESLI target and track specific impairments underlying dysfunction. The goal of improved measurement is to develop targeted interventions embedded in higher level tasks and to accurately track specific gains to understand the responses to treatment, and the impact the response may have upon higher level function such as participation in life. To further clarify the biological model of motor experiences and to understand the added value and role of virtual sensory stimulation and feedback which includes seeing one's own hand movement, functional brain mapping was conducted with simultaneous kinematic analysis in healthy controls and in stroke subjects. It is believed that through the understanding of these neural activations, rehabilitation strategies advantaging the principles of plasticity and motor learning will become possible. The present research assessed successful practice conditions promoting gesture learning behavior in the individual. For the first time, functional imaging experiments mapped neural correlates of human interactions with complex virtual reality hands avatars moving synchronously with the subject's own hands. Findings indicate that healthy control subjects learned intransitive gestures in virtual environments using the first and third person avatars, picture and text definitions, and while viewing visual feedback of their own hands, virtual hands avatars, and in the control condition, hidden hands. Moreover, exercise in a virtual environment with a first person avatar of hands recruited insular cortex activation over time, which might indicate that this activation has been associated with a sense of agency. Sensory augmentation in virtual environments modulated activations of important brain regions associated with action observation and action execution. Quality of the visual feedback was modulated and brain areas were identified where the amount of brain activation was positively or negatively correlated with the visual feedback. When subjects moved the right hand and saw unexpected response, the left virtual avatar hand moved, neural activation increased in the motor cortex ipsilateral to the moving hand. This visual modulation might provide a helpful rehabilitation therapy for people with paralysis of the limb through visual augmentation of skills. A model was developed to study the effects of sensorimotor experience in virtual environments, and findings of the effect of sensorimotor experience in virtual environments upon brain activity and related behavioral measures. The research model

represents a significant contribution to neuroscience research, and translational engineering practice. A model of neural activations correlated with kinematics and behavior can profoundly influence the delivery of rehabilitative services in the coming years by giving clinicians a framework for engaging patients in a sensorimotor environment that can optimally facilitate neural reorganization.

SENSORIMOTOR EXPERIENCE IN VIRTUAL ENVIRONMENTS

by
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To my beloved family, friends, and teachers

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"The mind is its own place, and in itself can make heaven of hell, a hell of heaven."
John Milton

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CHAPTER 1

SENSORIMOTOR EXPERIENCE IN VIRTUAL ENVIRONMENTS

1.1 Introduction

The present research investigated whether visual sensorimotor experience in virtual environments (VE) may be suitable to provide stimulation and feedback that is differential to moving the hand with no visual feedback at all, that is, whether interacting with the virtual hands avatar was somehow more compelling than exercising with no hand-related visual stimulus and feedback during execution of simple observation, observation with intent to imitate (OTI), and imitation execution tasks and how manipulations of visual feedback during interaction in a virtual environment affect neural activation in the brain. It is believed that through understanding behavior, kinematics, and neural activations, motor skills acquisition and rehabilitation strategies advantaging the principles of plasticity and motor learning will become possible and that many of the tasks and sensorimotor experience required to establish the desired exercise conditions may be realized through a VE. To understand the added value and role of concurrent and selectively modulating visual stimulation and feedback which includes motor skills practice while seeing one's own hand movement actuating the virtual hands proxy, healthy controls and a subject who suffered a stroke participated in experiments. In the present research, subjects used virtual reality teachers avatars in 1st and 3rd person perspective to observe and imitate, and virtual hands avatar 1st person hand proxies representing their own hands, in imitation exercises in the behavioral laboratory and also in the MRI where behavior and brain activations were recorded and analyzed. Gloves with sensors recorded the subjects' hand movements and the kinematic data collected were used to generate concordant and modulated visual feedback experience in the virtual environment, and to assess motor output of the subjects. For the first time, subjects were able to observe their own hands actuating complex motion of virtual reality hands while behavioral and kinematic measures, and neural correlates were recorded in real time. Implications of this research span a wide range of fields and applications.

Activation of neural pathways over time has been associated with plasticity-based changes in brain networks and together with motor learning principles provides inspiration for motor skills acquisition strategies and therapeutic interventions including close-to-normal movement repetition in a VE. For Aim 1, the fMRI compatible Virtual Environment Sign Language Instruction (VESLI) System was designed and developed to provide a number of interactive hand gesture imitation activities spanning various levels of difficulty and incorporating assessment and measurement features, to identify optimal learning conditions for individuals as well as to track changes in performance over time in training and research conditions. Elements of the system provided simple and complex hand gesture tasks such as action observation and action execution, and parametrically modulated stimulating visual sensory experience in (VE) using 1st and 3rd person perspective virtual agent models and a 1st person perspective virtual hands proxy. Therapies and measurements incorporated into VESLI present task-oriented training within the conscious control of the subjects, and target and track specific impairments underlying hand motor dysfunction to monitor specific gains and to more fully understand the individual's response to treatment, and the impact the response may have upon higher level function such as participation in life. Participation in life is essential to quality of life.

There is a need for effective therapy for the hand. Early intervention is associated with reduced loss of cortical representation, yet many patients are not capable of producing satisfactory movements required for close-to-normal function in intense and repetitive exercise sessions. In the absence of visual feedback that matches the intention and expectation of the severely impaired patient, sensorimotor experience in VE might be capable of providing safe and appropriate task-based sensory stimulation and feedback to extend available therapies and to introduce new neural plasticity-based therapy approaches. It is important to understand whether a virtual agent model and virtual hands avatar may be accepted as a proxy for visual sensory experience observation and feedback during exercise while imitating simple and complex hand gestures or performing other tasks. It is also important to understand whether and under what circumstance VE model observation actuates action-observation action-execution brain networks as will observation of real world human actions.

To investigate this important VE motor skills acquisition tool, and to see if this tool may offer some advantage through observation of the avatar model and of the avatar proxy hands replacing the subject's own hands, over exercising the hands without accurate visual feedback of the real world hands, a series of functional MRI experiments was conducted. In Aim 2, the present research investigated activation of brain networks associated with observation and imitation of hand gestures in the VE. There were three main findings. Observation with intent to imitate (OTI), and imitation with real-time virtual avatar feedback, were associated with activation in a distributed frontoparietal network typically recruited for observation and execution of real-world actions. Second, a time-variant increase in activation in the left insular cortex for OTI actions performed by the avatar was noted. Third, imitation with virtual avatar feedback (relative to the control condition) was associated with a localized recruitment of the angular gyrus, precuneus and extrastriate body areas, regions which are (along with the insular cortex) associated with the sense of agency. Data suggest that the virtual hands avatar may have served as a disembodied training tool in the observation condition and as embodied "extensions" of the subject's own body (pseudo-tools) in the imitation condition. Importantly, activation of secondary motor regions significantly increased during the move condition while seeing virtual hands avatar movement compared with the control condition, move while watching non-anthropomorphic shapes. Activation of these important secondary motor regions is associated with successful recovery of movement in patients with cortical injuries. These data advance the understanding of brain-behavior interactions when performing observation or actions in VE and have implications in the development of observation and imitation based VE motor skills acquisition or rehabilitation paradigms.

In Aim 3, parametrically modulated quality of visual feedback was investigated. Activation remained present in the insular cortex indicating that the subjects maintained a sense of agency throughout the visual sensory modulations. However, the angular gyrus and the premotor cortex activation were negatively correlated with the amount of distortion introduced to the visual sensory feedback. Variations in gain observed as a manipulation of visual feedback elicited changes in brain activation although subjects did not change the actual movement of hands confirmed by kinematic measures. Lost quality of the visual feedback appears to have a negative impact on the recruitment of motor planning and action observation regions of the brain. In the behavioral portion of this experiment, subjects were able to accurately report that the quality of the visual feedback had been modified during the exercises. These conditions with distorted visual feedback appear to deny the brain of important sensorimotor stimulus associated with performance and might be further investigated as a mechanism of learned disuse.

In Aim 4, a model for Mirror Virtual Therapy, or MVT was explored in a functional MRI experiment. In order to provide a meaningful visual feedback for a patient's movement with motor dysfunction such as hemiparesis, kinematics of the less affected hand might be used to generate visual sensory mirror image to serve as a proxy for the impaired hand in a number of diverse exercises in VE. Subjects moved the right hand, and saw the left virtual hand proxy move. Brain activations were relateralized resulting in activation of primary motor cortex ipsilateral to the moving hand. In other words, when the subject moved his or her right hand, and saw the left virtual hand move, brain activation associated with moving the left hand was observed. In order to determine if this protocol for treatment might be feasible for use with patients with motor dysfunction, a patient who suffered from stroke was included in the study. The same ipsilateral activation was observed when the patient performed the Mirror Virtual Therapy (MVT). The data indicate that once a relationship is developed between the subject and the virtual hands avatar, they may serve as a proxy and may enable modulations of sensorimotor experience to selectively activate important real world movement related brain regions. Consequently, accurate visual feedback of the dysfunctional limb, not possible in the real world, may be created using VE for the benefit of therapy.

In Aim 5, guided by the discoveries in Aims 2, 3, and 4, subjects observed with intention to imitate, and practiced complex hand gestures in a VE. Unlike the experiments in Aims 2, 3, and 4 wherein simple finger flexion sequencing was studied, in Aim 5 subjects imitated complex intransitive gestures. They observed a first and third person avatar model demonstrate gestures while descriptions were presented as either text or picture. The hand view treatment conditions were: see own hands, hidden hands, and see virtual hands. Findings indicated that control subjects were able to exercise in all conditions presented. Recall performance improved when exercising with the virtual hands avatar when gesture definitions were presented as pictures and when recall condition remained the same. The present research assessed successful practice conditions promoting gesture learning behavior in the individual. The VESLI system performed as designed, providing a flexible complex gesture exercise environment with multiple visual augmentation stimulus and feedback conditions, and capable of measuring performance of subjects in the experiment and during exercise.

In conclusion, an investigation was conducted to determine whether simple hand observation, observation with intent to imitate, and motor execution practice rendered in a VE can provide a skills acquisition environment for simple and complex hand gestures. Via both means – behaviorally and through functional MRI -- modulated task and visual sensory experience were investigated. A series of experiments was conducted to investigate the unique properties that might be present as a consequence of exercising in VE with the virtual hands avatar as a teacher model and proxy, and with modulated visual sensorimotor experience. For the first time, subjects were able to observe the visual feedback of their own hands actuating complex hand proxies in VE representing an analog of motor skills acquisition and rehabilitation-like activities while inside the MRI environment. The investigation determined that training in this VE with visual sensory feedback can engage brain network activations known to be involved with the sense of agency, and can also engage brain networks similar to those found during action-observation and action-execution in the real world. Resulting behavior and associated kinematics were examined and unique brain network activations were mapped. Being able to view modulated visual feedback of one's own hands actuating a virtual hands proxy during motor practice of hand gesture imitation in the functional MRI environment and in the laboratory establishes a unique method of studying potential mechanisms of action-observation and action-execution brain networks. Some of these methods might prove useful in motor skills acquisition, exercise, and may easily translate to rehabilitation environments.

Visual stimulus in VE was successful in actuating important action-observation action-execution brain networks and in establishing in the subjects a sense of agency. Modulating the visual feedback in VE selectively influenced the activation of the motor skills associated brain networks. Lost quality in the visual feedback reduced the desired brain activation. These are compelling findings and also establish a credible case for use of virtual body part avatars and visual modulations in VE with valuable applications in motor skills acquisition, exercise, and rehabilitation.

A research and exercise model was developed to study the effect of visual sensorimotor experiences in a VE on brain activity and related behavioral and kinematic measures linked to high level quality of life measures. Such a model can profoundly influence development of human computer interfaces and the delivery of motor skills acquisition, exercise, and rehabilitative services in the coming years by giving clinicians a framework for engaging patients in a sensorimotor environment that can optimally facilitate exercise and neural reorganization. The present research may hold particular value for designing tasks and environments that promote exercise, visual sensory therapies, and passive therapies for patients with paralysis from various motor conditions including stroke.

Results of this research may translate to important and often overlooked applications such as VE-based neuro-rehabilitation of hand motor skills.

1.2 Statement of the Problem

A goal of the present research was to investigate the possibility that virtual sensory experience engages the subject so as to actuate target brain networks through task design and visual sensory modulation, and to provide safe and motivating exercise to promote plasticity and motor skills acquisition. Many aspects of the neural systems involved in sensorimotor experience in VE's and how the experience compares with real world interactions, remains unknown. There are researchers who indicate that virtual elements are not effective in actuating target motor related brain regions in the way real world action-observation action-execution does. Heretofore, technology limitations have prevented investigations of the neural mechanisms of the observation (of the movement of others), imitation (with observation of one's own movement), together with observation with intent to imitate (OTI) and also the resulting stimulation of important motor skills and learning related networks, in the functional imaging environment. An fMRI compatible VE with features appropriate for action-observation action-execution of simple and complex hand gestures would enable behavioral and brain mapping experiments. Such a system would enable investigation of the potential for carefully crafted action-observation action-execution experience in VE to elicit effective activation of target brain regions in humans in health and in cases of ageing or injury, in some desired way. The activation of brain networks over time is associated with brain plasticity. Once such a VE system is developed, specific modulations of visual sensory experience in VE may be explored to determine effectiveness in recruiting target brain regions with specific visual modulations, and to track behavior, kinematics, and outcomes. In addition, recipes may be configured in association with various user groups and applications, to achieve desired outcomes. Also in future research, individuals and groups may be studied to determine prognostic indicators and to predict effectiveness of specific recipes to achieve the desired goals. Then in the future, the same research model can be used to investigate protocols, doses, and durations of treatment, other anatomic and functional regions, and combinations, linking connectivity, injury, prognostic indicators, prescription, target brain networks, behavior, and outcomes.

1.3 Hypotheses

The first hypothesis is that using an fMRI compatible VE (the VESLI system), neural underpinnings of visual sensory experience that advantages properties of brain plasticity, an ability for lifelong learning experience shaping networks in the brain, and simultaneously measured behavior, may be systematically investigated. The same features may be used in a flexible VE system for exercise and skills acquisition.

A hypothesis is that through experience in the VE, a relationship between the subject and the visual elements may be developed. In the presence of practice experience with virtual hands avatars in the VE moving in concordance with one's own movements, sensations of involvement will develop that engage the insular cortex reflecting a sense of agency. At that point, the virtual avatar hands might be incorporated, or accepted as a proxy, or tool, or extension of one's own body. Observation, OTI, and imitation of motor sequences in VE's may modulate cortical properties, which when present over time, are typically associated with plasticity. The experience in VE may serve as a proxy for observation, OTI, and imitation of living models in certain situations such as motor skills acquisition, exercise, or rehabilitation experience.

Another hypothesis is that following training with virtual hands avatars in a the VE, visual sensory feedback of complex virtual hands avatars moving in concordance with one's own hands will activate secondary motor regions in the brain associated with action-observation action-execution during movement in the real world.

Another hypothesis is that brain activations associated with action-observation action-execution might be selectively influenced using parametrically modulated sensorimotor experience in VE's for motor skills acquisition, exercise, or rehabilitation. Modulations include adjusting the gain or varying the accuracy of the VE viewed movement compared with measured movement of the subject's hand movement.

Another hypothesis of the present research is that following training, hand motor related regions become activated as a result of visual sensory modulations in VE's alone, even when the hand ipsilateral to the viewed movement (of the virtual hands avatar) is not moving. Following training with the virtual hands avatars in the VE, visual sensory feedback of one's own right hand movement displayed in a mirror position representing a left hand moving in concordance with one's own right hand will actuate ipsilateral brain regions associated with moving the left hand. Following the training period, the sense of agency and visual sensory augmented stimulus may override other sensory experiences and establish a credible sensory feedback experience demonstrated in ipsilateral brain activation.

Another hypothesis is that through concurrent visual feedback provided in VE of a correctly performed movement, intention of the subject is satisfactorily reinforced. The satisfactory visual feedback results in activation of target brain regions associated with moving the hemiparetic hand in the case of a subject who has suffered from stroke.

Another hypothesis is that in the flexible VE environment, subjects will be able to observe, OTI, and imitate the 1^{st} and 3^{rd} person avatar teacher, perform the gestures with or without viewing their own hands or virtual hands reflecting their own practice movements, with definitions in text or picture, and when tested, remember the gestures.

1.4 Specific Aims

The goal of the present research was to investigate the possibility that virtual sensory experience engages the subject so as to actuate target brain networks through task design and visual sensory modulation, and to provide safe and motivating exercise to promote plasticity and motor skills acquisition. There were five Specific Aims in the present research. In Aim 1, the Virtual Environment Sign Language Instructor (VESLI), a functional MRI compatible VE, was designed and developed. The VESLI system integrates protocols and sensorimotor experience for motor skills acquisition, training, and research, in a flexible environment. In Aims 2, 3, and 4, functional MRI was used to map brain networks involved in simple virtual hands avatar movement in tasks including observation, OTI, and execution paradigms with 1^{st} and 3^{rd} person perspective virtual teachers, and 1^{st} person perspective virtual hands avatar proxy and modulated visual sensory feedback responses. In Aim 5, memory, behavioral and kinematic aspects of interacting in VE, with complex intransitive hands gestures from the American Sign Language dictionary accompanied with picture or text definitions, were investigated. Visual sensory experience and tasks may be systematically manipulated in VESLI providing significant functionality and personalization. Prior to this research, many of the effects of training in a VE on brain activations were not known.

In one experiment subjects studied intransitive gestures with the 3rd person perspective virtual teacher avatar, and one experiment subjects studied intransitive gestures with the 1st person perspective virtual teacher avatar. The subjects practiced the gestures in three visual sensory feedback conditions in the VE. The subjects were able to view their own hands, or they viewed virtual hands during the learning tasks, or their hands were entirely hidden from view during learning and practice tasks. The experiments investigated whether seeing one's own hand while practicing hand gestures, or whether seeing one's own hands actuating a virtual hands avatar in real time to practice hand gestures, affects remembering the gestures as compared with the control condition, wherein the subjects' hands were hidden from view.

The MRI compatible analog of VESLI was used to study cortical activations associated with observation, OTI, and imitation of simple hand movement protocols such as finger flexion or finger flexion sequences, and the systematic modulation of visual sensory experiences such as feedback corresponding with subject movement, in VE's. For the first time, an MRI compatible VE visual sensory feedback system enabled subjects to observe and interact in real-time with a complex virtual hands avatar, viewing the effects of their own movements embodied in the avatar. Revolutionary technologies and widespread availability of tools has increased the appeal of virtual reality and associated peripherals and it is timely to investigate the affect of visual sensory experiences in VE's on cortical activation and behavior. Methods demonstrated herein contribute an important fundamental research framework for initial discovery in neuroscience, rehabilitation, for human computer interface, and motor skills acquisition task design. Implications are far reaching. Findings of the present research can inform a wide number of fields.

All previous functional MRI studies investigating cortical activations associated with observation of motor skills relied upon the subjects viewing still pictures, videos or observation of subject movement which resulted in the movement of an image representing essentially a hand shaped cursor on the screen. The hand shaped cursor in previous studies moved with two degrees of freedom and with no individuated finger movement.

The present study represents experiments wherein subject kinematic measurements, visual displays of feedback, and brain imaging capture were synchronized. Subjects were able to observe effects of moving their own hand with concurrent synchronized visual feedback displayed by the virtual hands avatar in real time while brain imaging data was captured. In addition, experiments in the functional imaging environment have accompanying kinematic analysis to confirm compliance and to correlate brain activations and degree of movement produced accounting for the activation in the brain and its relationship with the motor efforts made by the subjects. Also, behavioral data was taken, and inquiries determined subjective measures and corresponding brain activation patterns in the modulation of quality of the visual feedback experiment for Aim 3 wherein the gain of the feedback images of virtual hands avatars was modulated, and also correctness of fingers demonstrating the movements was modulated.

The present experiments represent the first time brain imaging investigated the subject's own movement of a virtual hand proxy capable of independent movement of fourteen joints; the protocols used in the present experiments encompassed four fingers on each hand in virtual reality compared with two degrees of freedom represented by virtual hands in prior studies. The perspectives used in prior brain imaging studies used an ambiguous point of view (hand appeared in a position where it may represent subject's own hand or it may represent the hand of another agent) whereas the present study employed a hand proxy for the subjects in the first person perspective in a position overlapping the subject's own hands. The system used in the present study utilizes the 5DT MRI compatible glove with a capability to measure sixteen degrees of freedom. Future work will investigate more complex protocols, for example, observation with intention to imitate (OTI), followed by imitation itself, with actual accurate visual feedback of the subjects actuating the virtual hands avatars themselves concurrently with the viewed feedback, and associated cortical activations, related behaviors, subjective opinion, and kinematics. For the first time, there is brain imaging evidence that virtual hands avatars activate motor related brain regions during exercise differentially from exercising while observing an unrelated image. In addition, the relationship developed during training, evidenced by increased activation of the insular cortex over time, appears to prime brain regions for further exercise protocols, for example, Left-Right Therapy or Mirror Virtual Therapy (MVT), wherein the subject moves his or her right hand, and sees feedback of his or her left hand through modulation of visual sensorimotor feedback in the VE.

An ideal application for sensorimotor experience in VE's is for motor skills acquisition or for rehabilitation of the hand. In the case of motor skills acquisition or rehabilitation as an example, it is important to understand whether replacing the natural hand with a virtual hands avatar is a viable option, and whether there is any hope that such a virtual hands model might engage the subject and or the patient in a lifelike real world experience such that it might offer a greater value in the motor skills acquisition or rehabilitation environment over and above viewing no hand at all.

In addition to developing a suitable research and exercise VE system, the research presented herein answers the following questions: Does movement observation in a VE stimulate important brain areas associated with action-observation action-execution as does action-observation action-execution in real-world movement? Does action-observation action-execution in a VE enable imitation exercises of intransitive complex hand gestures with a flexible configurable sensory experience?

In order to accomplish Aim 5, to understand how subjects imitate complex hand gestures in a VE with their own hands, with virtual hands, and with no view of hands, two behavioral experiments were conducted using the system developed in Aim 1. Subjects observed and practiced the gestures, and performed a memory task. The hypothesis is that engaging in training and practice of complex intransitive gestures in a VE will be possible with observation, OTI, and imitation of 1st and 3rd person avatars, with pictures and text definitions, and with real hands or virtual hands proxy, or with hands hidden from view (control condition) in the case of control subjects. In the case of persons with motor dysfunction or cognitive issues, personal learning styles will emerge and the training system will provide personalization for imitation model (1st or 3rd person perspective), for task design, and for augmentative visual and other sensorimotor stimulus and feedback enabled through a number of convenient modulation programs. Ongoing data gathered by the personalized system may enable features, tracking, and monitoring of individuals, as well as provide informative research content regarding treatment methods, disease, ageing, and trends.

To understand the neural mechanisms underlying sensorimotor experience in a VE, a system was designed and created and several specific sensorimotor experiences were manipulated. Resulting cortical activations were recorded. In particular, the research showed that sensorimotor interaction with ecologically relevant virtual hand and finger models in congruence and dissonance with simultaneous subject movement selectively affected cortical activations. The experiments investigated use of virtual reality hands and fingers for imitation and proxy models.

Aim 1) To design and develop an accurate and reliable MRI-compatible interactive VE for training and research.

Aim 2) To see if observing virtual hand actions activates observation-execution networks known to be activated when one observes real hand actions. This aim investigated neural activation present when visual sensory stimulus of the virtual hands matches subjects' own hand behavior in an imitation protocol. The subjects interacted with the virtual hands while functional brain imaging records activated brain networks.

Aim 3) To investigate how quality of visual feedback affects brain activation during observation of virtual hand motion. For the second objective, sensory manipulations of the virtual hand (that are not achievable in the real world) were tested in behavioral studies wherein subjects interacted in a VE while receiving various visual feedback that was of either high, moderate, modest, or poor fidelity of the subjects' moving hand.

Aim 4) To investigate whether target brain areas may be activated through specific tasks in a VE. Particularly, this aim investigated tasks that are not easily performed in the real world by those with paralysis of the hand and therefore, would make a good rehabilitation activity. The subjects moved the right hand and they saw the left virtual hand move. The ipsilateral hemisphere was examined in functional brain imaging to see if the sensory manipulation in virtual reality resulted in a shift of activation laterality.

Aim 5) To investigate whether seeing one's hands helps in learning novel hand gestures and to investigate whether interacting with the virtual hands helps in learning novel hand gestures. In this behavioral study, subjects imitated and learned American Sign Language gestures. They observed 1st and 3rd person perspective virtual teachers and practiced while viewing their own hands, while observing 1st person perspective virtual hands as a proxy of their own hands, or without seeing hands for visual feedback of their own movements.

In Chapter 2, Background of the present research is presented with a brief overview of the plight of Americans who have suffered disabling stroke, the nature of their injuries, and promise of recovery. Diverse neural mechanisms might facilitate motor skills acquisition and rehabilitation through visual sensory support provided using more widely available and flexible technologies such as VE's.

Optimism for novel rehabilitation strategies is inspired by recent work in rehabilitation using virtual reality systems for limb training and also by human brain imaging of observation and imitation wherein it was discovered that brain networks are activated by observing others and also by performing motor tasks oneself. Discovery of this common brain network has led to a new interdisciplinary enthusiasm for the creative development of innovative rehabilitation applications supported by technologies including virtual reality and robotics and advantaging the plastic properties of the adult brain to reorganize itself anatomically and functionally through experience and training, or brain plasticity. Sensory systems seem to offer a strong means to influence the activation of important and malleable brain networks associated with motor skills acquisition. Sensory input integrated in the human brain is subject to influences of heightened or diminished perception of counterpart senses; these senses may be cleverly manipulated through augmentation to achieve attenuation or an extinction of one or more of the senses to the advantage of another, providing a potential avenue to subtend target networks in the human brain for rehabilitation or other purposes. A new concept of sensory support inspiring the present research is discussed along with advances technology holds for delivery of such services. There is a brief discussion of plasticity, rehabilitation, and visual sensory-related research in Chapter 8, a summary of findings and highlights of proposed future work in Chapter 9.

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 acquisition in control subjects and in the hemiplegic hand of patients post-stroke. 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. Bernstein believed that the upper extremities are centrally linked and function as a coordinative structure. Therefore, several exercises discussed in the literature and experiments involving transfer of skills from one arm to the other, or involving practice of two hands functioning in mirror synchrony provided inspiration for specific visual sensory manipulations explored as part of the present research including but not limited to left-right or virtual mirror therapy.

In Chapter 3, the Virtual Environment Sign Language Instruction (VESLI) system design is described. The system provides first and third person observation and imitation and virtual hands avatar visual feedback for practicing American Sign Language (ASL) intransitive complex hand gestures. The system is MRI compatible and the virtual hands avatar was used to conduct human subject research consisting of simple hand imitation experiments with functional imaging. In Chapter 4, the fMRI compatible system experiments designed to explore brain activations present during observation of virtual hand motion are described and discussed. Movement in VE's while viewing virtual hands avatars moving in concordance was demonstrated to be effective in provoking activation of important secondary motor areas associated with recovery of motor skills in patients who have suffered from stroke, whereas, movement while watching non-anthropomorphic blobs led to very little brain networks activations. Importantly, gradual activation of the insular cortex, related to a sense of agency and involvement in the scene, is observed prior to the activation of secondary motor areas in subjects.

In Chapter 5, the behavioral study and the functional brain imaging study investigating the effect of modulating the quality of the visual feedback of the virtual hands avatar behavior is described and discussed. Subjects were capable of determining the degree of modulation of the visual feedback in a subjective experiment and brain network activations were positively or negatively correlated in relationship to the loss of quality of the associated visual feedback.

In Chapter 6, another functional imaging study investigated visual feedback manipulations. When the subjects moved their right hands following the training period in VE's, they saw unexpected visual feedback: they saw their left virtual hands avatar move in correspondence with their own right hand movement. This protocol which may be a potential treatment for patients with motor dysfunction called Left-Right Therapy, or Mirror Virtual Therapy (MVT) resulted in relateralization of activation in the brain. The ipsilateral motor cortex brain region became active during the move hand condition. The ipsilateral brain region activation is associated with movement of the true left hand which is not moving.

Then in Chapter 7, the VESLI American Sign Language study investigated more complex hand sequences associated with intransitive gestures. Intransitive gestures in an imitation model represent a direct method of preparing a hand exercise that does not require decisions about aiming or grasping objects, and therefore it is a more simple exercise to perform. Chedoke-McMaster scales were used to classify the complexity of the gesture poses. Subjects learned gestures using real hands and virtual hands with first person and third person teacher avatars and with pictures and text descriptions of the signs. The control subjects were capable of practicing the gestures and completing all the tasks. When studying with natural hands, pictures helped to learn the gestures, and text definitions helped to recall. Meanwhile with virtual hands avatars, the picture descriptions resulted in better performance. This system represents a hand exercise system suitable for early intervention, personalization, data capture, assessment and monitoring, Left-Right Therapy, and MVT.

In Chapter 8, a brief discussion, outcomes, findings, and also recommendations for future work are summarized. The new research model implemented in the present research represents a novel means to investigate human behavior and corresponding brain network activations of controversial hand therapy protocols with objective measures. Specifically, visual sensory experience in VE's was investigated. Several important findings were made: practice in the VE with virtual hands avatar led to increased activation of the insular cortex, reflecting a sense of agency, and secondary motor areas, important in recovery from cortical injury. Modulating gain of the visual feedback will negatively affect important activations in the motor related regions of the brain. Visually supported virtual mirrors may actuate brain regions ipsilateral to the moving body part. Together these findings indicate that VE may provide an environment at once similar to real world action-observation action-execution and also with certain advantages for providing visual sensory support for training and exercise relating to motor skills acquisition, for example.

All of these conditions may become features in effective skills acquisition therapy, such as sensory augmentation support tools. Exercising in VE's with visual augmentation including the OTI and Left-Right Therapy shows exceptional promise for the early intervention of stroke subjects who may be weak or hemiparetic and therefore unable to participate in traditional therapies. The present research presents a new model for studying the effects of visual sensorimotor experience in virtual environments upon associated behavior, kinematics, and brain networks with significant contributions to basic neuroscience research and translational engineering.

BACKGROUND AND SIGNIFICANCE

2.1 Neural Mechanisms of Action Observation

A growing body of evidence supports bolstering sensory information to improve human performance (Haggard, Christakou et al. 2007). This appears to be true for healthy subjects in some circumstances and is true in cases wherein one sensory skill is diminished, such as is the case for some patient populations including those who have suffered from stroke (Serino, Farne et al. 2007), and in aging (Ward 2006). Recent theories of learning provide models to integrate selective experiences into VE's with successful track records for facilitating skill learning in healthy and patient-based populations. However, it remains unknown how visual sensory modulations implemented to exploit a rich computer based VE might selectively affect the brain for a number of important applications. It is also not known how these forms of feedback can be optimally integrated into systems such as those that support training or rehabilitation of the hand to elicit the desired outcome.

The pervasiveness and accessible cost of VE's presents a perfect opportunity to investigate features wherein well defined parametrically adaptive modulated visual sensory stimulus and feedback support systems can be crafted to accommodate various techniques and experience in ways not possible using natural world settings and is accompanied by an unprecedented degree of personalization providing liberal application of appropriate features to accommodate individuals in health, age, cognitive state, or disease, through a wide range of situations, and with various levels of task complexity management, employing various learning models. Therefore, this research is uniquely enabled and timely. By creating a safe environment wherein sensory experiences can be controlled, various mechanisms present in the human brain may be targeted potentially leading to short term modulation of somatosensory cortical (SI) networks. Continuous support of SI networks might be effective in promoting long term reorganization of target areas, associated with properties of plasticity, and may be included in a training or rehabilitation plan. Motor learning and rehabilitation may involve similar brain networks or procedures, although the underlying mechanisms remain relatively unknown.

Modulation of visual stimulus and feedback through VE might provide an ideal test case for sensory experiments to engage target brain regions. Visual sensory experience by itself may be effective in influencing motor learning, may be manipulated independently of other sensory experiences such as proprioception, may provide a potent signal for reorganization of sensorimotor circuits, and can override other afferent modalities in conditions of sensory conflict (Snijders, Holmes et al. 2007). For example, when tactile information is limited as in the case of some patient groups, vision might modulate tactile performance (Serino, Farne et al. 2007). In cases when subjects have identified a goal, as in imitation or OTI, movement intention may additionally influence the expectation of the content of feedback experiences. When visual feedback matches expectation, there may be an online realtime reinforcement of learning behavior not present when incongruous visual feedback is experienced in response to movement intention and movement effort. A goal of the present research was to design and develop a flexible MRI compatible exercise system to investigate effective ways of using visual sensory experience to optimize observation, imitation, feedback, and imagery conditions and to identify methods to selectively modulate brain activation in a target action-observation and action-execution network through VE visual sensory manipulations that may result in establishing a realistic and effectual environment for imitation and practice for learning or rehabilitation.

A number of imitation models have been investigated and there is a tradition of using imitation of gestures in clinical applications to observe the effects of injury upon motor programs. Imitation of actions, meaningful (MF) and or meaningless (ML) (such as moving a key held at an inappropriate angle, moving a knife in an up and down motion rather than in a slicing motion) may require multiple or differing strategies for a patient undergoing physical therapy after suffering a stroke. Empirical studies of healthy subjects with temporarily reduced capacities, as might happen after stroke, (Tessari and Rumiati 2004) demonstrate that MF actions may be stored semantically in long-term memory, being retrieved in their entirety for imitation, whereas ML actions may be parsed into many chunks, more than those already known and stored in long-term memory, and that these chunks are held in short-term and working memory with associated greater cognitive burden. Mingling types, MF and ML, lead to compensatory switching to the

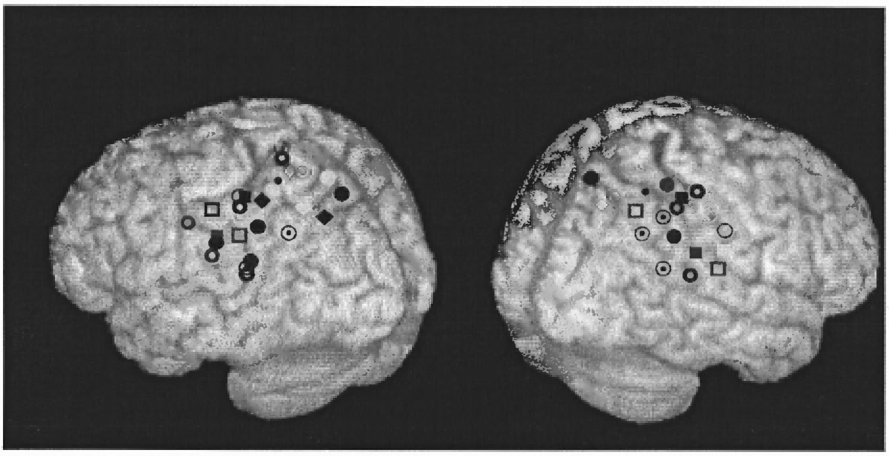


Figure 2.1 Summary of hand imitation studies.

direct strategy and away from semantic strategies, reducing performance in speed and accuracy for all the activities including the MF ones (Tessari and Rumiati 2004) with implications on task design for learning and rehabilitation. Peak parietal activation found in imaging studies on active imitation and pantomiming is illustrated below. Angular symbols represent activation in experiments with control conditions of motor rest, round symbols represent experiments with control conditions of movements. The following color coding of the figure illustrates the task type: black, complex imitation; red, imitation of simple finger movements; green, pantomiming; blue, imitation of and with active object manipulation (Muhlau, Hermsdorfer et al. 2005;Krams, Rushworth et al. 1998; Iacoboni and Woods 1999; Moll, de Oliveira-Souza et al. 2000; Peigneux, Salmon et al. 2000; Choi, Na et al. 2001; Tanaka, Inui et al. 2001; Chaminade, Meltzoff et al. 2002; Decety, Chaminade et al. 2002; Koski, Wohlschlager et al. 2002; Tanaka and Inui 2002; Grezes, Armony et al. 2003; Rumiati, Weiss et al. 2004).

Positron Emission Tomography (PET) brain imaging was used to study preparation of and copied movement. In prior studies, subjects had been instructed using arbitrary patterns of light whereas in the Krams study, subjects prepared to copy a movement (Krams, Rushworth et al. 1998). There were 5 findings: (1) preparing to make a copied movement causes rCBF changes in area 44 in posterior Broca's area; (2) set-related activity can be recorded in the cerebellar hemispheres and midline; (3) the supramarginal gyrus has a general role in preparing movements - there was more rCBF in the Prepare Only than the Execute condition; (4) the cerebellar nuclei and the basal ganglia may be particularly involved in the initiation and execution of a planned movement; these regions were more active in the Prepare and Execute condition than in the Prepare condition; (5) the ventrolateral prefrontal cortex and a left anterior cingulate area are part of a distributed system involved in the suppression of a motor response; these areas were significantly more active in the Prepare than the Prepare and Execute condition. These findings suggest a role for Broca's area in learning dexterous hand behavior and rehabilitation, and illustrate characteristic neural activations associated with the various steps of observing, OTI, planning, and executing imitated tasks.

An fMRI study of imitated index finger movements in the absence and presence of visible goals (red dots that were reached for by the finger movement) (Koski, Wohlschlager et al. 2002) demonstrated that the pars opercularis of the inferior frontal gyrus showed increased BOLD signal bilaterally for imitation of goal-oriented actions, compared with imitation of actions with no explicit goal. Bilateral dorsal premotor areas demonstrated greater activity for goal-oriented actions, for contralateral movements and an interaction effect such that goal-oriented contralateral movements yielded the greatest activity. Implications for finger exercise targeting specific brain network activation favors imitation tasks wherein subjects may become engaged in achieving goals rather than imitating actions with no apparent goals.

Perception of target actions and mental image manipulation during imitation of finger configurations was investigated in functional imaging (Tanaka, Inui et al. 2001). Results suggest the involvement of the supramarginal gyrus especially for the imitation of novel actions. Whereas in Tanaka, 2002, functional MRI was employed to study the human imitation of hand/arm postures and finger configurations, only the finger condition showed significant activation in Broca's area and symmetrical activation in the bilateral inferior parietal lobes, while the hand condition showed left lateralized superior parietal activation. Findings suggest that Broca's area might be involved more in the imitation of finger configuration than that of hand/arm postures and revealing an interesting and potentially unique brain region to target to facilitate dexterous finger training and rehabilitation. Parietal activation patterns, consistent with formerly reported clinical findings, point to a relationship between lesion laterality and patients' performance of hand/finger action imitation. These findings imply that finger imitation and behavior may be linked to neuronal networks involving Broca's area. There might be evidence, therefore, to investigate therapies that involve activation of neuronal networks that include Broca's area and for individuation of fingers rather than limiting exercise to moving the hand as a unit, reaching, pointing, or grasping.

Functional imaging investigated the neural basis of visual gesture analysis in naming and orientation tasks using static pictures of intransitive (symbolic or meaningless postures without objects) upper limb postures strongly activating the lateral occipitotemporal junction, encroaching upon area MT/V5, involved in motion analysis, or tridimensional objects activating mainly occipital and fusiform gyrus activity, resulting in a significant functional segregation (Peigneux, Salmon et al. 2000). Findings suggest that the lateral occipitotemporal junction, working with area MT/V5, plays a prominent role in the high-level perceptual analysis of gesture, the construction of its visual representation, available for subsequent recognition or imitation. Implications upon training mechanisms and available brain networks must be considered in patient populations.

A number of reports show that patient subjects have selective deficits for imitation of either meaningless (ML) or meaningful (MF) actions (Goldenberg and

Hagmann 1997; Bartolo, Cubelli et al. 2001) (Peigneux, Salmon et al. 2000; Tessari and Rumiati 2004) . Training exercises directed at motor rehabilitation might advantageously engage brain networks through task design and sensory augmentation, and through understanding of the types of dysfunction associated with specific injury in specific patients.

In reports of patients suffering from apraxia, subjects were asked to produce the gestures to verbal command and to imitation. The subjects with left parietal damage were unable to maintain proper linearity with verbal command and produced most pronounced inter-joint coordination deficits of spatiotemporal attributes of their wrist motions under that task condition. The subject with the left occipital and inferior temporal lesion that spared parietal cortex, however, showed an opposite pattern exhibiting close to normal performance during verbal command, but significant deficits when imitating (Merians 1997; Merians, Clark et al. 1997) and with implications for task design for individuals. Imitation of intransitive movements is differentiated in neural mechanisms of action from movement with goals or objects perhaps for a number of reasons. Differences in imitation of transitive and intransitive movements in healthy control subjects' performance has been previously explained within a dual route model ascribing deficits in imitating ML actions to a defective sub-lexical or direct route and a deficit in imitating MF gestures to a malfunctioning lexical-semantic route, and with actions stored in long term memory; in some studies, subjects performed better with intransitive actions, implicating the direct route for imitation of MF transitive actions (Tessari and Rumiati 2004; Tessari, Canessa et al. 2007). Control subjects imitated intransitive better than transitive gestures providing support to the complexity account of the impairments of apraxia.

Control subjects under time pressure produced cognitive shortage and errors in a study of transitive gestures or object-related actions (Boroojerdi, Ziemann et al. 2001; Blake, Heiser et al. 2006) Findings indicated object-related actions to be generally more difficult to imitate than intransitive gestures (actions having nothing to do with objects and often conveying communication content, such as waving goodbye) (Carmo and Rumiati 2009). Study participants imitated meaningful (MF) intransitive gestures significantly better than MF transitive gestures associated with tool use. These findings indicate that transitive actions pose greater processing demands on the cognitive system, perhaps because they are intrinsically more complex. However, because MF and ML actions resembled each other in kinematic analysis, the resulting differences in imitation performance of subjects between MF and ML actions can not be interpreted as being different in terms of motor complexity. Complexities in the tasks might be due to their association with the object representations, and in the case of pantomiming tool use, perhaps within the level of difficulty imaging the tool particularly when it is not present.

Elderly subjects have greater difficulty in producing transitive actions over intransitive actions upon verbal command (Mozaz, Rothi et al. 2002) another reason to test subjects with a variety of tasks and sensory augmentation when planning activities for remediation of seriously impaired patients including persons who are older. Elderly or patients with brain-damage experience deficits in imitation and their performance does not reach ceiling; therefore it may be possible to use a testing instrument to determine strongest skills in the individual and the teacher or therapist can arrange tasks accordingly. Patients with apraxia and healthy elderly subjects performed intransitive gestures better than transitive gestures upon verbal cue. The complexity of the movements seems to be the best explanation (Roy, Square-Storer et al. 1991; Foundas, Macauley et al. 1995; Rapcsak, Ochipa et al. 1995; Roy, Black et al. 1998; Dumont, Ska et al. 2000; Haaland, Harrington et al. 2000; Harrington, Rao et al. 2000; Roy, Heath et al. 2000; Heath, Roy et al. 2001; Mozaz, Rothi et al. 2002). This task difficulty effect in these cases seems to be driven by the actions' characteristic motor complexity, and also perhaps by the subject's familiarity with the gesture or action, thereby simplifying a specific task for an individual -- there may already be motor programs resident in some form in the patient's memory. Intransitive actions are easier to imitate providing support for the task difficulty argument and applied this model to explain the selective impairment of transitive actions in individuals or in groups of patients with apraxia. These findings suggest that there may not be different mechanisms, or different brain structures dedicated to the imitation of transitive and intransitive gestures. Task design and sensory experiences might establish a situation wherein performance is modulated.

2.2 Visual Sensory Experience in VE

Observation and imitation are among the most powerful and influential human communication and learning experiences. Observation can affect action as well as skills acquisition. There appears to be benefit to visual sensory augmentation in motor skills acquisition. Technologies such as VE's offer options to support and possibly introduce significant advantages over naturally occurring events including means to manage and selectively modulate tasks and sensory experiences involved in complex skills acquisition. Yet many aspects of the related neural systems involved in sensorimotor experiences in VE's and how these special experiences compare with real world interactions, remain unknown. Heretofore, technology limitations have prevented investigations of the neural mechanisms of the observation (of the movement of others), imitation (with observation of one's own movement), together with observation with intent to imitate (OTI) and also the resulting stimulation of important motor skills and learning related networks, in the functional imaging environment. Visual augmentation has been incorporated into the VESLI model focused upon individuation of the fingers in dexterous tasks.

Various previous studies have alternatively investigated the viewing of an agent moving in a movie clip or the agent in context in still images, often focusing on third-person (allocentric) or ambiguous models. The novel present research was designed to uncover relationships among: 1) observation, OTI, and imitation of hand and finger behavior, 2), visual feedback of real hands, no visual feedback, and visual feedback of virtual reality, 3) in simple, or more complex tasks, 4) with programmable visual models of first person perspective (egocentric), and third person perspective (allocentric), 5) and perfectly synchronized egocentric feedback, or unexpectedly altered visual feedback, or without visual feedback, 6) in an exercise environment within the laboratory, and in the MRI environment. Behavior, kinematics, and associated underlying neural mechanisms of hand and finger function were examined. Using the VESLI system, the present research investigated behavior and neural underpinnings of visual sensory experiences that may advantage properties of plasticity (Cramer and Riley 2008)(Boroojerdi, Ziemann, Chen, Butefisch, & Cohen, 2001), an ability for lifelong learning experiences shaping networks in the brain .

The VESLI system uses virtual reality to depict and animate models of hands and fingers for both demonstration of motor sequences (virtual teachers), and also for the engagement of the subject, to observe his or her own action, occurring simultaneously with the viewed scene (virtual hands proxy or their own hands). Cognitive tasks access motor programs and might provide an alternative means of influence (Kerzel, Hommel et al. 2001) suitable for training of motor tasks. Therefore, a language-related imitation task involving complex gestures was included in the training system. The subjects practiced intransitive hand gestures (not tool related) using VESLI while viewing virtual teachers in 1st or 3rd person perspectives and observing their own hands (Hamilton, Wolpert et al. 2006), their own hands actuating the virtual hands proxy, or with their hands hidden from sight (control condition). In this way, the experimental conditions were capable of comparing viewing hands with not seeing hands in both real hand and virtual hand conditions. For the first time, a rehabilitation-like practice system has been developed with an MRI compatible analog, to provide a window on the real-time action-observation action –execution neural mechanisms elucidated in a functional MRI environment wherein a subject may observe complex movements of individual fingers and joints of his or her own hands actuating a virtual entity in simultaneous concurrent movement with his or her own movement (August 2006). Brain mechanisms associated with observation, OTI, and imitation of the virtual hands were investigated. Visual feedback of this movement was synchronized or parametrically modulated and changes in brain activations revealed the influence of visual sensory experience in VE's on action-observation action-execution brain networks.

One of the pathways to sensorimotor learning lies in the human ability to learn by imitation (Iacoboni 2005; Pomeroy, Clark et al. 2005; Buccino 2006). Functional imaging studies of imitation have shown activation of the mirror neuron system (pars opercularis of inferior frontal gyrus and inferior parietal lobule), a frontoparietal network active during action imitation. Imitation is influenced by observation of the appropriate body part (Dechent and Frahm 2003; Wheaton, David F. Abbott et al. 2004) which may not be innate (Catmur, Gillmeister et al. 2008) but may be acquired, therefore, it seems likely that body part related imitation might find a place in training and rehabilitation and in addition, humans appear to be somewhat flexible with regard to the nature of the specific associative sequences . Imitation of simple body gestures requires a visuospatial description of the observed model through visual perception areas (right occipitotemporal and superior parietal cortices) and a visuospatial description of one's self (left inferior parietal lobule) (Chaminade, Meltzoff et al. 2005). Automatic imitation of intransitive gestures has been demonstrated in human research experiments based upon improvement in speed and accuracy in imitation (Press, Bird et al. 2008). When longer imitation sequences are considered, and when considering the imitation task itself performed within sequences, performance suffered immediately following imitation of meaningless gestures when compared with imitation following meaningful gestures (Press, Bird et al. 2008). VE's enable a personalized programmable computerized environment to present observation and imitation models unachievable in the real world, yet may provide effective neural sensorimotor stimulation similar to experiences in the natural world, and even inclusive of biological motion (Grezes, Fonlupt et al. 2001) which may serve to facilitate engagement of the subject during training. However, neural mechanisms are still not understood.

In addition, it appears that humans have an ability to perceive goals of action observed, and may be capable of accepting or understanding non-human entities

(Gazzola, Rizzolatti et al. 2007) such as virtual agents or robots performing goal oriented actions through the action observation brain network enabling proxies to establish implicit learning models (Boyd, Quaney et al. 2007) demonstrated to be more effective than explicit or mixed task models in populations of patients, for example.

Intransitive gestures imitation may be an interesting motor skills acquisition exercise since humans appear to have a unique neural mechanism for that purpose. VESLI incorporates intransitive gestures not reliant upon reaching a three dimensional location in space (complicated by involving coordination of brain regions other than M1) in an implicit imitation learning task.

In imitation tasks there are effects of the specific stimulus response (Heyes, Bird et al. 2005), and according to some research, perspective taking (Jackson, Meltzoff et al. 2006) however, healthy humans are often capable of rapidly shifting perspective and adapting to mirror images. The associative sequence learning (ASL) (Brass, Derrfuss et al. 2005) (Heyes, Bird et al. 2005), and Hebbian models (Keysers, Wicker et al. 2004), suggest that the mirror system of action-observation develops through a learning process (Hommel, Musseler et al. 2001), driven by experiences with concurrently observed and executed actions and that implicit learning continues between training sessions (Press, Casement et al. 2005; Press, Bird et al. 2008) providing researchers with another area of affect to ponder and explore along with dose, maintenance, and order of treatment, which are outside the scope of the present research, and are interesting topics to pursue in the future.

The mirror neuron system might provide some support to the motor learning process through facilitating the physical performance of training movements (Buccino 2004), in and of itself, a useful learning or rehabilitation mechanism. In recent literature it has been suggested that action observation alone may be sufficient to induce a motor memory in M1 similar to physical practice (Stefan, Cohen et al. 2005), whereas mental imaging, a passive therapy, has been found to activate M1 briefly in initiating movement, and only in some healthy subjects (Dechent, Merboldt et al. 2004) and yielding a keen incentive for visually supported skills acquisition models as an alternative to a method that relies on self-guided behaviors. Action observation modulates formulation of motor memories if performed in synchrony with training motions relative to training alone. Recent research demonstrated that observation of directionally congruent movements facilitated response by an extra 11.2% (Stefan, Classen et al. 2008).

Activation of neural pathways over time has been associated with plasticity-based changes in brain networks and together with motor learning principles provides inspiration for therapeutic interventions including close-to-normal movement repetition in a VE. Plasticity is broad topic related to the ability of the adult brain to modify structure and to re-map functions, and has been demonstrated through studies in health and in disease (for example, of stroke recovery), showing the region of motor control shifting while adjacent tissue (Asanuma 1991; Jacobs and Donoghue 1991; Nudo 1996) or the contralateral hemisphere (Glees 1980; Fisher 1992; Sabatini, Toni et al. 1994) takes over functions of damaged cortical tissue. Cortical representation can be altered in the adult system as a naturally occurring event, as a reaction to injury, or as a result of experience.

Is it possible that carefully crafted action observation therapies can be effective in engaging the patient in some helpful exercise? If so, are there recipes for these therapies?

The present research confirmed that subjects can interact to imitate gestures and that moving and viewing virtual hands activates important secondary motor regions whereas moving and observing blobs did not. Researchers report that taken together, the effect of simultaneous observation and practice may represent more value than either intervention (Stefan, Cohen et al. 2005), particularly for older people (Celnik, Stefan et al. 2006) where the individual interventions were insufficient. Observation of a model agent performing the task in a proper dynamic environment (Celnik, Webster et al. 2008) resulted in modulation of practice-dependent memory formation in subjects of a recent experiment, while performance of competing movements during skill acquisition interfered with action-observation dependent memory (Mattar 2005). Dysfunctional limbs might be viewed as interfering feedback.

Whereas viewing non-congruent movements could impair performance through competing mirror activity (Kilner, Paulignan et al. 2003; Grol, Majdandzic et al. 2007), patients with hemiparesis might be experiencing this non-congruent visual feedback for much of the time due to their own motor dysfunction, suffering untold affects on their motor programs and with associated consequences on their ability to benefit from rehabilitation.

Patients can use sensory augmentation generated in VE's to mitigate the effects of meager visual feedback of their own dysfunctional limb. Further, patients of stroke are more likely to experience tactile sensory dysfunction and vision is known to improve performance of patients with such a deficit, possibly extinguishing influences of the other sensory modalities (Serino, Farne et al. 2007). Providing real-time visual sensory feedback might improve aspects of the formation of mental imagery of the tasks. This effect might particularly benefit patients who might be implicated in cognitive deficits, and also in formation of motor memory representations since sensory information is continually updated online during performance of a real task (Kennett, Taylor-Clarke et al. 2001). With a dysfunctional limb, there is little opportunity to formulate either sensory experience naturally. Even non-important visual information of the body part can improve sensory discrimination (Haggard, Christakou et al. 2007) (Eng, Siekierka et al. 2007) lending significant credibility to the notion that visual augmentation such as VE visual sensorimotor experience might improve motor acquisition and exercise conditions and can outlast the sensory experience.

The present research demonstrated a paucity of neural activations in control subjects when they moved while observing non-anthropomorphic blobs, with possible implications for patients with motor dysfunction and potential implications regarding mechanisms of learned disuse (Dechent, Merboldt et al. 2004). Visual sensory augmentation appears to be an important tool to modulate motor skill experiences. With VESLI, options are now available to provide casual sensory feedback where none or dysfunctional feedback previously existed. Deutsche is providing such visual feedback for ankle rehabilitation (Deutsch, 2007). Morganti is providing a video table for arm rehabilitation (Morganti, Gaggioli et al. 2003). Both establish a visual sensory experience not present in the patient's real world experience. VESLI establishes a programmable modulated visual sensorimotor modeling and feedback experience in the VE for the arm and hand including the complex movements of all fingers and advantaging the individual's own innate neuro-motor programming patterns.

VE's can be programmed to enhance the sensory experience associated with performance even in cases when the patient cannot perform the action independently. Robotic assistance may be added to improve physical function and haptics may enhance the sensory experiences during training. While many hemiparetic patients may not be strong enough to participate in traditional rehabilitation exercises, VE's provide a complex sensory experience suitable for the creation of agent model observations, and complex virtual reality hands for patient visual sensory feedback. Features such as Left-Right Therapy, and Mirror Virtual Therapy (MVT) (See Aim 4), improve self-observation by recording the able limb, and playing the movement sequences in an overlapping position replacing the dysfunctional limb movements with accurate limb movements. The features may be used for unimanual, bilateral, symmetric, and mirror movements exercises (Adamovich, 2007).

Intention, proprioception, and vision match in many healthy subjects. Yet modulating one sensory experience can affect the relative contribution of another sense. Modulating sensory experiences can attenuate or extinguish contributions of other sensory experiences influencing overall performance as a result. When the expected sensory experience is missing or dysfunctional, modulating remaining sensory input might serve as an important aide in establishing a reasonable practice environment for skills acquisition. The human motor system is relatively stable requiring intense practice of close-to-normal movements in order to make incremental improvements in quality of skills. Intensity of practice plays an important role in skills acquisition. Skills acquisition as part of natural development trends in one direction and therefore, a major setback such as a brain injury, is not a typical condition for the developing brain. In Multiple Sclerosis, for example, a somewhat gradual degradation of skills is observed that is not necessarily equivalent to the observed brain injuries (Dobkin 2004). The injury occurs slowly in Multiple Sclerosis, and the brain adapts in a different manner from brain injury in stroke. There may be some phenomenon at play which relates to the fact the remaining brain networks have suffered a sudden injury and a sudden calamity in a stroke changing the available connectivity and rendering complex processes disjoint. Receptive field (RF) in the hand region of the brain may have altered inhibitory properties, enabling competing functions to occupy cortical representation previously dedicated to hand function and further reducing function. One hypothesis of a possible therapy mechanism is that through concurrent visual feedback provided in VE of a correctly performed movement, intention of the subject is satisfactorily reinforced. Since visual stimulus can form a motor memory on its own, combined practice, intention, and visual feedback enabled in a VE might provide an excellent practice environment. Perhaps visual sensory augmentation in itself can provide a useful therapy experience. The present research demonstrates that hand motor related regions become activated as a result of visual sensory modulations in VE's alone, even when the affected hand is not moving. More likely, the intention to imitate establishes a condition in the brain that is receptive to the visual feedback by aligning intention with sensory feedback. In the present research, observation with intent to imitate (OTI) was the condition associated with activation of the important insular cortex and frontoparietal motor related brain regions (see Aim 2).

The VESLI system integrates visual sensory experience of the virtual hands avatar with a cognitive language related task with the intention to draw upon common neural representations (Kerzel, Hommel et al. 2001; Binkofski and Buccino 2004;

Binkofski and Buccino 2006). High level cognitive tasks can modulate motor networks and might serve an important role in engaging motor networks for the purposes of motor skills acquisition and rehabilitation.

Manipulations of tasks and sensory experience associated with motor skills acquisition may also be achieved in VE's. Skills acquisition requires weeks or months of training and skills may be lost if the skill is not practiced. VE's can provide a practical and efficient means to deliver training and practice experience in intense long repetitive sessions (Plautz, Milliken et al. 2000) over time, and to also gradually improve feedback to engender the sense of improvement on the part of the learner. Gradually increasing task difficulty or complexity, modulating improvements in the visual feedback, tapering off robot and or visual support when the patient performance improves, may all be incorporated into VE's. Providing feedback regarding successful goal achievement over time creates a more effective training environment for motor skills acquisition and rehabilitation. Of course with personalization and flexible VE's, goals can be iteratively established, monitored, and modified.

VE's may be used to present models for observation with intent to imitate, socially synchronous action, models for mental imaging, and various replications of limb proxies. Proxies may be generated using the subject's own kinematic data gathered from unaffected limb in the case of a patient with hemiparesis. In order to be somewhat convincing, models that use biological movement programs may have an advantage. The human brain is capable of distinguishing between biological motion (Servos, et al. 2002) of human movement and biological motion of other animals (Pinto and Shiffrar 2009) in a similar neural network, and linear or programmed movement and also understanding of actions across sensory modalities (Baumgaertner, Buccino et al. 2007). Self-perception and other perception experiments suggest that perception and performance of the same action alters visual-motion processes (Jacobs, Pinto et al. 2004; Jacobs, 2005) and may provide some inspiration for further research into healthy and patient performance to gain some additional insight into potential modulations that may be rendered through visual sensorimotor augmentation in VE's.

To what degree will the subject's own body movement profiles augment the therapy experience? Results of creating the VESLI proxy using biological motion and even incorporating the subject's own motor profile, although in some cases, the motor profile of the opposite limb, may enhance the acceptance of a virtual reality proxy and thus provide a unique training environment wherein a patient with motor dysfunction can achieve a level of practice not possible in his or her natural condition. Questions regarding the success of accepting another person's biological movement profile are beyond the scope of the present research, but leave an interesting query for future work.

Further study can investigate applications of VE exercises in specific domains of skills acquisition, exercise, and physical therapies, and explore more of the features and VE tools within context. It is important to investigate practical aspects as well as effectiveness of training in the VE in control subjects and in patient populations. One application is in the use of VE platforms for convenient and practical rehabilitation therapies for stroke, early intervention even when the patient is weak and may not be able to move, and to extend therapies to other motor conditions that might also advantage the action observation network to drive plasticity for recovery of motor dysfunction, particularly of the hand and arm. In Left-Right Therapy, or Mirror Virtual Therapy

(MVT), the virtual proxy replaces the subject's own dysfunctional limb and associated sensory feedback with a mirror view of the functioning limb matching intention in the same peripersonal space as the non-acting limb. Evidence demonstrates that exercise in VE has improved the performance of patients in upper limb exercises (Adamovich, Qinyin et al. 2007). Brain imaging studies in the present research demonstrate influence of visual stimulation and task design on motor related brain networks (Genereux, Augustyn et al. 2008). Increasing the potential power and influence of this novel practice environment through methods demonstrated to recruit important motor related brain regions might transform applications. Augmenting visual feedback using VE's for the purpose of creating a suitable hand rehabilitation platform shows exceptional promise as a means to substantially extend the tools available to therapists.

2.3 New Technology Improves Research and Practice

Technology innovations over the past few decades and the advancement of knowledge within the fields of engineering and neuroscience have provided a new conceptual framework. Multi-function sensors and transmitters with very low costs-to-entry enable diversity in technology for a host of revolutionary applications delivered through a VE penetrating a number of fields. The proliferation of technology advances (hardware and software) provides an attractive platform for neuroscience research and also for motor skills acquisition, training, and rehabilitation using existing and cutting edge neuroscience principles; almost any experiential environment may be recreated, may also be blended with real world objects, and may be presented through a VE safely bringing the great majority of real world experiences into the laboratory or treatment facility for experiments, treatments, and observation. With these innovations, the possibility of mapping the neurological underpinnings of sensorimotor experience in VE has become relevant and practical.

These VE systems offer a wide range of sensory experiences, require a less sophisticated level of development skills than previous versions, and are programmable to the degree that they can accommodate requirements of individuals for personalization. They can even provide accommodations for patients who have neurological disorders making them attractive for rehabilitation. MRI compatible VE systems make significant and important investigations into the nature of human neuroscience and motor control and associated behavior possible. MRI compatible VE systems enable research that can extend existing neuroscience knowledge, can provide translational applications, and can bridge knowledge gained in animal model and human motor control research.

Exercise, training, and rehabilitation treatment interventions can exploit recent technological advances in computing, biological signal processing, robotics and haptics. Integrated solutions are poised to transform the nature of applications available to the community through connectivity to extensive resources via communications channels such as wireless, the web, private and public networks, and databases. The relative ease of access to such technology advances enables a vast array of products and services in many domains with compelling levels of sophistication, personalization, consistency, and transparency never before possible.

A better understanding of the underlying neurological principles and theories of task design manageable through design and parametrically modulated sensorimotor experiences in VE may inform tools and protocols available for various applications. In particular, implications of this research may serve an important role in motor skills acquisition, training, and in the rehabilitation of hand motor skills. There appears to be a significant overlap of features enabled in flexible computer VE's and in the requirements for a system to provide neuro-rehabilitation of hand function. The present research focused upon designing and developing a suitable flexible MRI compatible virtual hands training and research system to accommodate visual sensorimotor features appropriate for gesture training and for rehabilitation.

Patients are assessed to determine their participation in Activities of Daily Living (Fugl-Meyer and Jaasko 1980). Targeted interventions associated with hand rehabilitation included in the VESLI system, are classified using the Chedoke-McMaster Inventory (Gowland, Stratford et al. 1993). The Chedoke-McMaster is traditionally used to classify patients by level of motor ability, and to prepare therapeutic interventions. Since the Chedoke-McMaster has been incorporated into the VESLI system, each gesture task relates directly to a level of function typically used to measure outcome in rehabilitation. Each kinematic performance measurement of hand gestures included in VESLI is also present in the Chedoke-McMaster Inventory clinical measurement system. Computerized systems such as VESLI may offer configurable models for rehabilitation and research, allow trials of controversial protocols, and for the development of evidence based recommendations. The current prevailing paradigm for upper extremity rehabilitation following a brain injury such as stroke describes the need to develop proximal control and mobility prior to initiating training of the hand. During recovery from a lesion the hand and arm are thought to compete with each other for neural territory (Muellbacher, Richards et al. 2002). Therefore, training proximal control first or along with distal control may actually have deleterious effects on the neuroplasticity and functional recovery of the hand. However, neural control mechanisms of arm transport and hand-object interaction are interdependent. Complex multisegmental motor training is thought to be more beneficial for skill retention and systems such as VESLI may serve an important role to explore appropriate protocols and to investigate the underlying neurological mechanisms within the same systems thereby providing advantages and simplifying experiments. The VESLI system provides a means to easily compare findings in behavioral studies with functional brain studies. The significant findings may then be easily implemented into a motor skills acquisition or an exercise environment since it is matched with the research environment.

Within the research domain, in vivo studies of the human brain in the laboratory enabled through functional brain imaging including MRI provide a greater understanding of the complex networks engaged during human sensorimotor experiences. This is an exciting new path in research and translational engineering design. Innovations in human brain research and the discoveries made through controlled manipulation of sensorimotor experiences in current literature and also made in the present research described herein offer a foundation for evidence-based VE human computer interface design, with profound implications in such diverse fields as computational neuroscience, neuroplasticity, neural prosthetics, and rehabilitation therapies. Greater understanding of neuroscience and motor control informs design of interfaces, tasks, diagnostic instruments, and also informs new therapies for motor rehabilitation.

Emerging evidence shows that interactive virtual environments (VE's) may be a promising tool for studying sensorimotor processes and for a wide variety of applications including rehabilitation. Activation of neural pathways in the brain over time has been associated with plasticity-based changes in various brain networks. A long term vision is to identify the essential elements of the VE sensorimotor experience that may selectively modulate neural reorganization for a number of applications including rehabilitation of patients with neural dysfunction.

The very nature of the complexities of human brain networks, not present in animal models, may be revealed through studies in human brain imaging. VE's can support a wide array of sensory experiences, motor practice, and exercise protocols. By using MRI compatible equipment and applications to study controlled and modulated sensorimotor experiences, the present research uncovered important neurological underpinnings of human interaction in VE's yielding an important research tool and also important findings that may serve as a foundation for evidence based human computer interface design and rehabilitation. Kinematic analysis synchronized with fMRI studies show, for the first time, direct evidence of modulation of sensorimotor experiences and corresponding shifts in brain activation during observation of one's own complex finger movement. Behavioral studies and kinematic analysis using the same VE sensorimotor experiences demonstrate personalization features, a wide range of parametrically controllable visual sensory experiences, imitation exercises (of various models important to rehabilitation), OTI, unimanual, mirror, and bilateral exercises, clinical evaluation, kinematic analysis, and monitoring of movement in VE's. Instruments developed herein can be used to identify optimal training conditions for individuals and associated protocols including, for example, dosage, and intensity requirements. Also in future research individuals and groups may be investigated using functional connectivity studies to determine prognostic indicators and to predict effectiveness of specific recipes to achieve the desired goals. Then the same research model developed in the present research can be used to investigate protocols, doses, and durations of treatment, other anatomic parts, and combinations, linking connectivity, prognostic indicators, prescription, target brain networks, behavior, and outcomes transforming the approach to training and rehabilitation.

2.4 Visual Sensory Experience in VESLI

Visual sensory experiences may lead in some cases to motor skills learning. VESLI is a VE incorporating virtual hands avatars models and proxies, for visual sensory augmentation (Kennett, Taylor-Clarke et al. 2001) for research, for brain imaging experiments in the MRI, and for exercise of the nature typically found in rehabilitation. Providing visual observation and imitation models incorporated into a variety of tasks and sub-tasks with stratified complexities (Lestou, Pollick et al. 2008), establishes an adaptive training environment to present visual stimulus and visual feedback to benefit research, or for motor skills acquisition or for example, for the patient in rehabilitation. Visual information alone can influence motor programs as well as multimodal sensory experiences (Kennett, Taylor-Clarke et al. 2001). Visual errors can influence motor cortical areas during motor learning (Muellbacher, Ziemann et al. 2001; Muellbacher, Richards et al. 2002; Richardson, Overduin et al. 2006; Bray and O'Doherty 2007; Hadipour-Niktarash, Lee et al. 2007) and the present research demonstrates that an absence of visual feedback regarding movement of the hand results in significantly less brain activation than moving and seeing the virtual hand avatar move in congruence with the subjects' movement.

Active and rewarded practice by which one learns to use feedback to reduce errors in movement shapes neural activity in motor and premotor areas (Wise, Moody et al. 1998; Bray, Shimojo et al. 2007). Repeated and intentional observation of actions can facilitate the magnitude of MEPs and influence corticocortical interactions (both, intracortical facilitation and inhibition) in the motor and premotor areas (Strafella 2000; Patuzzo 2003; Stefan, Cohen et al. 2005; Leonard and Tremblay 2007).

Visual enhancement of touch has been shown to illicit changes in SI activity in healthy subjects (Fiorio and Haggard 2005). Perception of hand and fingers appears to take differential mechanisms. Identification of fingers is somatotopic, and identification of hands appears to use a general body schema which is influenced by external spatial location (Haggard, Kitadono et al. 2006) and may hold implications for methods of exercising hands and fingers in patients. The effect of sensory stimulation (Taylor-Clarke, Jacobsen et al. 2004; Taylor-Clarke, Kennett et al. 2004) outlasts the visual sensory experience and occurs when concurrent visual information regarding the stimulated body part is presented (Haggard, Taylor-Clarke et al. 2003)and has been attributed to backward projections from multisensory brain areas (Macaluso, Frith et al. 2000; Bremmer, Schlack et al. 2001; Macaluso, Frith et al. 2005) probably in the parietal lobe (Ro, Wallace et al. 2004) perhaps head centered within the ventral intraparietal area (Fogassi, Gallese et al. 1996; Duhamel, Colby et al. 1998) with a representation of peripersonal space (Graziano, Yap et al. 1994). Evidence supports the presence of direct projections between different primary sensory areas (Schroeder and Foxe 2005; Ghazanfar and Schroeder 2006). Even at the very basic levels, multiple sensory integration appears to be taking place.

The VESLI avatar can provide a sensory experience whereby through interactions, the fingers are assigned to the hands perhaps extending the possible benefits for training and rehabilitation. Following a training experience with the avatar's individual fingers wherein the present research demonstrates activation of the insular cortex previously associated with a sense of agency, a number of therapies may be readily experienced within the VE system. Neural activation during imitation exercises is found in the action observation action execution brain regions when using the VE system following the training period. With VESLI, individuated finger exercises appear to draw attention to each finger. This approach might have an advantage over other methods that focus on moving the entire hand (Haggard, Kitadono et al. 2006) by means of directing the brain to its model wherein each finger is represented.

An important feature of the VESLI system is that through virtual hand proxies, an interfering effect produced by an incompatibility between body schema and body-related visual information (Farne, Pavani et al. 2000; Pavani, Spence et al. 2000) may be mitigated, at least for some time, during practice with VE presenting unavailable feedback to bolster sensory experience, and also by removing views of dysfunctional limbs. This might serve to enhance extinction effects of sensory experience of the non-viewed limb since sensory experience benefit is enhanced for one limb when the other limb is hidden. Bilateral condition or Mirror Virtual condition creates a duplicate of one limb and overlaps the other limb with the desired visual feedback of a limb. Bilateral movements are common in the real world, and bilateral exercise is an essential part of achieving quality of life. Transfer strategies may train one limb, and then transfer the goal to the other limb. Task oriented design offering implicit training of dexterous intransitive gestures may be one important means to establishing an effective VE training environment for hands. Observation, observation with the intent to imitate, and imitation offer important vision-based protocols for exercise. There are several important mechanisms involved.

Properties of the mirror neuron system believed to exist in the human brain may explain the human ability to learn by imitation (Fadiga 1995; Maeda 2002; Patuzzo

2003). VE systems might be capable of tapping into the properties of the human mirror neuron system to stimulate secondary motor systems and plasticity of motor control through hand imitation VE rehabilitation. Imitation exercises are more effective in activating pars opercularis of IFG during finger lifting than symbolic or spatial cues (Iacoboni 1999). Higher level functioning mediates motor skills learning by imitation (middle frontal gyrus for learning novel hand actions) (Buccino, Vogt et al. 2004). The hypothesis is that in the presence of VE protocols, a complex visuo-neuro stimulus can be achieved that engages mirror neurons for sensorimotor imitation, engage the insular cortex representing a growing sense of agency, and engage secondary motor systems. It is hypothesized that training and rehabilitation interactions in the VE might benefit important cognitive networks. Higher level tasks that necessarily recruit brain regions associated with movement and movement planning, or movement understanding, such as tasks that engage Broca's Area, seem like good targets for these plasticity based exercises.

Training in a VE that is matched for observation and action (Wheaton, David F. Abbott et al. 2004) is appropriate since it has been shown that performance improves for such task configurations. It has also been shown that presenting a first-person perspective for imitation tasks, might stimulate more direct and stronger cognitive networks (Jackson, Meltzoff et al. 2006) than third-person perspective, particularly when a subject may encounter difficulties in performing rotations or translations.

It is hypothesized that part of the effect of viewing virtual hand movement during VE exercises in VESLI might stimulate activation of hand-relevant parts of the brain (right MT/V5, left and right anterior IPS, right precentral gyrus, and right inferior frontal sulcus (Wheaton, David F. Abbott et al. 2004)), and through action and visual feedback, VE interaction with the virtual avatar hands might promote engagement in feelings of ownership of the virtual hands (Ehrsson, Spence et al. 2004; Ehrsson, Wiech et al. 2007). It is further hypothesized that during observation with intent the intent to imitate, subjects may come to understanding goals of the observed virtual action (Hamilton and Grafton 2006), they may perceive and recognize biological movement (Servos et al. 2002) of the virtual hand in the scene, and they may come to develop a sense of other and self-awareness and agency (Decety, aDepartment of Psychology et al. 2006; Jackson, Meltzoff et al. 2006). The MRI compatible VE might enable further analysis of the feedback and feed-forward realtime dynamics of the brain network associated with the interaction of visual recognition of actions and the control of actions (Hamilton 2006).

Studies involving humans observing computer generated, or recorded movements, or static poses representing human movement provide some insight into the design of the VESLI system. Humans are very good at discerning biological movements of other humans compared with animals (Pinto and Shiffrar 2009) and linear motion even with a few points of light defining the motion (Servos et al. 2002). Even when random dots are used in a background, grating appeared to drift in a direction opposite to the points of light human walking(Fujimoto 2003) activating premotor cortex (Saygin, Wilson et al. 2004). Humans are also capable of differentiating the gender present in a moving image from points of light. Therefore, in the VESLI system, there appears to be a design advantage for recording the subject's own movement and displaying the avatar proxy representation using the recorded data for various visual sensory experiences (Agnew and Wise 2008) and tasks that might be considered appropriate for training or therapy. It may be possible that an individual will adopt a representation created from his or her own motor program more readily than a linear computer based program. Future work can investigate whether a program based upon a person's own body schema may help to re-set or reinforce many of his or her own movement characteristics, and whether a program recorded from another human might also be effective.

2.5 Patients May Benefit from VE Training

Significant evidence of support exists for the use of features in VE's to promote motor skills acquisition (Merians, Jack et al. 2002; Adamovich 2004; Merians, Poizner et al. 2006) and facilitate voluntary motor production. Evidence from the literature provides insight into design principles that might be useful in a VE to augment traditional therapies including observation of a model and imitation exercises since it is known that action observation and action execution activate the same brain networks (Iacoboni 1999 ; Buccino 2004), and while kinematic analysis demonstrates that movement observation facilitates movement (Castiello 2003; Edwards, Humphreys et al. 2003). At the same time, some patients with damaged action observation systems did not demonstrate the same facilitation.

Complexity of the rehabilitation tasks themselves may present challenges for the patient (Rushworth, Nixon et al. 1997; Rushworth, Nixon et al. 1998). There is evidence and inspiration for visual guidance to support performance through a number of mechanisms as in visual social models to facilitate movement through directly (explicitly) or indirectly (implicitly) communicating the parameters or the intentions of action (Becchio, Adenzato et al. 2006; Pierno, Becchio et al. 2006; Becchio, Sartori et al. 2008), simplifying the tasks and parametrically increasing levels of difficulty and complexity , and through the reduction of cognitive burden compared with self-guided tasks (Hanlon, Buffington et al. 2005).

Direct task training appears to be important in yielding results from rehabilitation when compared with impairment focused approaches, for example, strength training (Kwakkel, van Peppen et al. 2004; Van Peppen, Kwakkel et al. 2004; Smidt, de Vet et al. 2005). Indeed sensory experience due to incoming information along with appropriate task design (Merzenich, Wright et al. 1996), perhaps provided within a VE (Adamovich, Merians et al. 2004; Adamovich 2007), might lead to an ideal platform for implicit learning (Boyd and Winstein 2001) and intensive (Kwakkel, van Peppen et al. 2004) exercise and practice (Liepert 2000; Liepert, Graef et al. 2000) with increasing task complexity and motivating factors to promote sensory-enriched (Byl, Roderick et al. 2003) task-oriented (Richards, Mulavara et al. 2007) experience-dependent changes (Nudo 1997) in synaptic and functional connectivity across multiple sessions (Press, Casement et al. 2005), and could promote plastic reorganization (Robertson and Murre 1999; Taub, Uswatte et al. 2002 2002).

In particular, subjects who have suffered stroke may be too paralyzed to participate in traditional rehabilitation therapies. Yet it is known that rehabilitation improves the outcome of patients who have suffered from stroke (Jorgensen, Kammersgaard et al. 1999). These patients may be impaired in planning and guiding of hand shape posing great demands on visual error-based processing, and putting them at a further disadvantage. Approximately 5 to 20% of stroke survivors who have initial upper limb impairment regain full use of the limb while about thirty to 66 percent regain no functional use of the upper limb at six months (Sunderland, Tinson et al. 1992;

Nakayama, Jorgensen et al. 1994) and about half of all stroke survivors are left with severe problems (Lawrence, Coshall et al. 2001).

An interesting feature facilitated through technology enabled visual sensorimotor experiences in VE's as therapy might involve training the upper limb using observed virtual models and also through the use of virtual proxy feedback including mirror images representing the subject's own limb. This technique has already been demonstrated to facilitate learning in the untrained limb following mirror observation training of one limb in healthy controls (Dionne and Henriques 2008). It has been hypothesized as a beneficial therapy for patients with hemiparesis from stroke, and to benefit amputees through pain reduction (Altschuler, Wisdom et al. 1999; Ramachandran, Altschuler et al. 1999). Mirror images, and other likewise enabled virtual visual sensory stimulations (see Aim 4) might be good candidates for technology facilitated rehabilitation. By mapping the underlying neurological responses to modulation of the selected tasks and sensory experiences in VE in the present research, for computer interface design and rehabilitation applications, essential understanding of the neural underpinnings enabled through this particular set of features of the technology may become known and harnessed. The present research demonstrates a unique model for neurorehabilitation investigation and the findings map some of the mechanisms of virtual reality rehabilitation (August 2006; Lewis, August et al. 2006) that might lead to plasticity based therapy.

A specific set of sensory experiences in VE's, visual stimulus for modeling and augmented visual feedback mechanisms, such as Left-Right Therapy or Mirror Virtual Therapy can potentially enable patients with recent stroke injury or hemiparesis who might be very weak to successfully participate in intensive computerized training paradigms. A new VESLI system feature set for virtual reality hand training and exercise was designed and developed, providing an inventory of imitation hand gestures (exercises of intransitive hand gestures) across a range of kinematic difficulties corresponding with the Chedoke-McMaster Inventory, and incorporating a library of language and graphic describers based upon American Sign Language, which offers more than seventeen unique hand shapes in its taxonomy and over 150 combinations not including finger spelling.

In rehabilitation, compliance with mental imaging and mental practice tasks can be difficult to confirm (Pomeroy, Clark et al. 2005). Intelligent VE can provide imitation applications, visual guidance, and can monitor compliance, making VE an attractive choice for rehabilitation. The hypothesis is that in the presence of VE protocols, a complex visuo-neuro stimulus can be achieved that engages the action observation and action execution network or mirror neurons for sensorimotor imitation, and secondary motor systems, known to be necessary for motor output in stroke patients while providing visual guidance, thus simplifying the tasks, and also known to benefit stroke patients as well as older persons. It is hypothesized that training and rehabilitation interactions in the VE might stimulate important cognitive networks. Since patients may still be in voluntary control of cognitive networks, and may have lost motor skills, higher level tasks that necessarily recruit brain regions associated with movement and movement planning, or movement understanding seem like good targets for plasticity based rehabilitation, for gain or salvage. The VESLI platform might provide helpful exercise for patients who have suffered stroke.

In addition to mechanisms that directly support learning models, enhanced sensory experiences may also support deficient sensory systems in healthy and in patient populations. Somatosensory deficits in patients are typically related to lesions in the primary somatosensory cortex (SI) (Wikstrom, Roine et al. 2000). Loss of body sensations occurs in approximately fifty percent of stroke patients (Feigenson, McCarthy et al. 1977; Feigenson, McDowell et al. 1977) affecting patients' ability to manipulate and use objects, to feel stimuli, and can lead to a complete nonuse of upper limb even when the limb shows normal function and limiting functional recovery of skills of everyday living (Carey, Abbott et al. 2002). It is difficult to predict what recovery may be possible for patients suffering the effects of stroke and in one recent case study of a stroke subject recovery was limited to re-emergence of activation in the somatosensory cortices (Carey, Abbott et al. 2002) while recovery of somatosensory skills preceded neural changes observed . Perceptual and functional training methods were compared and were found to yield similar results in stroke patients implicated in perceptual deficits (Edmans, Webster et al. 2000)

In a recent study, visual enhancement effects were found to be inversely related to a baseline measure of tactile acuity indicating that visual enhancement helped more when subjects presented poor tactile abilities (Serino, Farne et al. 2007) and might be useful to improve performance of patients. This effect is believed to be compatible with the inverse effectiveness rule (Stein, Jiang et al. 2001; Stein, Wallace et al. 2002; Stanford, Quessy et al. 2005; Rowland, Quessy et al. 2007) and appears to super-additively enhance performance.

The human brain may be capable of sophisticated levels of integration among sensory regions, utilizing additional information presented to one modality when deficits of other modalities or regions are present. Even in the case of healthy controls, manipulation of sensory experiences, even without providing additional information about the stimulus, was effective in improving performance. Serino and colleagues hypothesized that where some residual function is present, vision might serve to enhance tactile spatial resolution and make it more functionally useful (Serino, Farne et al. 2007). This is an interesting area for investigation and might shed some light on important mechanisms that if used in VE, might assist in creating an environment for learning and rehabilitation through modulation of tasks and sensory information. By creating a safe environment wherein sensory and task experiences can be controlled, various mechanisms present in the human brain may be targeted. Since the system can simultaneously monitor performance of the patient, performance may continually be known. Variability in performance throughout sensory and task manipulation may yield effective input for algorithms to update the rehabilitation application and to selectively present appropriate tasks and customized sensory augmented stimulus for the individual patient.

Functional and anatomical connections are both involved in the performance of complex motor programs. When a person suffers a brain injury, location and physical extent of the injury will affect the motor programs as well as the physical connection of neural networks, blood supply, and physical structures involved in performing. Early therapy has been credited with reducing loss of function as a plastic response. Animal studies have resulted in such plasticity in the presence of therapy (Nudo 1997). It is theorized that neural networks are unmasked through Hebbian mechanisms (Hebb 1949) and less sophisticated motor programs become activated, yielding compromised motor functions. When this happens early in life, as in cerebral palsy, the interhemispheric inhibition programs have not fully developed. In older stroke patients, disinhibition may be seen between hemispheres as a result of the injury. The significance of unmasking, changes in the balance of the inhibition and excitation, is the subject of controversy. Structural synapses may no longer be functioning. Mechanisms advantaging bilateral brain activities may play a role in the neural plastic recovery of these patients. (Bernstein 1967; Kwakkel, van Peppen et al. 2004) believed that the upper extremities are centrally linked and function as a coordinative structure (Bernstein 1967). Since there is a 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 synergistic bilateral movements activate similar neural networks in both hemispheres and facilitation of an inherent inter-limb coordination and might improve functional therapeutic outcomes (Schwartz, Moran et al. 2004; Cauraugh and Summers 2005). After a stroke, the ipsilateral hemisphere plays an important role in the recovery of function of the hemiplegic arm (Cohen, Dixon et al. 2003; Werhahn, Conforto et al. 2003) . Ipsilateral pathways from the undamaged hemisphere may contribute to the improved movement patterns (Mudie 2000; Stinear 2004; Mudie and Matyas 2000; Stinear and Byblow 2004). It is believed that during unilateral movement ipsilateral neuronal activity is inhibited in order to prevent mirror movements of the opposite hand (Cauraugh and Summers 2005; Cauraugh, Stinear et al. 2004). However, during synergistic bilateral movements, both hemispheres are activated and cortical inhibition is reduced (Stinear and Byblow 2004; Cauraugh, Stinear et al. 2004; Stinear, Coxon et al. 2008). This disinhibition may allow for recruitment of undamaged neurons into new task-related neural networks. In separate bodies of literature investigating bilateral training positive outcomes have been shown in small studies (Mudie and Matyas 2000; Whitall, McCombe Waller et al. 2000; Hesse, Schulte-Tigges et al. 2003; Hesse S 2003; Luft, McCombe-Waller et al. 2004). In the system designs of VESLI in the present research, unimanual, bimanual, hand alone, hand and arm separately, and hand and arm together exercises (Adamovich, Fluet et al. 2008) are enabled thus providing a rich platform for a continuum of therapies, experiments, and exercise protocols.

Training with the ipsilesional limb, or the unaffected hemisphere (UH), might offer a paradigm to stimulate neurons associated with movement in the affected hemisphere (AH). This conclusion has been made in a number of studies investigating various mechanisms of motor skills learning. Depending upon the techniques used, results appear to be related to the retained neural connections. Understanding the combination of these retained neural connections and appropriately selected therapies appears to be a key to improving recovery through training. There may be an important role for the unaffected hemisphere. Meanwhile, the retained networks may have some adaptive characteristics or alternative mechanisms that play a role in the lack of recovery frequently observed in the population of patients, for example, a change in inhibition among neural representations of the hand region may serve to enhance cortical loss to other body parts. It is also important to consider brain mechanisms required by virtue of the task design itself (Shallice, Stuss et al. 2008). Perhaps retained networks might interfere with development of new networks in some types of therapies. Literature provides some inspiration to pursue investigating mechanisms of retained networks to drive some skills acquisition in the affected limb. Programming and recognition of motor actions involves the premotor cortex (Freund and Hummelsheim 1985; Fadiga, Fogassi et al. 1995; Jeannerod, Arbib et al. 1995). Prefrontal cortex is involved with self control of cognition and action and is also involved with selecting strategies for problem solving and trouble-shooting (Damasio 1989;Vogt, Buccino et al. 2007;Shallice, Stuss et al. 2008). Prefrontal lesions may reduce the patient's awareness of these deficits. In addition, it may become more difficult for the patient to apply compensatory strategies for overcoming the deficits (Stuss, Murphy et al. 2003). Therefore, task design and strategy of practice might support alternatives that accommodate patients implicated for this dysfunctional strategy. Virtual visual sensory augmentation, stimulation and task design might provide an important intervention in this situation.

Skills learned in one limb might be transferred to the other limb, offering another mechanism of plasticity to tap for rehabilitation and skills acquisition. Handedness scores are related to factors that might influence intermanual transfer, such as engagement of the ipsilateral hemisphere during movement (Dassonville, Zhu et al. 1997) and corpus callosum volume (Witelson 1985; Witelson 1989). Researchers tested whether the degree of handedness is correlated with transfer magnitude of sensorimotor adaptation of sequence learning in hand skills and results indicated that less strongly left handed individuals exhibited better intermanual transfer, while less strongly right handed individuals exhibited better intermanual transfer. These findings suggest that involvement of the ipsilateral hemisphere during learning may influence intermanual transfer magnitude (Chase and Seidler 2008). In a functional imaging study focusing on right handed subjects, prior right-hand practice led to reduced endpoint errors but not trajectory errors for the left hand and is consistent with work showing that the right arm is specialized for trajectory control while the left is specialized for endpoint control (Sainburg 2005).

Early adaptation processes were associated with activation in frontal and parietal regions, including bilateral dorsal premotor cortex. At transfer, activation was seen in the temporal cortex as well as the right medial frontal gyrus and the middle occipital gyrus, and findings suggest that the left dorsal premotor cortex contributes to trajectory control, while the left visual and temporal cortices contribute to endpoint control (Anguera, Russell et al. 2007). Therefore, unimanual exercises, transfer exercises, and bilateral exercises might offer good practice for a patient and perhaps varying mechanisms by which they influence rehabilitation of dysfunction, providing a feature for providing a variety of therapy tasks and mixing it up. Even learning the skill with the unaffected hand, particularly if it is the right or dominant hand, might offer some benefit through a specialized mechanism that facilitates transfer of skills to the other hand. Definitions of the goals and abstract representation of those goals in the memory of the patient might cause some problems in imitation and hand gesture production (Hermsdorfer, Hagl et al. 2004), however, some retained skills might enable patients to produce desired skills under certain conditions (Hermsdorfer, Goldenberg et al. 2001). Studies of apraxia (Basso, Capitani et al. 1980; Kertesz and Ferro 1984; Basso and Capitani 1985) indicated that parapraxias were found to accompany frontal, parietal and subcortical lesions. It might be helpful to define neurological underpinnings of the complexities of these tasks to provide a more informative guide to therapy.

For example, there are various adaptations made by patients with apraxia that seem to result in symptoms rather than the symptoms being an expression of the apraxia. Research implies that the basic deficit manifesting in apraxic errors concerned the fact that the patient had an inadequate representation of the motor target position and if patients tried to compensate for their inadequate abstraction of the target location, movement kinematics deteriorated although patients were not always aware of the nature of the problem. They eventually succeeded in reaching the correct position or if they do not succeed, apraxic errors and degraded movements resulted.

Research evidence implies that a rehabilitation practice environment that compensates for inadequacies in problem solving strategies related to goals of the movement might offer an accommodation for those who have prefrontal lesions thought to interfere with awareness of deficits as well as the ability to apply compensatory strategies for them (Stuss, Binns et al. 2002). The VESLI system offers intransitive gestures imitation and practice with options to use the 1st person proxy to view successful execution action of the goals, and by offering Left-Right Therapy, or MVF that visual sensory manipulation can be configured for bilateral, unimanual, or other movement practice. The VESLI system seems to be ideally suited to accommodating these important issues and this accommodation might be very difficult in the real world. In a traditional rehabilitation environment, several challenged skills may be necessarily tapped in the hemiparetic patient. The subject will almost always be required to perform motor skills without perfect feedback of a well-functioning limb, with compromised sensations, with compromised memory skills, or while attempting mental imaging of the movement and or gazing at the ceiling. Even in the cases when therapists request the patient to close his or her eyes and imagine performing the skill, dysfunction may interfere with adequate mental imaging. Some patients have difficulties following verbal orders or initiating movement following another cue. Establishing an imitation model reduces the anxiety and concern about mental imaging and other types of compliance. Reach to grasp tasks necessarily complicate tasks by incorporating hand shaping and complex three dimension location and positioning problems. The subject will almost always be required to abstract the goal or target location and or follow instructions, often verbal, which challenge the cognitive skills following a lesion. Patients perform better in implicit learning tasks than in explicit tasks. VESLI transforms all these complexities providing an intransitive, direct imitation model with no demand on memory, interpolation, or interpretation. In sensorimotor experience in VE's, subjects may receive visual sensory input representing the instructions for imitation, and also the 1st person feedback of virtual limbs performing the task. VESLI therapy might be well-suited to patients to have difficulties formulating abstract goals and performing without perfect visual feedback. The latter condition has not been easy to identify until the creating of the VESLI system wherein patients may be studied for their response to seeing dysfunctional visual feedback of their limb, compared with very good concordance of visual feedback based upon the Left-Right Therapy or the MVF. There may indeed be particular groups of patients who will benefit more from the visual support of a VE sensorimotor experience due to the nature of their dysfunction.

2.6 Stroke Statistics

Approximately 906,000 Americans sustain stroke annually (ASA http://www.strokeassociation.org), with incidence remaining constant over the last 3 decades. Although mortality has decreased, stroke is the third leading cause of death in the United States behind diseases of the heart and cancer and is the leading cause of disability, with an increasing number of survivors requiring rehabilitation. Stroke related medical costs and costs of disability were forecasted to be $62.7 billion for 2007 .

2.7 Residual Deficits

With approximately two thirds of survivors experiencing residual neurological deficits impairing function, and only about five percent regaining full arm function (Gresham, Fitzpatrick et al. 1975) and about two thirds experiencing ongoing neurological deficits, in spite of therapy. About fifty percent suffer hemiparesis after six months. About twenty percent regain no functional use of the arm, interfering with activities of daily living such as dressing, bathing, self-care, and writing (Gowland, deBruin et al. 1992). Even when demonstrating high function in clinical tests, there is a reported reduced actual use of the limb in real life situations. The result of these losses includes limitations of independence, and reduced quality of life. This is an indication that research is needed to increase the prospects of recovery for survivors of stroke. Research is needed that addresses the recovery processes of more people who are more affected by stroke. Improvement in recovery can offer hope to avoid dependence on relatives, nursing homes, accidents, emergencies, hospitalizations or other interventions. Recovery can give people back their lives.

2.8 Variability of Clinical Outcomes

Variability of clinical outcomes may be explained by a number of underlying mechanisms including issues involving circulation and blood supply. There may be reabsorption of the edema, variable perfusion, and collateral blood supply contributing to successful improvement. The ischemic penumbra, the tissue surrounding the lesion and its necrotic region, has the potential to recover in the presence of sufficient blood supply. However, if blood supply is not preserved, very quickly post-ischemic or post-anoxic long-term potentiation occurs (believed to be a plastic mechanism) (Rossini and Dal Forno 2004).

2.9 Shifts in Brain Activations During Recovery

In humans, early movement post-stroke is associated with massive recruitment of motor regions (attention-dependent movement) whereas patients who experience a full recovery have functional studies that are indistinguishable from healthy subjects (shift to automated performance) (Ward, Brown et al. 2003; Ward, Brown et al. 2003). Changes in brain activation during motor tasks may be observed in regions remote from the region of the lesion. The remote activation seen in functional studies may represent diaschisis or a compensatory strategy. Compensatory strategies might give clues to paths of or obstacles to recovery. Or they might reveal other processes affected by the brain injury.

2.10 Motor Changes in Both Limbs

Motor skills changes take place in both limbs; in ipsilateral limb, changes are observed such as subtle impaired dexterity (nonparetic hand), (Yelnik, Bonan et al. 1996; Marque, Felez et al. 1997; Sunderland, Bowers et al. 1999; Sunderland 2000) , increased movement segmentation, and impaired segment coordination.

2.11 Brain Networks of Patients

Many people suffering hemiparesis following stroke fail to make a full recovery. The potential for an individual recovery is not fully known. Functional brain imaging studies are being used to reveal important information about the underlying neural basis of motor skills learning and recovery, yet much remains unknown. Likewise, little is known about the neuroanatomical conditions of patients, and how that condition relates to potential for recovery or the nature of appropriate therapy. Research is needed to understand necessary networks that might be required for therapies to be successful.

Recent advances in brain imaging demonstrate that connectivity may be determined from resting state fMRI (Fox, Snyder et al. 2005) the patterns are shown to be altered in patient populations using task-based methods (Quirk and Gehlert 2003; Heinz, Braus et al. 2005; Pezawas, Meyer-Lindenberg et al. 2005; McClure, Monk et al. 2007). Resting state fMRI can be used to investigate intrinsic differences in brain activation networks of interest without potential confounds of the group differences (patients and healthy controls) in task performance and might be useful in personalization or determining therapy strategy for individuals. Still, the measures of patient groups will yield important information needed to understand disease state and potential for recovery including prognostic indicators, connectivity and anti-connectivity (Fox, Snyder et al. 2005), dynamics of the brain networks in active and deactive conditions. Such studies might also yield important information about brain networks to target with therapies for recovery (Price, Mummery et al. 1999).

2.12 Rehabilitation

The goal of rehabilitation is to reduce impairment and provide functional improvements resulting in quality participation in activities of life (Dobkin 1998; Cramer 2008). Technologies play an important role in today's rehabilitation environment. In addition to the intrinsic values of technologies such as increasing access and reducing work, extending the rehabilitation capabilities from the clinic to the home and community (Deutsch, Lewis et al. 2007; Holden, Dyar et al. 2007), maintaining consistency, analyzing lots of data easily, measuring and tracking and more, there are implications of customization, personalization, and perhaps most importantly, of affects on the brain through various mechanisms (August 2006), of various types of technology-enabled therapies including virtual reality, robots, haptics, and TMS (Patton, Kovic et al. 2006; Riener 2007; Adamovich, Fluet et al. 2008; Bolognini, Pascual-Leone et al. 2009). Technology supported platforms may uniquely facilitate multimodal and interdisciplinary approaches to rehabilitation, neurorehabilitation and research (Hlustik and Mayer 2006). Technologies can fill an important niche if they enable broad feature sets relating to the activities appropriate in training and rehabilitation. Desired features include the ability to apply systematic modulation of sensorimotor experiences, particularly if these modulations are a benefit above real world experiences by virtue of their presence, ease of use, accommodation of disabling conditions, through a number of means such as clever presentation, repetition, manipulation, task design, cognitive support (McEwen, Huijbregts et al. 2009), sensory support, to transform the therapy location, or to enhance available experiences.

2.13 Significance

The present research combined behavioral and brain mapping techniques to investigate mechanisms of visual sensorimotor experience in VE in a new training and research model. For the first time, as part of the present research, an MRI compatible flexible VE capable of providing sensorimotor modulations and concurrent measurement of performance, kinematics, brain imaging, and behavior has been developed for training, research, analysis, and functional imaging brain mapping in health, in ageing, and disease. Visual sensorimotor experience in VE were investigated covering observation, OTI, and imitation of simple and complex hand gestures using virtual teacher models in 1st and 3rd person perspective, and virtual hands proxy in 1st person perspective replacing the subject's own hands in the tasks, and in control conditions. Future work may use the same research and training model to uncover many aspects of interacting in a VE with modulations in sensorimotor experience. Controversial protocols may be investigated using the present model to elucidate conditions conducive to exercise and motor skills acquisition in VE. Training conditions promoting safe and effective therapies early following cortical injury (demonstrated to reduce loss of cortical representation) may be investigated and implemented.

RESEARCH AIM 1

Aim 1) To design and develop an accurate and reliable MRI-compatible interactive VE for training and research.

3.1 Virtual Environment Sign Language Instruction System

The VESLI System was designed and developed to provide a sensorimotor learning platform for research and training, for motor skills acquisition, and rehabilitation, for kinematic, subjective, and behavioral measurements, in the laboratory and for use functional MRI imaging studies.

The fMRI compatible Virtual Environment Sign Language Instruction System, or VESLI, provides VE sensory experiences incorporating the virtual arm and hand (1^{st} person and 3^{rd} person virtual teacher avatars) for studying and for improving complex fine and coordinated motor skills of the fingers, referred to as Hand-Alone (HA), or the hand and arm as a unit referred to as Hand-Arm-Together (HAT), or Hand-Arm-Separately (HAS). VESLI may be used as a motor skills acquisition training system, a rehabilitation system, and to investigate the kinematic, behavioral, and neural correlates of sensorimotor learning in a VE. A behavioral study was completed as part of the research in Aim 5. Functional brain imaging was used to investigate the nature of neural activations associated with training simple finger flexion and movement sequences with these virtual hands avatars in 1^{st} person perspective in the VE, and the nature of neural activations associated with modulated visual sensorimotor experiences in VE's including: training with virtual hands, modulating visual feedback – changes in gain between subject's physical movement and the movement displayed by the virtual hands, and the Left-Right Therapy, wherein a Mirror Virtual Feedback, left virtual hand movement is displayed when the subject moves his or her right hand. Future research will include fMRI studies incorporating practicing gestures and language tasks. The future studies will investigate correlation between behavioral and neural correlates of sensorimotor learning of transitive and intransitive gestures, observation and imitation of gestures, influence of vision on complex hand motor skills, etc. in the VE. An important feature of the VESLI system is that through virtual hand proxies, an interfering effect produced by an incompatibility between body schema and body-related visual information (Farne, Pavani et al. 2000; Pavani, Spence et al. 2000) may be mitigated, at least for some time, during practice. It is the goal of the present research to begin to uncover controllable aspects of the sensorimotor experience in VE's that might strategically enhance the exercise experience for individuals and patients. The MRI compatible VESLI system may be useful in the investigation of the neural underpinnings of hand eye coordination and the complexities of how the vision system informs the individual's perception of self and motor space.

3.2 VESLI System Introduction

This chapter describes the Virtual Environment Sign Language System Instructor (VESLI) features and functionality including: the taxonomy of hand gestures selected for VESLI, the procedure for classifying the hand gestures by levels of difficulty, descriptions of the avatar models, and sample hand gestures rendered in VESLI. Exercises included in VESLI are described in this chapter. Chapter 6 describes the behavioral experiment conducted using this system and all the experimental findings. A complete list of hand gestures and associated levels of difficulty included in VESLI may be found in this chapter.

There is little information on: the relationship between various virtual sensory stimulations and neural processing, the effect of these stimuli and the perception of self and other (agent or teacher) on motor learning (David, Bewernick et al. 2006; Corradi-Dell'acqua, Ueno et al. 2008), the science of task design and relationships with target neural processing, and how to exploit modalities available in VE's to access target neural correlates (August, Lewis et al. 2006). Many of the studies regarding imitation of hand gestures available in the literature rely on phenomenological data and or are limited in action observation during brain imaging. Studies are limited by use of still images in the fMRI for imitation hand shapes, fist, scissors, gun (Bhimani, Hlustik et al. 2006), and sequential piano key tasks developed along the model of Luria's postulates, and is further limited by the fact that the subject cannot see his or her own hand as he or she performs the hand shaping task, creating a greater demand on the skills of proprioception in the test environment and missing the opportunity to discover other visual influences and associated networks engaged.

Learning or relearning a motor skill is hypothesized to involve a widespread and distributed neural network where sensory input and proprioception are integrated in a variety of configurations. Learning in controls and patients may be vastly different in a number of ways. It may be some time before sufficient research can be conducted on controls and patient populations to understand the neural underpinnings of rehabilitation and how it may be similar to motor learning or differential to it (Baron, Cohen et al.

2004). Engaging specific sensory experience in VE for motor learning and rehabilitation may provide a select mechanism to address attention, and to selectively engage specific sensory networks in a learning process, not necessarily the only learning process. Brain regions involved include but are not limited to regions associated with 'mirror neurons,' regions associated with action observation and action execution (Rizzolatti and Craighero 2004). Literature indicates that neural models fail to incorporate all known function for given anatomic structures. Broca's area (Iacoboni and Wilson 2006), traditionally associated with language, is also implicated in premotor function and is demonstrated to be active when finger imitation tasks are performed (Tanaka and Inui 2002), providing evidence for task design in dexterous finger rehabilitation. Tasks may be designed in VE's that necessarily access neural correlates including Broca's area. VE's enable observation of novel hand tasks for imitation and also enable the subject to observe his or her own hands producing the hand gestures during rehabilitation, in the behavioral lab, for fMRI, and for TMS studies, while sensory stimulus and feedback may be modified to explore a variety of learning protocols.

A variety of hand and arm exercise games and simulations have been developed in virtual reality and have been used successfully to train patients who have suffered stroke, improving their function even after training ceased (Adamovich, Fluet et al. 2008). Another hand exercise system has been designed and developed to incorporate additional features and to extend research to include functional brain imaging (August 2006; Lewis, August et al. 2006) and memory (Davachi 2006).

To further clarify the biological model of motor learning and to understand the role of virtual sensory stimulation and feedback which includes seeing one's own hand movement, it is important to study the underlying science, to develop functional brain mapping of sensorimotor learning in the VE and correlate the kinematics, behavioral measurements, and outcomes. Understanding resting state connectivity (Biswal, Yetkin et al. 1995) in health, aging, and disease is important in developing prognostic indicators and in differentiating healthy and impaired populations, and in understanding the nature of recovery and how it might relate to healthy learning processes and is outside the scope of the present research. With such future efforts, one may predict the success of task, application and interface design for sensorimotor learning in VE's that can accomplish desired learning conditions for specific goals, and characteristics of target audiences may become better understood.

For Aim 5 of the research, VE behavioral experiments were conducted in the laboratory where the subjects followed a learning and memory protocol. The subjects observed with intention to imitate (OTI) a virtual actor (avatar) in either 1st person perspective (1PP) or 3rd person perspective (3PP) demonstrate American Sign Language (ASL) gestures accompanied with either text or picture descriptions. The subjects imitated the hand gestures beneath a special two-way mirror in either 1) a hidden (control) or seen condition, or 2) hidden (control) or virtual hand condition. The subjects then performed memory tasks to identify gestures as familiar or new, provided definitions from two choices, and indicated source of the initial learning condition as either text or picture. Speed and accuracy in remembering the item and source and accurately rejecting new signs presented as lures during the memory session, determined whether seeing the hands or seeing the virtual hands during practice contributed to remembering each sign, its meaning, and also remembering source learning conditions. This research revealed whether seeing hands or virtual hands during motor learning of hand gestures improves learning over not seeing hands or virtual hands during practice of hand gestures in a VE.

Findings indicated that for the healthy control subjects who participated in the study, all subjects were able to follow instructions, to observe, OTI, and imitate the hand gestures demonstrated by the virtual avatar instructor, and answer the memory questions presented to them using the keyboard to indicate selections. The VESLI system functioned as designed and was successful in presenting the VE sequences and in capturing all experimental data.

The same experimental tasks may be repeated in future studies in the fMRI for brain mapping of neural correlates associated with viewing virtual hands actively making gestures, OTI, or imitating virtual agent in 1st or 3rd person perspectives during learning, and to uncover neural correlates in initial condition when successful gesture memory has taken place. Interesting comparisons for functional brain analysis include: initial brain activation condition when gesture is successfully recalled, initial brain activation condition when the initial study pair definition is recalled, differences in recognition strategies of picture or text definitions, the effects of teacher perspective on brain network activation and recall. Also, resting anti-correlation studies would provide interesting contrast between successful learners and those who produce more errors, or between ages, or between healthy control subjects and persons who have suffered from some motor dysfunction injury such as stroke.

The present research study focused on virtual sensory experiences, the virtual hands and gesture learning models including those described elsewhere in this document may be incorporated into protocols for motor skills acquisition, or rehabilitation. It is believed that an action-observation action-execution network is activated when a human observes another and when one observes another with intention to imitate (OTI) (Buccino, Binkofski et al. 2004). Current rehabilitation models endeavor to employ practice-induced plasticity, to stimulate action-observation action-execution networks or ‘mirror neurons,’ to stimulate other known neural mechanisms of skills acquisition or learning (Buccino, Solodkin et al. 2006), employ protocols such as observation with intent to imitate OTI, incorporate therapies such as bilateral exercises (Carson 2005), and simulation for bilateral, unimanual, mirror, and contralateral hand exercises. VESLI features include tasks involving intransitive meaningful hand gestures from the American Sign Language (ASL) focusing on fine motor control, isolated finger control, and coordination. In dyspraxia and apraxia, there is motor deterioration, diminished accuracy, speed, and force. The Virtual Environment Sign Language Instructor (VESLI) system incorporates hand postures or gestures for practice and learning. The VESLI system has included intransitive and meaningful hand gestures from ASL in order to engage common brain areas involved with motor planning networks and communication neural pathways such as Broca’s area. Intransitive gestures are believed to simplify the imitation task, particularly for persons with brain injuries, over transitive gestures involving tool use or tool abstraction. Tool configurations and three dimensional space configurations are not required in the ASL gesture imitation task, thereby simplifying the task from a neural processing point of view. In addition, each hand gesture has been analyzed for difficulty in motor skill production using the Chedoke-McMaster Impairment Inventory for Skill Level. The ASL taxonomy and associated content provides an easy and systematic means to reference the gestures (to be practiced and recalled). Of course, the same VESLI system may be used for tool demonstration, OTI, and imitation tasks using real, virtual, or blended objects. Various protocols may be administered depending upon level of impairment. Hand dexterity and imitation exercises may be presented in increasing levels of kinematic, task component, or abstraction difficulty using the VESLI system. Reach to a target may be separated from the basic hand practice task, facilitating the exercise for patients who have diminished abilities to deal with abstraction of targets, or spatial goals. Direct imitation may enhance abilities of those who have difficulties: following explicit instructions, using mental imaging, or using another sensory modality (such as hearing).

An important feature of the VESLI system is that through virtual hand proxies, an interfering effect produced by an incompatibility between body schema and body-related visual information (Farne, Pavani et al. 2000; Pavani, Spence et al. 2000) may be mitigated, at least for some time, during practice. It is the goal of the present research to begin to uncover controllable aspects of the sensorimotor experience in VE's that might strategically enhance the exercise experience for individuals and patients.

Dosages may be controlled within the system and analysis of progress may be made from behavioral measures offered through tasks accomplished using the system and from kinematic analysis of hand gesture production.

The VESLI System has a simple user interface to prepare and administer exercise protocols, comprising a number of features including but not limited to: observation with intent to imitate (OTI), observation for mental imaging, Left-Right Therapy, Mirror Virtual Feedback (MVF), intense practice environment, error-less feedback, etc. A simple text file is created to select the list of gestures for practice, to indicate the definition style, and to arrange the speed, repetition, and components of the testing conditions. The

VESLI System also records and automatically analyzes subject responses to simple memory questions for gesture and meaning recall. Kinematics are recorded. Matlab programs analyze kinematic properties of the gesture production recorded by the data gloves and Flock of Birds and can also compare performance with a model. Kinematic analysis may compare gesture production over time, and also may compare the affected hand with the less affected hand to assess performance based upon the subject's own neurological movement model.

Virtual Reality (VR) within a VE provides useful rehabilitation applications and simulations, motivation, and feedback, for motor skills acquisition for healthy subjects, and for rehabilitation for example, for chronic stroke patients, and others who might benefit from intensive attended, massed therapies required to take advantage of brain plasticity to modify neural organization and improve motor skills during the chronic phase after a stroke and may also offer opportunities for acute stroke therapies. Several features of the VESLI System may be used even when the subject is paralyzed. Traditional therapies require that the person who has suffered from a stroke be capable of moving the finger at least 10 degrees before participating in rehabilitation activities. However, the VESLI system may generate visual therapy. By itself it may provide a passive, or a visual sensory augmented activity.

The VE system may be used as a means to deliver therapy, as a method to monitor patient compliance by measuring patient responses, as a method to objectively measure patient motor skills and kinematics, behavior, and learning by direct and indirect means. It is also as a means to deliver task experiences for functional MRI brain activation studies. For these reasons, VE's such as VESLI play an important role in research for motor skills acquisition, for therapeutic methods and for their correlation with motor skills performance, behavioral learning, subjective experience, and for understanding the underlying mechanisms of plasticity-mediated therapies.

During brain imaging studies, training using virtual hands in a VE elicited desired brain activations associated with motor skills thought to be important for rehabilitation of the paretic hand. The systems used also enable low-cost freely-moving measurement of joint excursions in a variety of settings including research, the clinic, community center, or in the patient's home during free exercise or during imitation joint excursion maneuver. VESLI combines sensorimotor stimulations with imitation tasks for the hand and fingers for a rehabilitation and sensorimotor learning experience in a VE.

3.3 VESLI Gesture Training System

VESLI uses finger, hand and arm gesture imitation protocols. First person and third person perspective avatars demonstrate American Sign Language hand gestures with definitions given in text or picture thereby increasing the flexibility and customization properties of training protocols.

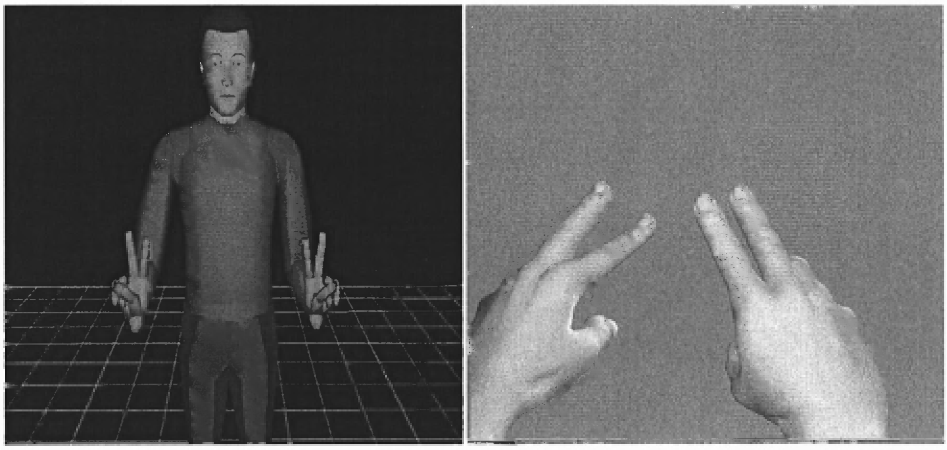


Figure 3.1VESLI Teacher Avatar in Third Person Perspective and First Person Perspective.

Subjects who are unable to read are not restricted: they may find picture definitions of hand gestures to be helpful in rehabilitation. Subjects might perform better when imitating first or third person perspective avatars. Also, subjects might perform better in either picture or text mode. VESLI System features may include audio definitions or sound effects for increased sensory experiences. In addition to observation, sounds such as tearing paper are also believed to actuate 'mirror neurons'. Sound is often used as a stimulus for movement therapies, for example, metronome or music is used to provide rhythm for gait training. Future research will investigate sound as a sensory stimulus in VE's for motor skills acquisition. Robot assistance such as CyberGrasp integrated with VESLI can assist the subject in performing the gestures. Analysis of subject preferred sensory and learning modes may be evaluated using VESLI data collection and analysis module, and results may be used to craft an ideal motor learning VE experience for the subject.

The initial VESLI System was designed to focus on hand and finger rehabilitation and includes hand shapes associated with varying motor skills levels. American Sign Language hand gestures with their own codified taxonomy are included in the VESLI designs. Hand shapes from ASL were compared with the scale described in the Chedoke-McMaster Assessment Hand Impairment Levels frequently used to classify patients with similar rehabilitation goals, as well as the Fugl-Meyer. These scales are used by clinicians in order to measure changes in physical function, and to assess impairment in physical function. Signs used in the present research studies were notated and organized in the database for levels of difficulty according to the referenced scales and performance measurement techniques with Angel, for example at level 3 and Cage, for example at level 5.

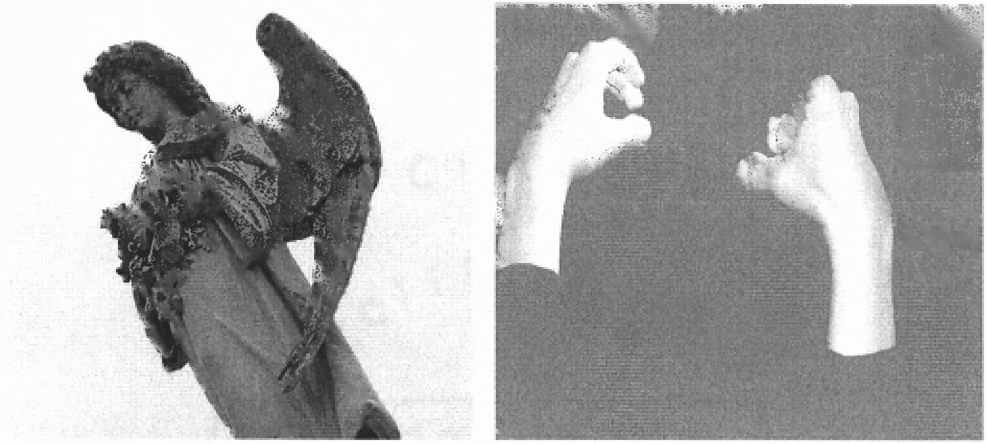


Figure 3.2 ASL Sign "Angel" Difficulty Level 3

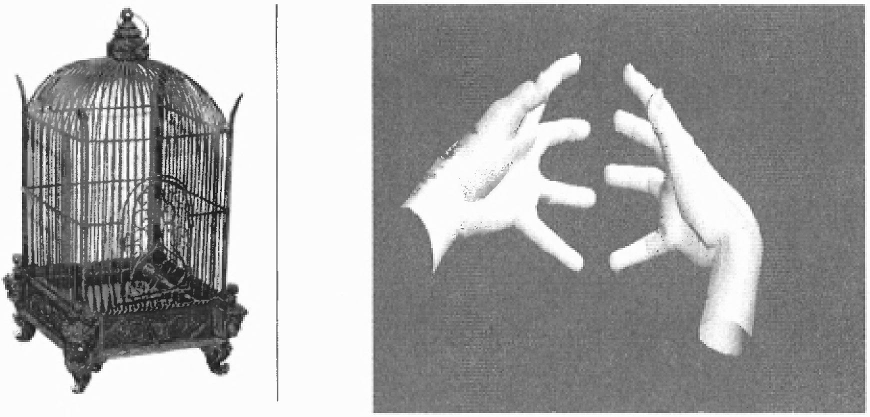


Figure 3.3 ASL Sign "Cage" Difficulty Level 5.

Of course, hand together with arm (HAT) performance might similarly be assessed using Chedoke-McMaster Stroke Assessment and Fugl-Meyer hand and arm impairment scales, and correlated with ASL or other codified or developed gesture system to include finger, hand and arm, or simply to focus on isolated arm protocols.

Skills may be traversed from simple to more complex as the individual progresses through rehabilitation. Biometric data may be gathered from the sensors in the gloves used in the VESLI System to determine functional level of performance of the individual.

VESLI features enable unilateral, bilateral, and mirror exercises or time shifted exercises with or without concurrent robotic assistance. The VESLI system may be used to reverse gestures. Movements noted for the right hand may be demonstrated and imitated using the left hand, increasing the flexibility of the system to provide custom rehabilitation protocols. Mirror protocols may be achieved simply by using biometrics captured by the glove of the unaffected hand and actuating opposite or both virtual hands with the same data. VESLI Mirror hand features may be incorporated into Hand Alone (HA), Hand and Arm Together (HAT), or Hand and Arm Separately (HAS) protocols. Future research is to investigate transfer of the skill to the affected hand.

Gestures in the database have been classified for Symmetric motion. These Symmetric motion gestures are compatible with VESLI Mirror exercises enabling simultaneous mirror image of the skilled hand to overlap the hemiparetic hand for rehabilitation. In this VESLI Mirror feature, biometrics from the skilled hand are captured and are used to animate the virtual hand representing the less-skilled hand, providing a unique sensory experience for rehabilitation that may not easily be achieved outside the VE. The subject may therefore participate in rehabilitation, even if he or she cannot move his or her own hand enough to participate in traditional therapies. Traditional rehabilitation typically requires a twenty degree minimal MCP joint voluntary movement of the affected hand. VESLI features might offer rehabilitation even to people who cannot participate in traditional therapies. VESLI Mirror therapy might be ideal for early intervention for acute stroke. An example of a gesture that may be used in bilateral symmetric exercise such as Left-Right Therapy or Mirror Virtual Therapy (MVT) is Lobster figure. In addition to providing an environment wherein a proxy hand model may be used, VESLI may be used with the subject's own hands hidden during practice.

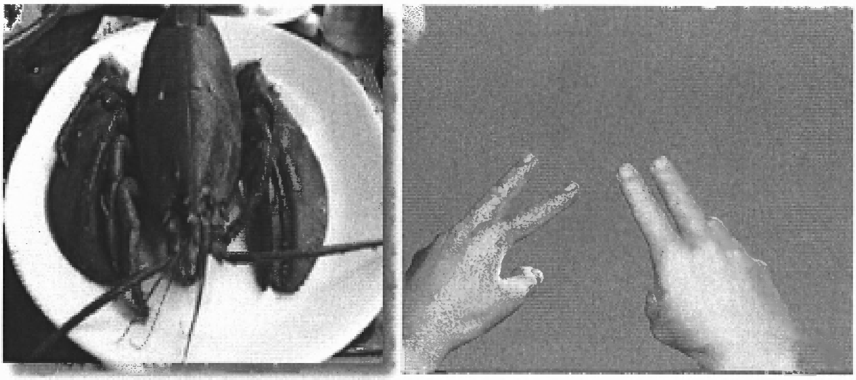


Figure 3.4 ASL Symmetric Gesture for Virtual Mirror Exercise.

The VESLI System may be used to provide sensory motor training and Memory Exercises to engage target brain regions associated with learning hand gestures and rehabilitation of the hand. Gestures may include transitive (associated with tool use or pantomime of tool use) or intransitive (associated with language and not tools) and believed to be easier to imitate. The system measures and provides feedback of performance as the subject selects definitions of previously practiced hand gestures. It is believed that such tasks necessarily actuate target regions associated with hand movement planning such as Broca's Area, and provide observation opportunities. This method represents a unique hand therapy technique. In the example, a subject sees two pictures, Cat and Lobster, and one gesture. The subject selects the picture associated with the gesture.

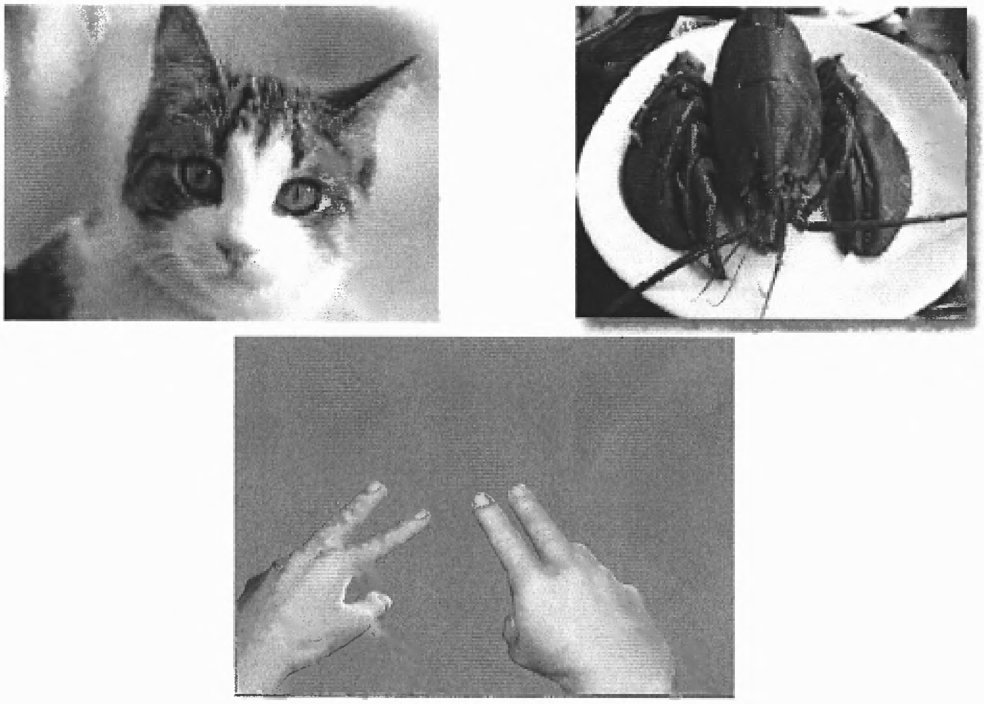


Figure 3.5 VESLI Memory Task - Select the Definition for the Hand Gesture.

3.4 VESLI Uses American Sign Language

A database of American Sign Language gestures and definitions including illustrations has been included in the VESLI System for imitation protocols. Gestures are demonstrated by avatars in 3rd Person Perspective and in 1st Person Perspective for flexibility and to accommodate to subject's individual learning style. Some individuals have difficulty rotating signs demonstrated by 3rd person avatars and may benefit from direct imitation offered by the 1st person avatar.

Within the American Sign Language, there are approximately 150 hand shapes. Not including finger spelling, there are seventeen ASL hand shapes considered to be phonemically distinct. In order to identify the motor related complexity or difficulty in producing hand gestures included in VESLI, the following classification systems were used to rate and group the gestures:

- Chedoke McMaster Stroke Assessment (CMA). The Impairment Inventory for the arm and hand is quantified using a seven point staging system and has been shown to have excellent validity and reliability (Gowland, Stratford et al. 1993).

- Fugl-Meyer. The shoulder/elbow/wrist/hand section (Fugl-Meyer et al., 1975). This scale is perhaps one of the most commonly utilized tests of impairment and has strong validity and reliability scores (Sanford, Moreland et al. 1993; Platz, Pinkowski et al. 2005; Woodbury, Velozo et al. 2007) .

The ASL hand shapes have been classified using the Chedoke-McMaster Stroke Assessment and Fugl-Meyer. The following relationship between the hand shapes and the Hand Impairment Levels was determined:

- the fist for ASL letters A, S, T, or 10 correlated with Chedoke-McMaster Stroke Assessment, Mass Finger Flexion, Hand Impairment Level 3
- the "okay" hand with thumb touching index finger for ASL letters F, or 9, correlated with Pincer Grasp, Hand Impairment Level 3

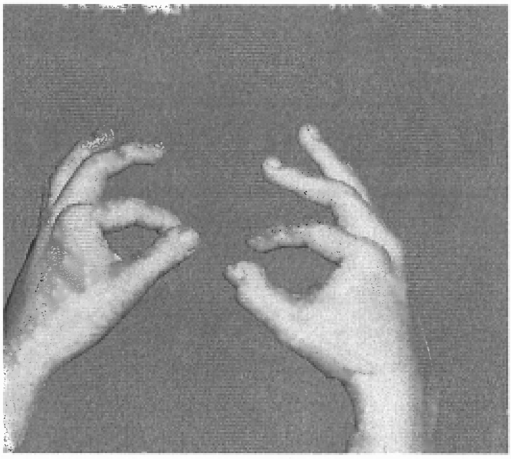


Figure 3.6 ASL Gesture for Cat.

- the flat hand for ASL letters B, or 4 correlated with Mass Finger Extension, Hand Impairment Level 4
- the spread and sometimes clawed hand for ASL letters E, or 5, correlated with Abduction With Extension, Hand Impairment Level 5

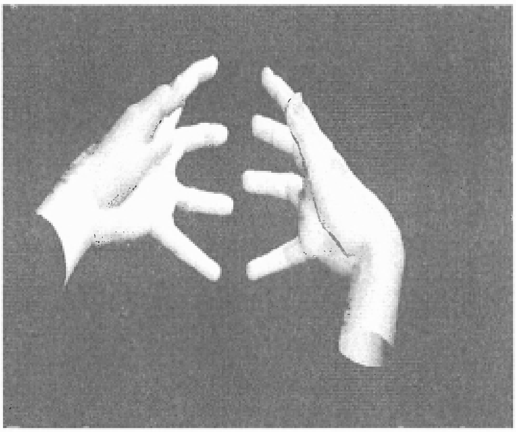


Figure 3.7 ASL Gesture for Cage.

- the thumb touching pinkie as in ASL letters W or 6, correlated with Pinkie Extended and Thumb Pincer, Hand Impairment Level 5
- the thumb, index, and middle finger extended as in the ASL 3 hand, correlated with First, Second, and Third Digit Extension With Fourth, and Fifth Digit Flexion, Hand Impairment Level 5
- the pinkie with thumb and/or index finger, or a spread hand with bent middle finger as in the ASL letters Y, 8, "devil's horns", bent middle-finger, and "I love you" or airplane hands, correlating with Isolated Thumb, Index, and Fifth Digit Extension With Third and Fourth Digit Flexion, Hand Impairment Level 5
- the index and middle fingers together for ASL letters U, H, or N, correlating with Abduction With Finger Extension, Hand Impairment Level 5/6
- the index and middle fingers apart for ASL letters V or 2, correlating with Hand Impairment Level 5/6

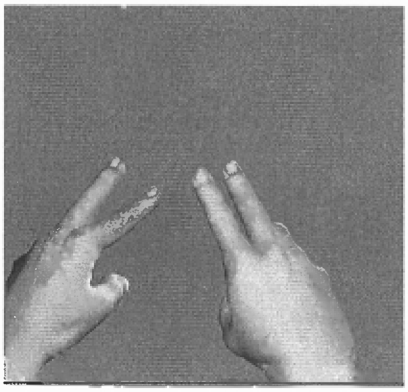


Figure 3.8 ASL Gesture for Lobster.

- the thumb and index finger apart for ASL letter L, correlating with Thumb Abduction With Index Finger Extension, Hand Impairment Level 6
- a pointing index finger for ASL letters D, B, Z, Q, and 1, correlated with Pistol Grip Then Flexion, Hand Impairment Level 6
- a hooked index finger for ASL letter X, correlated with Pistol Grip Then Flexion, Hand Impairment Level 6
- the "chopsticks" hand for ASL letters K, or P, correlating with Third Finger Lumbrical Extension With Second Finger Extension, Hand Impairment Level 6/7
- the thumb touching fingertips for ASL letters O, or M, correlated with Thumb Touching Tips, Hand Impairment Level 7
- the cupped hand for ASL letter C, correlated with Cylindrical Grasp, Fugl-Meyer
- the crossed index and middle fingers as in ASL letter R, correlated with Extension of First and Second Fingers, Adduction With Crossover, Fugl-Meyer
- a pointing pinky finger then hooked for ASL letters I, or J, correlated with Isolating Fifth Finger Then Flexion, No Associated Hand Impairment Level, Fugl-Meyer.

3.5 VESLI – Hand Gesture Definitions

Hand gestures listed herein were used in the design of the behavioral and fMRI Study with First Person and Third Person Avatar for Imitation. Corresponding hand shape description and level of difficulty corresponding to the Chedoke-McMaster Scale and Fugl-Meyer are included.

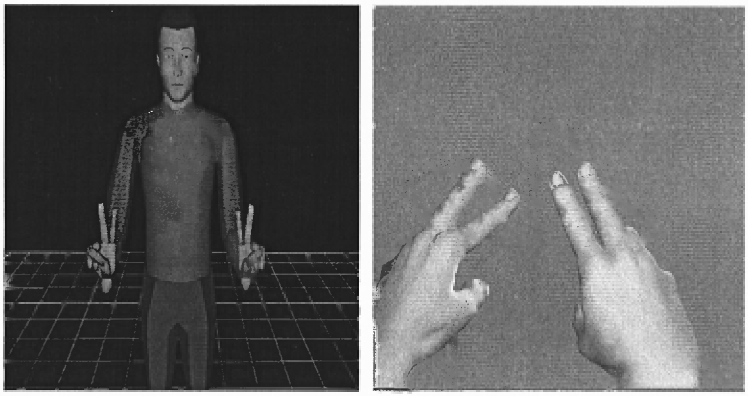


Figure 3.9 VESLI Avatar Third Person Perspective and First Person Perspective.

Third Person Avatar gestures were created using Jack software and movies were recorded and included in the database. First Person Avatar gestures were created using Virtools and CyberGloves, and movies were recorded and included in the database.

The VESLI System database also includes pictures for use as definitions during rehabilitation exercises, during behavioral and during functional imaging studies.

Some signs are described as 'symmetric' and they may be convenient for mirror and bilateral exercises since both hands will perform the same action and the VE is ideally suited to depict the more affected or less skilled hand moving in unison with more skilled hand. The virtual proxy hand may be conveniently displayed in a 'where is' position, overlapping the less skilled or hemiparetic hand.

Since the Flock of Birds may be used, position of the hand in VESLI may be obtained from the subject's own wrist position so a more extensive inventory of gestures and exercises may be included in rehabilitation activities. The flock of birds can position the proxy hand in a suitable position in virtual reality to provide a stronger visual feedback experience for the trainee. Performance and animation data is gathered from sensors in the gloves and the Flock of Birds. The Flock of Birds may also be used to drive a robot that assists the less skilled limb to match movements of the more skilled limb.

For symmetric gestures, a selection may be made regarding which glove generates animations for which visible virtual hand thereby providing Virtual Mirror Therapy, unachievable in the real world. Signs with symmetric characteristics may use the same hand biometric data (postures) for both hands even when the gesture involves varied or overlapping positions of the hands. Symmetry of hand shape may be achieved using data from unaffected hand, but motion of the two hands might vary with regard to position of the wrist, or temporal aspects of the hand gesture itself. For example, the hand gesture to be produced by the affected hand may have been previously recorded using sensors on the less affected hand and may be alternately replayed to the subject at an appropriate time, independently from the movement to be produced by the less affected hand thus increasing the types and variations of the exercises.

Execution of the ASL and other gestures in the VESLI System might simplify arm motion to provide hand gesture exercise, or might include the arm for combined Arm-Hand Therapy. Hand gestures depicted herein may be reversed to target opposite hand and to provide alternate hand unilateral exercise. Skills training may be conducted with less-affected hand and then transferred to the affected hand. Future research will investigate the transfer skills protocol. Future research will investigate hand-eye coordination during practice and recall. More detailed descriptions of hand gestures may be found in referenced dictionary.

3.6 Third Person Avatar-Gestures for Imitation

The following gestures were included in the behavioral and functional imaging study design involving the First Person Avatar.

3.7 Learning Session One

- Angry Text: Curved 5 hand, Impairment Level 5.
- Baby Picture: Bilateral – flat hands, Impairment Level 4.
- Love Picture: Bilateral S hands crossed at wrists, Impairment Level 3.
- Bear Picture: Symmetric – bilateral – curved hands, crossed at wrist, Impairment Level 5.
- Cat Text: Symmetric motion – bilateral – F hands, Impairment Level 3.
- Flower Picture: Flattened right O hand, Impairment Level 7.
- Floor Text: Symmetric motion – bilateral – flat hands, Impairment Level 4.
- Fruit Picture: Right F hand, Impairment Level 3.
- Lobster Text: Symmetric motion – bilateral V hands, Impairment Level 5/6.
- Sheep Picture: Left flat hand, right V hand, Impairment Level 5/6.
- Drive Text: Bilateral S hands, Impairment Level 3.
- Pray Picture: Symmetric motion – bilateral open hands, Impairment Level 4.
- Book Text: Symmetric motion – bilateral open hands, Impairment Level 4.
- Game Picture: Symmetric motion – bilateral 10 hands, Impairment Level 3.
- Gift Text: Symmetric motion – bilateral X hands, Impairment Level 6.
- Machine Picture: Symmetric motion – bilateral curved 5 hands, Impairment Level 5.
- Cross Text: Symmetric – bilateral open hands, Impairment Level 4.
- Sketch Picture: Left open hand, right isolated pinkie, left Impairment Level 4, right Isolated pinkie, Fugl-Meyer.
- Bread Text: flat left hand, bent right hand, Impairment Level 4.
- City Text: Symmetric – bilateral bent hands, Impairment Level 4.
- Chair Text: Symmetric – bilateral U hands, Impairment Level 5/6.
- Cup Text: left open hand, right C hand, left hand Impairment Level 4, right hand Cylindrical Grasp, Fugl-Meyer.
- Plane Picture: right extended index and pinkie, bent middle and ring fingers, Impairment Level 5.

- Café Picture: right C hand, Impairment Level Cylindrical Grasp, Fugl-Meyer.
- Cake Picture: left open hand, right curved 5 hands, left Impairment Level 4, right Impairment Level 5.
- Child Picture: right bent hand, Impairment Level 4.
- Drill Picture: right L hand, Impairment Level 6.
- Kiss Text: right O hand, to open hand, Impairment Level 7.
- Bus Text: Symmetric – bilateral B hands, Impairment Level 4.
- Eat Picture: right flattened O hand, Impairment Level 7.
- Mother Picture: right 5 hand, Impairment Level 5.
- Dress Text: Symmetric motion – bilateral 5 hands, Impairment Level 5.

Control Signs

- East Text: right E hand, Impairment Level 5.
- Dig Text: Symmetric – bilateral modified X hands, Impairment Level 6.
- Eye Picture: right extended index finger, Impairment Level 6.
- Egg Picture: Symmetric motion – bilateral H hands, Impairment Level 5/6.
- Black Text: right extended index finger, Impairment Level 6.
- Door Picture: Symmetric – bilateral B hands, Impairment Level 4.
- Jacket Picture: Symmetric motion – bilateral A hands, Impairment Level 3.
- West Text: right W hand, Impairment Level 5.
- House Picture: Symmetric motion – bilateral extended index fingers, Impairment Level 6.
- Luggage Picture: Symmetric motion – bilateral S hands, Impairment Level 3.

3.8 First Person Avatar—Gestures for Imitation

The following gestures were included in the behavioral and functional imaging study design involving the First Person Avatar.

3.9 Learning Session Two

- Guitar Picture: Left curved 5 hand – Level 5, right F hand – Level 3.
- Piano Picture: Symmetric motion – bilateral -- curved 5 hands – Level 5.
- Flute Text: Symmetric – bilateral – curved 4 hands – Level 4.
- Band Text: Symmetric – bilateral – open right hand, both C hands – Level 4 flat hand, Cylindrical Grasp bilateral.
- Coffee Picture: Symmetric – bilateral – fist – Level 3.
- Cereal Picture: Symmetric – bilateral – open hands – Level 4.
- Bacon Picture: Symmetric motion – bilateral – H hands – Level 5/6.
- Certificate Text: Symmetric motion – bilateral – C hands – Cylindrical Grasp.
- Berry Picture: Isolated left pinkie -- right O hand – Level 7.
- Pear Text: Left O hand, Level 7 – right 5 hand, Level 5.
- Corn Picture: Symmetric motion – bilateral – C hands – Cylindrical Grasp.
- Bone Text: Symmetric – bilateral – A hands, Level 3 – bent V hands, Level 5/6.
- Calendar Text: Left open hand, Level 4 -- right C hand, Cylindrical Grasp.
- Celery Picture: Right G hand – Level 5.
- Cage Text: Symmetric motion – bilateral -- 4 hands – Level 5.
- Ball Text: Symmetric motion – bilateral – 5 hands – Level 5.
- Butterfly Picture: Symmetric – bilateral – open hands – Level 4.
- Lightning Text: Pointing index fingers – Level 6.
- Lake Picture: W hand, Level 5 – C hand, Cylindrical Grasp.
- Angel Text: Symmetric motion – bilateral – bent hands – Level 3.
- Temple Picture: Right T hand, left S hand – Level 3.
- Trophy Text: Isolated Thumb, and Fifth Digit Extension With Index, Third, and Fourth Digit Flexion.
- Autopsy Picture: Symmetric motion – bilateral – open hands, Level 4 – 10 hands, Level 3.
- Candle Text: Right index extended, Level 6 -- left 5 hand, Level 5.
- Church Picture: Right C, Cylindrical Grasp – Left S, Level 3.

- Blue Text: Symmetric – bilateral -- Flat hand – Level 4.
- Bridge Picture: Right V hand – Level 5/6.
- Pennant Text: Left index finger, Level 6 -- right L hand, Level 6.
- Bird Picture: right G hand – Level 5.
- Person Text: Symmetric motion – bilateral -- P hand -- Third Finger Lumbrical Extension with Second Finger Extension, Hand Impairment Level 6/7.
- Headlight Picture: Symmetric motion – bilateral – O hands, Level 7 to 5 hands, Level 5.
- Corner Text: Symmetric motion – bilateral – flat hands – Level 4.

No Go – Control Signs

- Sketch Text: Open left hand – right I hand, Isolated fifth finger, Fugl-Meyer.
- Bus Text: Little-finger side of the right B hand touching index-finger side of left B hand palms opposite directions, move right hand back and forth to right shoulder, Impairment Level 4.
- Bear Picture: Symmetric – bilateral – curved hands, crossed at wrist, Impairment Level 5.
- Leaf Picture: Left extended index finger, right 5 hand, bent wrist, swing right hand, Left hand Impairment Level 6, Right hand Impairment Level 5.
- Cat Picture: Symmetric motion – bilateral – F hands, Impairment Level 3.
- Lobster Picture: Symmetric motion – bilateral – V hands, Impairment Level 5/6.
- Cake Picture: Left open hand, Hand Impairment Level 4 -- right curved 5 hand, Impairment Level 5.
- City Text: Symmetric – bilateral – bent hands, Impairment Level 4.
- Dress Text: Symmetric motion – bilateral – 5 hands, Impairment Level 5.
- Gift Text: Symmetric motion – bilateral – X hands, Impairment Level 6.
- Cross Picture: Bilateral open hands, Impairment Level 4.
- Chair Text: Bilateral curved U hands, Impairment Level 5/6.

Control Signs

- Flashlight Text: Left hand holds right wrist, right O hand to open 5 hand, Impairment Level 7.
- Baseball Text: Bilateral S hands, Impairment Level 3.

- Bottle Text: Open left hand, right C hand, Impairment Level 4 left hand, Fugl-Meyer Cylindrical Grasp right hand.
- Marble Text: modified X hand, Impairment Level 6.
- Banana Picture: Extended left index finger, curved 5 right hand, Impairment Level 6 left hand, Impairment Level 5 right hand.
- Broom Picture: Bilateral S hands, Impairment Level 3.
- Burn Text: Symmetric motion – bilateral – curved 5 hands, Impairment Level 5.
- Peace Picture: Bilateral open hands, Impairment Level 4.
- Person Text: Symmetric motion – bilateral – P hands, Impairment Level 6/7.
- Pepper Picture: Right F hand, Impairment Level 3.
- Tent Picture: Symmetric motion – bilateral – Isolated index and pinkie, flexed middle and ring finger, Impairment Level 5.
- Lime Picture: Closed left, right L hand, Impairment Level 3 left, and Impairment Level 6 right hand.

RESEARCH AIM 2

4.1 Experiment 1 fMRI Analysis of Neural Mechanisms Underlying Rehabilitation in Virtual Reality: Activating Secondary Motor Areas

A pilot functional MRI study on a control subject investigated the possibility of inducing increased neural activations in primary, as well as secondary motor areas through virtual reality-based exercises of the hand. These areas are known to be important in effective motor output in stroke patients with impaired corticospinal systems. We found increased activations in these brain areas during hand exercises in VR when compared to vision of non-anthropomorphic shapes. Further studies are needed to investigate the potential of virtual reality-based rehabilitation for tapping into the properties of the mirror neuron system to stimulate plasticity in sensorimotor areas.

4.1.1 Introduction

Virtual Reality (VR), a flexible computer generated environment used to develop exercise protocols for stroke rehabilitation, has been demonstrated to be effective in improving upper extremity motor function in adults with chronic stroke-related hemiparesis (Merians, Poizner et al. 2006). Underlying mechanisms of action, however, are poorly understood. Functional MRI compatible VR can be used to assess and track neural activation during exercises with somatosensory experience including manipulated or altered virtual experiences (Brewer, Fagan et al. 2005) modeled to stimulate 'mirror neurons' (Rizzolatti and Craighero 2004) associated with motor facilitation

(Fadiga, Fogassi et al. 1995) (Maeda, Kleiner-Fisman et al. 2002), and to determine activation of secondary motor systems important for effective motor output in stroke subjects with corticospinal system (CSS) impairment (Ward 2006). Stroke rehabilitation is moving into the realm of plasticity-mediated therapies (Stein 2004) related to the ability of the adult brain to re-map functions, shifting regions of motor control to adjacent tissue (Asanuma 1991) (Jacobs and Donoghue 1991) (Nudo, Wise et al. 1996), or the contralateral hemisphere (Fisher 1992) (Glees 1980) (Sabatini, Toni et al. 1994) to take over functions of damaged cortical tissue.

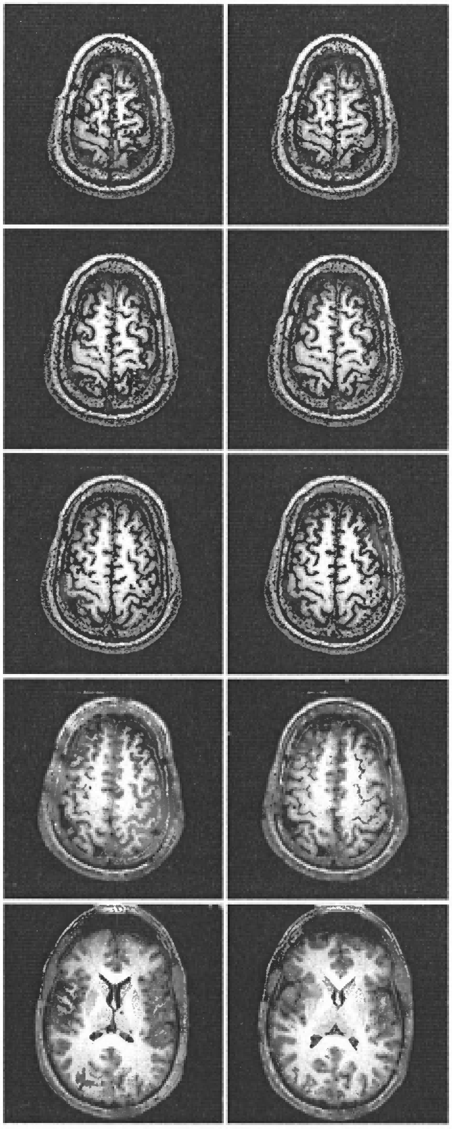


Figure 4.1 Move-Watch Hands and Move Watch Blobs Slices: Left - Move while watching moving VR hand   Right Move while watching Blobs.

In the figure, Move-Watch Hands and Move Watch BlobsSlices activations are depicted at specified Talairach Z coordinate with highlighted significant increases in activation relative to baseline, a) Condition 1: Left Column of Images - Move while watching moving VR hand   b) Condition 2: Right Column of Images - Move while watching static oval shape. Right side of the brain is shown on the left. In a recent study involving patients post-stroke, a shift from primary to secondary motor networks was observed corresponding to the impairment of the CSS, with both hemispheres engaged in the generation of motor output. Secondary motor systems including ipsilesional posterior primary motor cortex, contralesional anterior primary motor cortex, bilateral premotor cortex, supplementary motor area, intraparietal sulcus, dorsolateral prefrontal cortex and contralesional superior cingulate sulcus, are important for effective motor output when there is impaired function of the CSS, although this strategy for movement is not optimal (Ward 2006). Properties of the mirror neuron system believed to exist in the human brain may explain the human ability to learn by imitation (Fadiga, Fogassi et al. 1995) (Maeda, Kleiner-Fisman et al. 2002) (Patuzzo 2003). We are interested in tapping into the properties of the mirror neuron system to stimulate secondary motor systems and plasticity of motor control through our hand imitation VR rehabilitation. Imitation exercises are more effective in activating pars opercularis of IFG during finger lifting than symbolic or spatial cues indicating importance of mirror neurons (Iacoboni, Woods et al. 1999). Visual guidance can reduce cognitive burden in stroke subjects compared with self-guided tasks (Hanlon, Buffington et al. 2005). In rehabilitation, compliance can be difficult to confirm (Pomeroy, Clark et al. 2005). Intelligent VR can provide imitation applications, visual guidance, and can monitor compliance, making VR an attractive choice for rehabilitation. Higher level functioning mediates motor skills learning by imitation (middle frontal gyrus for learning novel hand actions) (Buccino, Vogt et al. 2004; Buccino, Vogt et al. 2004). Our hypothesis is that in the presence of VR protocols, a complex visuo-neuro stimulus can be achieved that engages mirror neurons for sensorimotor imitation, and secondary motor systems, known to be necessary for motor output in stroke patients while providing visual guidance, known to benefit stroke patients and older persons. We hypothesize that training and rehabilitation interactions in the VR environment might stimulate important cognitive networks. We believe that the training and rehabilitation in a VR environment that is matched for observation and action (Wheaton, David F. Abbott et al. 2004) is appropriate since it has been shown that performance improves for such task configurations. It has also been shown that presenting a first-person perspective for imitation, might stimulate more direct and stronger cognitive networks than third-person perspective. Viewing virtual hand movement during VR exercises might activate hand-relevant parts of the brain (right MT/V5, left and right anterior IPS, right precentral gyrus, and right inferior frontal sulcus (Wheaton, David F. Abbott et al. 2004)), might promote engagement in feelings of ownership of the virtual hand (Ehrsson, Spence et al. 2004; Ehrsson, Wiech et al. 2007), understanding goals of the observed virtual action (Hamilton and Grafton 2006), recognition of biological movement (Servos, 1 Department of Psychology et al. 2002) of the virtual hand in the scene, and sense of self-awareness and agency (Decety, aDepartment of Psychology et al. 2006; Jackson, Meltzoff et al. 2006). Ultimately, this MRI compatible VR environment might enable analysis of the feedback and feed-forward realtime dynamics of the brain network associated with the interaction of visual recognition of actions and the control of actions (Hamilton, Wolpert et al. 2006). We would like to determine whether secondary motor systems, recruited for motor control in stroke subjects with CSS injury, can be activated through engagement in hand VR training. Therefore, we conducted an initial pilot experiment in a VR environment using functional MRI.

4.1.2 Methodology

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= 22 cm x 22 cm, slice thickness = 4 mm, 32 slices) were acquired over 105 data points (210 seconds). The scan was obtained while subjects were instructed to perform hand exercises. Images were processed using AFNI software.

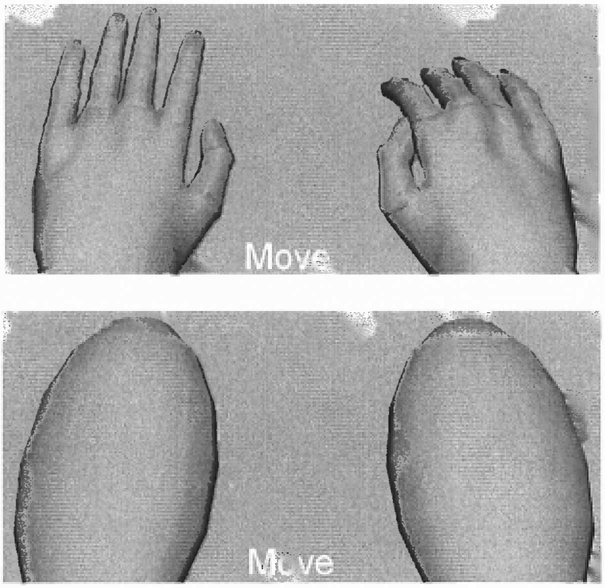


Figure 4.2VR representation viewed by subject, a) Condition 1: Move while watching moving hand, b) Condition 2: Move while watching static oval shape

All data were tested for the presence of any head motion induced signal changes using image registration algorithm. A synthesized box-car waveform corresponding to the stimulus presentation cycle was cross-correlated with all pixels on a pixel-by-pixel basis for each data set to identify the regions activated by the task. The correlation-coefficient threshold of 0.5, after a Bonferroni correction, corresponded to a statistical significance of $p < 0.001$. All pixels that passed this threshold were considered activated and belonging to the sensorimotor and its associated cortex.

In the trial experiment, the control subject is presented with a task to perform in the MRI environment, and in analysis, changes relative to a control state are mapped. A 41 year-old right-handed control subject participated in an imitation of hand movement protocol created in a three-dimensional VR environment. A 5DT MRI compatible VR glove was used on the subject's right hand to control the VR animated hand, to correlate brain activation with finger articulation, and to confirm subject compliance with instructions. Eight experimental runs were conducted, each beginning with a thirty second period of rest for baseline followed by four fifteen second test tasks separated by thirty second periods of rest.

The subject is first asked to watch the virtual hand animation (opening and closing of the hand at about 1 Hz), while intending to imitate the action. In Condition 1, he is asked to reproduce the observed hand motion by moving his right hand while watching the moving representation of his hand on the screen. In Condition 2, the subject moved his right hand while looking at oval shapes displayed on the screen the same color and size as the virtual hands.

4.1.3 Results

When Condition 1 was compared with Condition 2, greater activation in a number of regions associated with the sensorimotor control of the hand is observed in Condition 1 while the subject sees the virtual hand moving. In addition to increased activation in the primary motor cortex, we observed increased activation in a number of sensorimotor areas including dorsal premotor and supplementary motor areas, as well as anterior cingulate cortex, anterior intraparietal cortex and superior temporal gyrus. Analysis of the hand kinematics demonstrated that this increase in brain activation was not associated with any significant increase in the amplitude or frequency of finger motion.

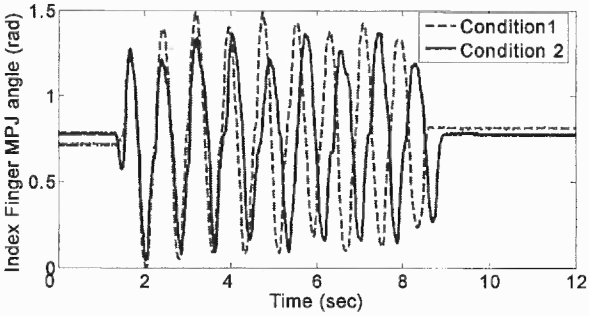


Figure 4.3 Representative example of angular displacements for the metacarpophalangeal joint (MPJ) of the index finger during brain imaging in Condition 1 and Condition 2. Condition 1: Move while watching moving VR hand. Condition 2: Move while watching static oval shapes.

4.1.4 Discussion

The control subject showed distinctly different activation under each condition. Relevant secondary motor systems were activated by observation of the virtual hand during exercises in the VR environment and were not activated when the subject performed the hand exercise in the absence of the virtual hand animation. The preliminary findings in this pilot study suggest that an imitation hand exercise protocol in VR might be an excellent choice for training stroke subjects since activation of secondary motor systems has been associated with successful motor skills performance in stroke subjects with CSS impairment. VR provides flexibility to manipulate visual feedback to the subject as part of the therapy, a desirable feature for stroke rehabilitation. Additionally, VR may be used to monitor compliance and to provide visual guidance for rehabilitation tasks.

Since multiple theories exist about brain plasticity and its role in motor skills recovery, we believe the computer-based intelligent VR physical therapy provides great opportunities to deliver therapy in a low-cost architecture, to study the mechanisms of human motor skills recovery, and to test these concepts through functional imaging while simultaneously measuring motor performance. It has been shown that an environment matched for observation and action improves performance (Jackson, Meltzoff et al. 2006), that first person perspective stimulates more direct cognitive networks, that viewing hands activates specific hand-relevant brain regions (Wheaton, David F. Abbott et al. 2004), that feelings of ownership of external objects can be developed (Ehrsson, Spence et al. 2004; Ehrsson, Holmes et al. 2005), that a person can understand the goal of the movement in an exercise (Hamilton 2006), that the brain can differentiate biological and linear (Servos, 1 Department of Psychology et al. 2002) movement through different regions (Decety, aDepartment of Psychology et al. 2006), and that the effect of causal involvement, agency, can be experienced.

It is possible that use of the complex VR environment may expose the subject to these experiences and may therefore activate many brain regions associated with motor skills and related experiences. We also believe that complex feed forward and feedback interaction of visual processing of body parts, actions and the motor control of actions (Kennett, Taylor-Clarke et al. 2001; Hamzei, Dettmers et al. 2002; Haggard, Christakou et al. 2007) may play a role in the rehabilitation of stroke subjects who are suffering from paralysis of the hand. A person may see their hand and its function more than most other parts of their body. Investigating the complex cognitive network associated with the perception and motor action of the hand might help to uncover relevant clues for rehabilitation of motor skills following stroke. Specifically, we are encouraged by the properties of mirror neurons and seek methods of accessing these properties to stimulate secondary motor systems recruited for motor movement in stroke subjects with CSS injury. VR enables development of rehabilitation systems and also investigation into this area. Future work will include extending this preliminary work to include additional control subjects, additional rehabilitation protocols, and studies including stroke subjects.

4.1.5 Conclusion

In our trial experiment, using functional MRI to understand underlying mechanisms of action of VR rehabilitation exercises, the subject trained in a VR environment for an imitation task resulting in desired activation of the brain regions associated with secondary motor systems. We are encouraged that through functional imaging experiments with VR, we will be able to understand underlying neural mechanisms leading to the development of rehabilitation protocols for imitation hand therapies for subjects suffering from various motor control issues such as stroke.

4.2 Experiment 2 Design of an fMRI Compatible System to Explore Neural Mechanisms Subserving VR Therapies

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.

4.2.1 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 (Merians 2002; Adamovich, Merians et al. 2005; Merians, Poizner et al. 2006). 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 (Merians, Jack et al. 2002). 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 (Paulignan 1990), training the upper extremity as a unit may lead to improved outcomes. Additionally, although treatment benefits have been reported with unilateral robotic-assisted training (Krebs, Hogan et al. 1998) and training in a VR environment (Holden, Todorov et al. 1999; Adamovich, Merians et al. 2005), most functional activities involving the upper extremities are bilateral in nature. Bernstein (Bernstein 1967) 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 (Cauraugh and Summers 2005). Several researchers have used bilateral training to harness these spatial and temporal interactions (Mudie 2000; Whitall, McCombe Waller et al. 2000; Lum, Burgar et al. 2002; Hesse, Schulte-Tigges et al. 2003). 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 (Iacoboni 1999 ; Maeda, Kleiner-Fisman et al. 2002; Rizzolatti and Craighero 2004). 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 (Perani 2001), though it is important to consider whether one is just watching an action, even a realistic natural movement, or whether one attributes the 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.

4.2.2 Methods - 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. 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 (2006) with the VRPack plugin which communicates with the open source VRPN (Virtual Reality Peripheral Network) (Taylor 2006). 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 (Immersion 2006) with the Ascension Flock of Birds (Ascension). The 5DT fMRI compatible glove , 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.

Figure 4.4 Virtual Reality Piano Trainer

4.2.3 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. 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.

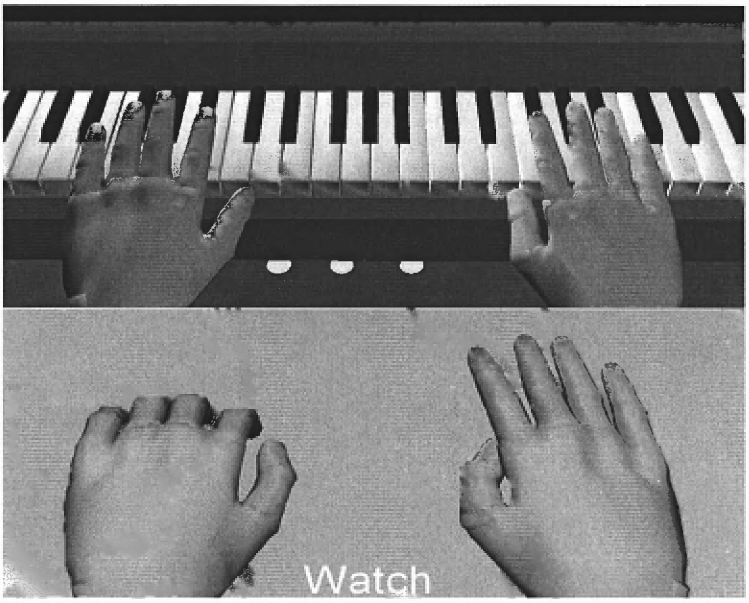


Figure 4.5 a) Subject View during Training Exercise, b) Subject View during fMRI Experiment.

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-anthropomorphic 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.

4.2.4 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.

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.

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. 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 (Biswal and Hyde 1997) 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, (Woods, Grafton et al. 1998) 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 semiempirical method that was described in an earlier paper (Biswal and Hyde 1997) 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 effect of aliasing is a concern, no significant problems have been detected in our work.

4.2.5 Initial Results

The figure 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 (Farrer, Franck et al. 2003) 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:) there was minimal activation relative to the baseline. In post-training, activation can be seen in the insular cortex (Trial 8, OTI:). Figure panels b and c 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 demonstrated in panel b when compared to the minimal activation during the non-anthropomorphic shape simulation illustrated in panel c. The panels illustrate 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. In post training, sections in panel b and d show increased activity above the baseline in the insular cortex (highlighted in white). The right side of the brain is shown on the right.

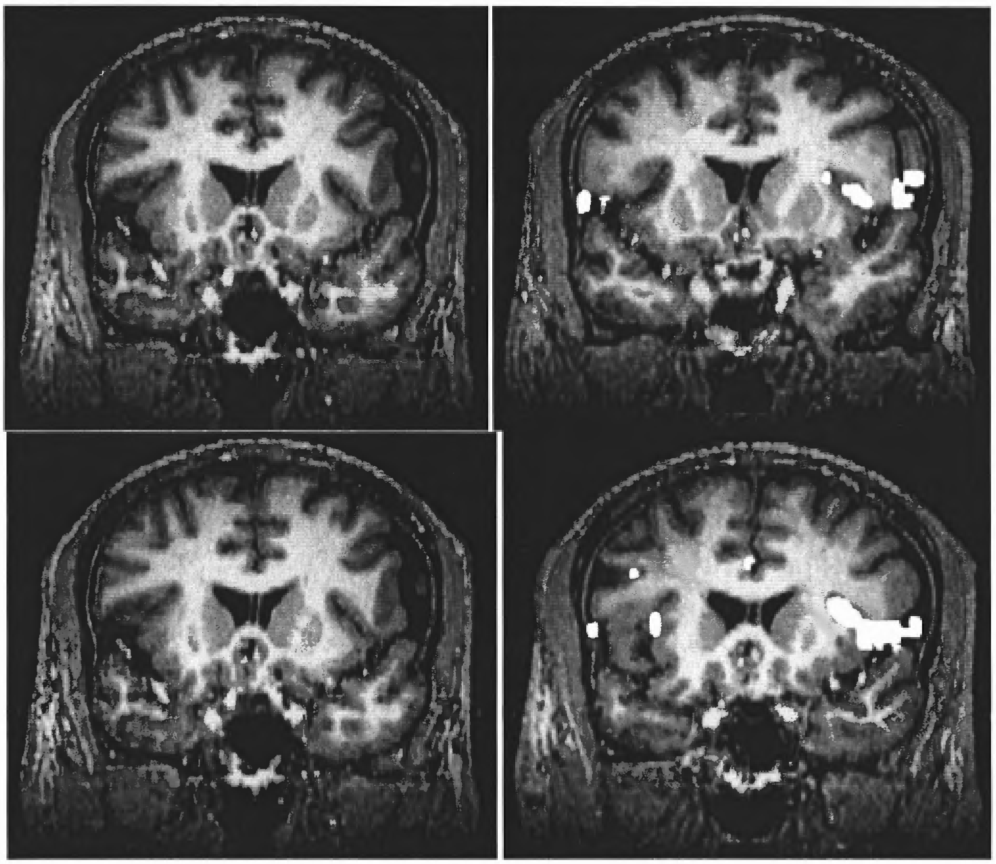


Figure 4.6 Four coronal sections showing activation in insular cortex, a, b, c, and d.

4.2.6 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 (Ward 2006). 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 (Farrer 2003). 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.

4.2.7 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.

4.3 Experiment 3 A Virtual Reality-Based System Integrated with fMRI to Study Neural Mechanisms of Action Observation-Execution: A Proof of Concept Study

Emerging evidence shows that interactive virtual environments (VE's) may be a promising tool for studying sensorimotor processes and for rehabilitation. However, the potential of VE's to recruit action observation-execution neural networks is largely unknown. For the first time, a functional MRI-compatible virtual reality system (VR) has been developed to provide a window into studying brain-behavior interactions. This system is capable of measuring the complex span of hand-finger movements and simultaneously streaming this kinematic data to control the motion of representations of human hands in virtual reality. In a blocked fMRI design, thirteen healthy subjects observed, with the intent to imitate (OTI), finger sequences performed by the virtual hand avatar seen in 1st person perspective and animated by pre-recorded kinematic data. Following this, subjects imitated the observed sequence while viewing the virtual hand avatar animated by their own movement in real-time. These blocks were interleaved with rest periods during which subjects viewed static virtual hand avatars and control trials in which the avatars were replaced with a moving non-anthropomorphic object. We show three main findings. First, both observation with intent to imitate and imitation with real-time virtual avatar feedback, were associated with activation in a distributed frontoparietal network typically recruited for observation and execution of real-world actions. Second, we noted a time-variant increase in activation in the left insular cortex for observation with intent to imitate actions performed by the virtual avatar. Third, imitation with virtual avatar feedback (relative to the control condition) was associated with a localized recruitment of the angular gyrus, precuneus, and extrastriate body area,

regions which are (along with insular cortex) associated with the sense of agency. Our data suggest that the virtual hand avatars may have served as disembodied training tools in the observation condition and as embodied "extensions" of the subject's own body (pseudo-tools) in the imitation. These data advance our understanding of the brain-behavior interactions when performing actions in VE and have implications in the development of observation- and imitation-based VR rehabilitation paradigms.

Keywords: Virtual environment, VR, motor control, imitation

4.3.1 Introduction

Technological advances, such as virtual reality (VR), are experiencing a period of rapid growth and offer exceptional opportunity to extend the reach of services available to a variety of disciplines. Virtual environments (VE's) can be used to present richly complex multimodal sensory information to the user and can elicit a substantial feeling of realness and agency on behalf of the individual immersed in such an artificial world (Riva, Castelnuovo et al. 2006). VR is an indispensable training tool in many areas including healthcare where physicians receive surgical training (McCloy and Stone 2001), patients receive cognitive therapies (Powers and Emmelkamp 2008), and soldiers benefit from post-traumatic stress disorder therapies (Rizzo, Graap et al. 2008). VR also demonstrates great value for the rehabilitation of patients with disordered movement due to neurological dysfunction (Holden, Dettwiler et al. 2005; Gaggioli, Meneghini et al. 2006; Adamovich, Qinyin et al. 2007; Merians 2007), wherein new models including observation (Altschuler 2005; Buccino, Solodkin et al. 2006; Celnik, Stefan et al. 2006), imagery (Butler and Page 2006) and imitation therapies (Gaggioli, Meneghini et al. 2006) which might be instrumental in facilitating the voluntary production of movement, may be incorporated. In spite of showing promise at improving some aspects of movement, the effect that interacting in VE's has on brain activity remains unknown – even in neurologically intact individuals.

The experiences of interest in the VR environment would be observation with intent to imitate, and the ability to integrate real experiences with virtual experiences of one's own movement. Virtual environments might effectively serve as a never-tired model for observation therapy for the facilitation of the voluntary production of movement. Moreover, interactive VE can be used as a powerful tool to modulate feedback during training and motor learning to facilitate recovery through various plasticity mechanisms. However, there is little evidence to enable the testing of this hypothesis in patients with neurological diseases (Pomeroy, Clark et al. 2005). Studies in control subjects are needed to determine the effectiveness of such approach.

The purpose of this project was two-fold: 1) to develop a VE that could be used with functional magnetic resonance imaging (fMRI) for concurrent measurement of motor behavior and brain activity, and 2) to delineate the brain-behavior interactions that may occur as subjects interact in the VE. Our overall hope is that a better understanding of brain-behavior relations when interacting in VE may better guide the use of VE for therapeutic applications. Our long term objective is to identify the essential elements of the VE sensorimotor experience that may selectively modulate neural reorganization for rehabilitation of patients with neural dysfunction. These discoveries will offer a foundation for evidence-based VR therapies, with profound implications in diverse fields as computational neuroscience, neuroplasticity, neural prosthetics, and human computer interface design. Here we present a proof of concept of a novel VR system that can be integrated with fMRI to allow the study of brain-behavior interactions. A sample of our currently developed virtual environments. *A.* Dining Table Scene, *B.* Piano trainer, *C.* The virtual environment used in the current paradigm appears in the figure below. We extracted the essential component common to all of our virtual environments, the virtual hands, over a plane background. Below them is a picture of a subject's hand wearing 5DT data glove that actuated motion of the virtual hand model.

Our initial goal was to design a system capable of measuring complex coordination of the hand and fingers (which have over 25 degrees of freedom), deliver reliable and real-time visual feedback of a virtual representation of the moving hand, with simultaneous acquisition of brain activation (via fMRI). We have developed a library of VE's for re-training hand-arm function in patients with stroke (Merians, Tunik et al. 2008). In all of these VE's, subjects move their arm-hand to control a virtual representation of their hands, in real-time, to interact with various virtual objects (i.e. piano, household items, etc). To directly investigate how controlling a virtual representation of one's hands, in real-time, affects neural activation, we have extracted the essential elements common to all of our environments, a pair of virtual hands. We imaged healthy subjects at 3T as they performed a simple finger movement task. We used the MRI-compatible 5DT data glove to measure subjects' hand movements in real-time to actuate motion of virtual hands viewed by the subjects in a 1st person perspective.

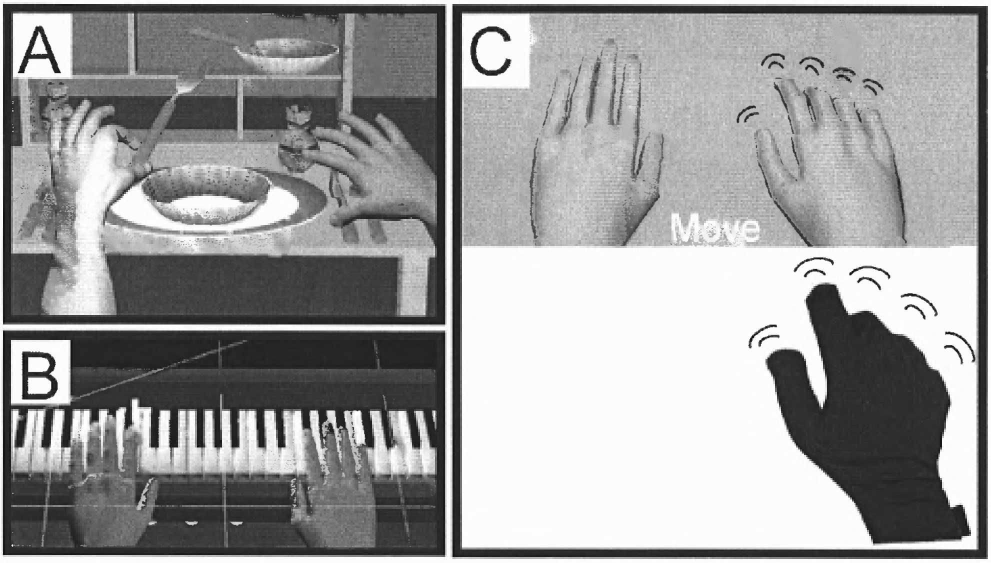


Figure 4.7 Training systems. A sample of our currently developed virtual environments. A. Dining Table Scene, B. Piano Trainer, C. Virtual Hands in the MRI, 5DT Glove.

Subjects observed virtual finger movements (animated with kinematic data that was collected previously from healthy subjects) with an intention to imitate afterwards. Subjects were subsequently required to imitate the observed movements while observing motion of the virtual hands animated in real-time by their actual movement. Perani and coworkers (Perani, Fazio et al. 2001) investigated the effects of observing animations of virtual and real hands on brain activity. The authors noted that observing animated virtual hands was associated with weaker activation in sensorimotor networks when compared to observation of real hands. However, in these studies visual feedback was not of the subject's own real-time movement and was not observed in 1st person perspective. Recently, Farrer and coworkers (Farrer, Frey et al. 2007) presented subjects with visual feedback from a live video feed of their moving hands during the fMRI session. By manipulating the temporal delay between the movement and feedback, the authors investigated neural networks involved in the sense of agency, or sense of control of the action. Their results from this and previous work (Farrer, Franck et al. 2003) suggested that the angular and insular cortices may be involved in this function. The data from the above studies leads us to hypothesize that interaction in a VE in the 1st person should elicit activation in the insular and inferior parietal cortices, regions that are known to be recruited in agency-related tasks (Farrer 2003; Corradi-Dell'acqua, Ueno et al. 2008). Additionally, our study allows us to investigate whether these networks can be recruited when observing with the intent to imitate movement of VR representations of human hands. We hypothesize that in individuals who are naïve to our VE, repeated exposure should induce an increase in activation of agency-related networks.

If we can show proof of concept for using virtual reality feedback to selectively facilitate brain circuits in healthy individuals, then this technology may have profound implications for use in rehabilitation and in the study of basic brain mechanisms (i.e. neuroplasticity).

4.3.2 Methods

13 healthy (mean ± 1SD, 27.7 ± 3.4 years old, 9 males) and right-handed (Oldfield 1971) subjects with no history of neurological or orthopedic diseases participated after signing informed consent form approved by the IRB Committees of NYU and NJIT.

To investigate the underlying role of VR in facilitating movement and activating motor related brain regions, a task-based virtual reality simulation was developed for use in an fMRI. Figure 1 shows the fundamental element of the training system, the VR representations of the user's hands. Movement of the virtual hand models is actuated in real-time by the subject's own hand motion. The virtual environment was developed using Virtools with the VR Pack plugin which communicates with the open source

VRPN (Virtual Reality Peripheral Network) (Taylor 2006). For the present experiments, we used an MRI-compatible right hand *5DT Data Glove 16 MRI* ((Adamovich, Qiu et al. 2008) Fifth Dimension Technologies, 5DT Data Glove 16 MRI, http://www.5dt.com) with fiberoptic sensors to measure 14 joint angles of the hand. The glove provided measurements for each of the five metacarpophalangeal (MCP) joints, proximal interphalangeal (Money, Pippin et al.) joints, and four abduction angles. The 5DT glove is metal-free and therefore safe to operate in an MRI environment. The data glove was worn by subjects in the magnet and a set of fiberoptic cables (5 meters long) ran from the glove into the console room through an access port in the wall. In the console room, the fiber optic signals were digitized and plugged into the serial port of a personal computer that ran the simulation. The simulation was displayed to the subjects through a rear projector behind the magnet and the subjects viewed this through a rear-facing mirror placed above their eyes.

4.3.3 Experimental Protocol

Naïve subjects never exposed to our VE interface were tested in four conditions: 1) OTI: Subjects observed with the intent to imitate a sequential index-middle-ring-pinky movement performed by the virtual hand. The virtual hands were anthropometrically shaped and resembled real hands. The virtual hands in this condition were animated by data obtained from pre-recorded movements of a subject performing a finger sequence. A new finger sequence was used on each trial. 2) MOVE_h: Execute the observed sequence. During movement, subjects received real-time visual feedback of the virtual hand actuated by the subject's actual movement, 3) WATCH_e: Observe a non-anthropometric object, an ellipsoid, rotating about its long axis. The ellipsoid matched the virtual hand in size, color, movement frequency, and visual field position and controlled for these non-specific effects. No intention to imitate was required in this condition, 4) MOVE_e: Execute a previously observed finger sequence. In all conditions, a pair of right and left virtual hands or ellipsoids was displayed but only the right object moved. All movements were performed with the subject's right hand. The scanning session was arranged as 16 nine-second long miniblocks. Each of the four conditions (OTI, MOVE_h, WATCH_e, MOVE_e) repeated four times throughout the session. During the miniblocks, subjects performed one of the tasks described above. In blocks requiring observation without movement, subjects were required to rest their hands on their laps and in blocks requiring movement, subjects were required to slightly lift their hands off their lap just enough to allow finger motion. The miniblocks were separated by a rest interval that randomly varied in duration between 5-10 seconds, to introduce temporal jitter into the fMRI acquisition. During this interval, subjects were instructed to observe the two virtual hand models displayed statically on the screen and to rest both of their hands on their lap.

4.3.4 Glove Calibration

The glove must be calibrated separately for each user before the start of the session. Two glove measurements are recorded: 1) with the hand fully closed into a fist such that the five MCP and five PIP joints are maximally flexed and form a 90° angle, and 2) with the hand fully open, palm down on a level surface (fingers abducted). To calibrate the fiberoptic signal to a joint angle, the difference in the sensor readings for the MCP and PIP joints between the open and closed hand postures positions is divided by 90 degrees.

This determines a calibration "gain" which is applied in real time to make virtual hand movements correspond to the subject's own movement.

4.3.5 Behavioral Measures

Finger motion data obtained from the 5DT glove during the fMRI session was analyzed offline using custom written Matlab (Mathworks, Inc) software to confirm that subjects conformed to the task instructions and that finger movements during the execution epochs were consistent across conditions (to assure that differences in finger movement did not account for any differences in brain activation). For this, the amplitude of each finger's movement was recorded and submitted to a repeated measures analysis of variance (ANOVA) with within factors: CONDITION (hand, ellipsoid), FINGER (index, middle, ring, pinky), and MINIBLOCK (1, 2, 3, 4). Statistical threshold was set at alpha=0.05.

4.3.6 Synchronization with Collection of fMRI Data

Three components of this system are synchronized in time: the collection of hand joint angles from the instrumented glove, the motion of the virtual hands, and the collection of fMRI images. After calibration, glove data collection was synchronized with the first functional volume of each functional imaging run by a back-tic TTL transmitted from the scanner to the computer controlling the glove. From that point, glove data was collected in a continuous stream until termination of the visual presentation program at the end of each functional run. As glove data was acquired, it was time-stamped and saved for offline analysis.

4.3.7 fMRI Data Acquisition and Preprocessing

Magnetic resonance imaging was performed at NYU's Center for Brain Imaging on a research-dedicated 3-T Siemens Allegra head-only scanner with a Siemens standard head coil. Structural (T1-weighted) and functional images (TR=2500 ms, TE=30 ms, FOV=192 cm, flip angle=90°, bandwidth=4112 Hz/px, echo-spacing=0.31 ms, 3x3x3 voxels, 46 slices) were acquired. Functional data were preprocessed with SPM5 (http://www.fil.ion.ucl.ac.uk/spm/). The first two volumes were discarded to account for field inhomogeneities. Each subject's functional volumes was realigned to the first volume, co-registered and spatially normalized to the Montreal Neurological Institute template, and smoothed using an 8 mm Gaussian kernel.

4.3.8 fMRI Analysis

fMRI data was analyzed with SPM5. We were interested in two primary effects. First, we analyzed task-specific activation related to interacting in VE; i.e. activation related to observation of virtual hand motion with the intent to imitate and activation related to execution. To rule out non-specific visual feedback effects, we subtracted activations in the conditions with ellipsoids from those in conditions with virtual hands. Thus, the resultant contrasts were: 1) OTI > WATCH_e and 2) MOVE_h > MOVE_e. Second, we were interested in whether increased exposure to the VE led to time-varying changes in activation; i.e. as the virtual hand became embodied. For this, we modeled the miniblock number as a separate column in the design matrix and analyzed whether activation parametrically increased across the miniblocks. This analysis was performed for each condition. Activation was significant if it exceeded a threshold level of $P<0.001$ and a minimum extent of 10 voxels. Each subject's data was analyzed using a fixed-effects model and the resultant contrast images were submitted for group analysis using a random-effects model.

4.3.9 Results

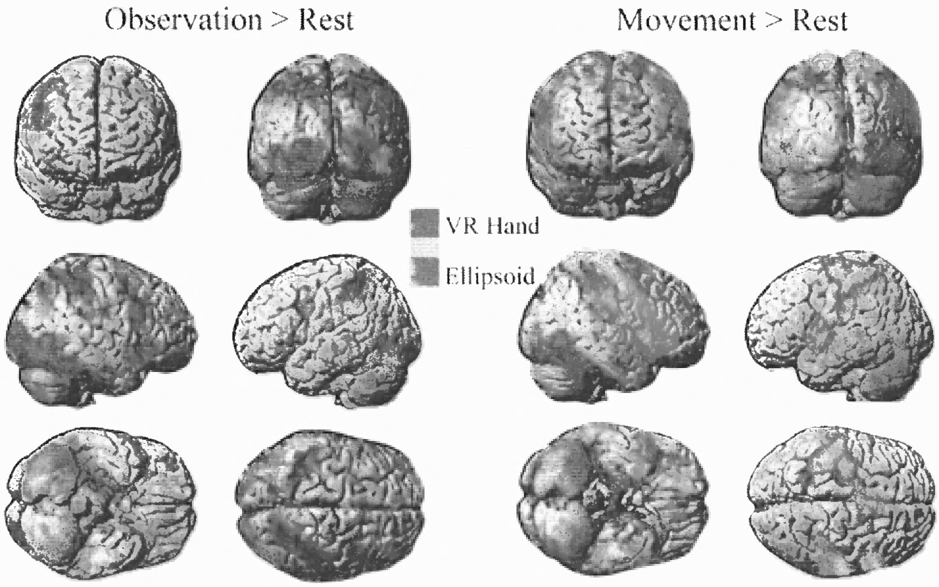
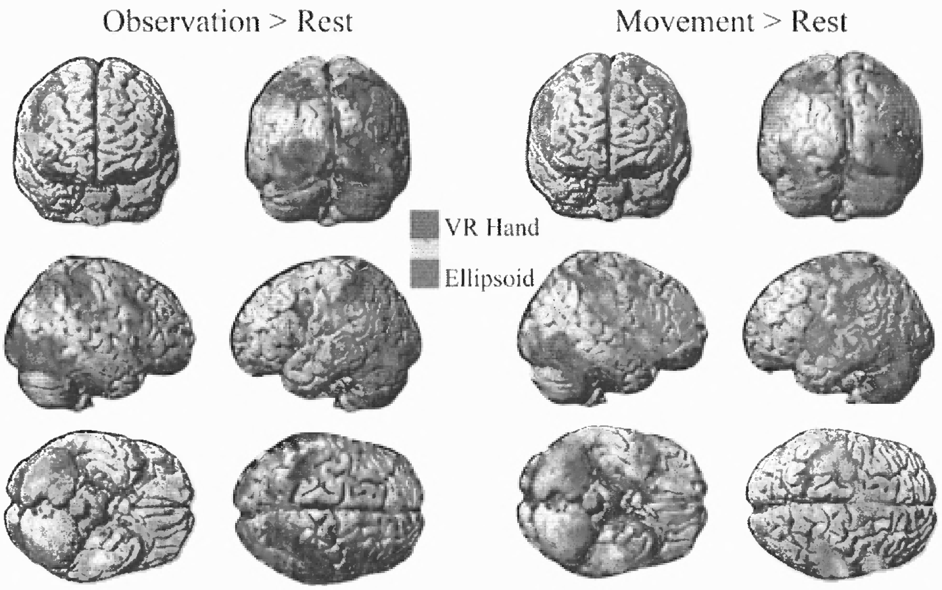


Figure 4.8 Simple main effects.

In the figure, left panes represent simple main effect of observation only in VR versus rest. In red are regions activated when subjects observed, with the intent to imitate (OTI), a virtual hand perform a natural pre-recorded finger sequence. In green are regions activated when subjects passively viewed a rotating ellipsoid (WATCH_e, see Methods). In the right panes, the simple main effect of execution versus rest is represented. In red are regions activated when subjects imitated the finger sequence (that they observed in the OTI condition) with real-time control of representations of their hands in VR (MOVE_h). In green are regions activated when subjects performed the finger sequence while viewing rotating ellipsoids that were not controlled by the subject's motion (Hamilton, a Department of Psychological and Brain Sciences et al.). All yellow colors depict regions where the activations in red and green overlapped. All activations are thresholded at $p<.001$ and extent of 10 voxels.In the imaging experiment, we sought to answer two critical questions. First, are the networks recruited for observing and executing actions in VE similar to those know to be engaged for observation and execution of real-world actions? Second, does activity in these neural circuits change as one becomes more familiarized with the VE?

4.3.10 Activation When Observing Movements in a Virtual Environment

The figure (left side) shows the activation patterns when subjects observed (left side of the figure) and executed (right side of the figure) a sequential finger movement in the virtual environment. Note that in the observation condition, subjects were instructed to "observe with the intention to imitate afterwards". Therefore, in the ellipsoid condition, subjects could observe all of the features that they saw in the virtual hands condition but were unable to make an intention to imitate. This allowed us to dissociate "passive" from "active" observation. Observing virtual hands perform a finger sequence was associated with a distributed network (see the Table) including the left parietal cortex (somatosensory and intraparietal sulcus) extending into the anterior bank of the central sulcus (motor cortex), bilateral anterior insula, bilateral frontal lobes (right precentral gyrus and left inferior frontal gyrus pars opercularis), bilateral occipital lobe, right anterior/posterior intermediate cerebellum. Conversely, observing the rotating ellipsoids was associated with activation limited to the bilateral occipital lobe and the left superior lateral cerebellum (see the table). The contrast of OTI > WATCH_e was performed to subtract out regions that may have been associated with low-level effects of observation in VR (such as object motion, position, color) and observation not associated with an intention to imitate an action. Regions activated in this contrast included the fusiform gyrus of the temporal cortex, superior parietal lobe including the precuneus and intraparietal sulcus, anterior insula, middle frontal gyrus, and the medial frontal lobe.



4.3.11 Activation When Executing Movements in a Virtual Environment

In the figure, (right side) shows activation when participants executed the sequential finger movements while receiving feedback in VR of either the virtual hands driven by the subjects' own motion (red areas) or of ellipsoids (green areas). Both conditions were associated with activation in the right cerebellar cortex, an extensive activation of the left sensorimotor cortex that included much of the postcentral gyrus and precentral gyrus, the right inferior parietal lobule, and the bilateral insular cortex (see the Table). Additionally, feedback of the VR hands was associated with activation of the right fusiform gyrus. The contrast for feedback of VR hands minus ellipsoids revealed activation of the bilateral angular gyri, precuneus, inferior occipital lobe, and the occipitotemporal junction. Note that since finger movement remained constant between the two conditions (see Behavioral Data section) it is not surprising that the sensorimotor cortex activation that was associated with each condition was not evident after the subtraction.

4.3.12 Activation During Observation That Changed Over Time

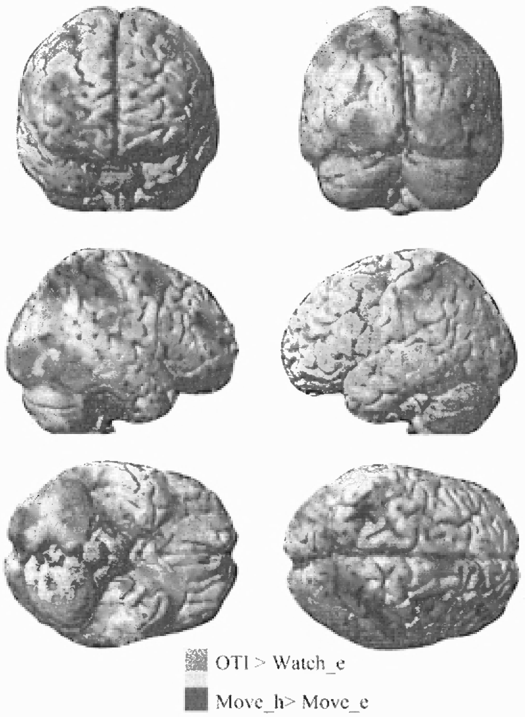


Figure 4.10 Regions activated. Regions activated in the OTI > WATCH_e (red) and MOVE_h > MOVE_e (green) contrasts.

To understand if brain activation changed over time as subjects became familiar with interacting in the VE, we analyzed the parametric changes in the BOLD signal across the four execution and observation blocks. Increases in the BOLD signal were noted in the OTI condition in the left posterior insula and in the Move_h condition in the right inferior occipital lobe. Note that the time-variant changes in the BOLD signal occurred despite no difference in movement kinematics across the blocks for the observation and execution conditions (see Behavioral Data section). No other significant time-variant changes in the BOLD signal were noted.

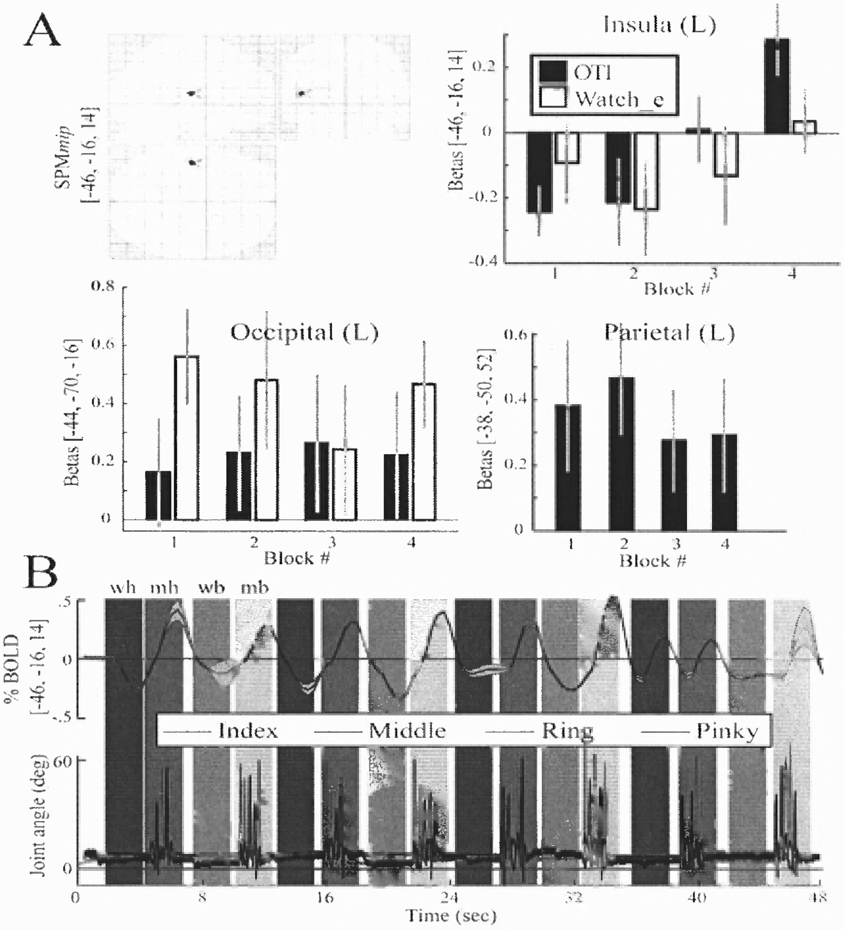


Figure 4.11 Bold signal and kinematic measures. Across conditions.

In the figure, A in the top left panel shows on an SPM glass brain the only region, the insula, that showed a significant time-variant increase in activation during the OTI condition. The remaining three panels show bar plots of the beta values at three cortical locations: in the insula shown in the glass brain and two control sites that were recruited in the simple main effect contrast. Note that the time-variant increase is evident only in the insula and only in the OTI condition. The bar plots for the parietal site in the Watch_e condition are not shown since this site was not recruited in the simple main effect. In panel B, the simultaneously recorded time-series data for the BOLD signal (top) (group mean ± 1SD) and the joint angles (bottom) (one representative subject) of the four fingers is shown. Shaded vertical bars denote the condition epochs (*wh*, OTI; *mh*, MOVE_h; *wb*, WATCH_e; *mb*, MOVE_e).

4.3.13 Behavioral Data

Inspection of the finger kinematics acquired during the fMRI experiment revealed that all subjects complied with the task by maintaining their fingers still during the observation epochs and performing the correct finger sequences in the execution epochs. The bottom panel of Figure 4 shows a representative subject's MCP joint angle excursion for the index, middle, ring, and pinky fingers across one block. An ANOVA for peak joint excursion (movement extent) at the MCP revealed a significant main effect of FINGER ($F_{(3,9)}=8.9$; $p=0.005$). Indeed, the greatest excursion occurred at the index MCP (range: 27°-38°) and the least excursion at the pinky MCP (range: 17°-25°). No other significant main effects or interactions were noted for movement extent ($p>0.05$), suggesting that movement was consistent for each finger across the epochs and conditions.

4.3.14 Discussion

Observation and imitation are among the most powerful and influential aspects of human skill learning. Since neural networks for observation and execution show a large degree of overlap, stroke patients may benefit from observation of embodied actions/effectors during the acutely immobile phase after stroke. In support of this, it has been demonstrated that simple observation of actions can accelerate functional recovery after stroke (Celnik, Webster et al. 2008). To afford subjects the opportunity to embody movement that they observe, we developed realistic representations of human hands in virtual reality that can be actuated in real time by the actor's hands. We used an MR-compatible interactive virtual environment to study the neural networks involved in observation and imitation of complex hand movements.

A longstanding challenge to understanding the real-time link between brain and motor behavior is partly due to the incompatibility of human motion measurement technology with MRI environments. Recently, innovative devices capable of measuring kinematics and kinetics of one- (1D) and two- (2D) degree of freedom movements (Diedrichsen, Hashambhoy et al. 2005; Ehrsson, Wiech et al. 2007; Tunik, Rice et al. 2007; Tunik, Schmitt et al. 2007; Vaillancourt, Yu et al. 2007) as well as delivering forces/torques to subjects' movements (Diedrichsen, Verstynen et al. 2005; Tunik, Schmitt et al. 2007) have been successfully integrated with MRI environments with negligible device-to-MRI and MRI-to-device artifacts. These devices allow one to study brain-behavior interactions in real-time for 1D and 2D movements. Moreover, the visual feedback presented in these studies was of a moving cursor rather than a moving body part. As knowledge of brain function advances, it becomes critical to understand how more complex movements (i.e. finger-hand actions) are controlled and how sensory feedback can modulate brain activation.

The study demonstrates four important findings. First, the study demonstrates the possibility of simultaneous integration of kinematic recording of hand movements, virtual reality-based feedback, and task-related measurement of neural responses using fMRI. Second, the study shows that intentional observation of to-be-imitated hand actions presented in VE recruits a bilateral fronto-parietal network similar to that recruited for observation of actions performed in the real world. Third, the findings demonstrate an increase in activation in the left insular cortex as participants became more familiarized with the relationship between their own movement and that of the virtual hand models. Fourth, the findings identify for the first time the involvement of the bilateral angular gyri, extrastriate body area, and left precuneus when controlling a virtual representation of your own hands viewed in real-time in the 1st person. Each point is discussed below.

4.3.15 Capabilities of our VE Training System

It is timely to consider how virtual environments can be exploited to facilitate functional recovery and neural reorganization. Although exercising in a virtual environment is in the nascent stage of exploration there are an ever increasing number of studies showing VE to have positive behavioral (Merians, Boian et al. 2002; Deutsch 2004; Adamovich 2005; Holden 2005; Merians, Poizner et al. 2006) and neural (You, Jang et al. 2005; You, Jang et al. 2005) effects. What remains untested is whether these benefits emerge simply because VE is an entertaining practice environment or whether interacting in a specially-designed VE can be used to selectively engage a frontoparietal action observation and action production network -- which if the latter is evident, can have profound implications for evidence-based neurorehabilitation methods and practices.

The overall VE architecture developed by our team was designed to be used in rehabilitation of hand function in patients with various neurological disorders including stroke and cerebral palsy. The system is capable of accommodating patients with a broad array of dysfunction and treatment goals. For example, our system can integrate various sensors and actuators to track seamlessly the motion of the fingers, hands, and arms as well as to induce mechanical perturbations to the fingers or the arms.

4.3.16 Frontoparietal Involvement for Observing with the Intent to Imitate OTI Actions in VE

For the OTI condition, subjects observed finger sequences performed by a virtual hand representation. The finger movements were not performed by consecutive fingers and varied from trial to trial, requiring subjects to actively observe each finger sequence for reproduction on the subsequent trial. The simple main effect of observe-with-the-intent-to-imitate afterwards (OTI) condition versus viewing static virtual hands was associated with activation in a distributed, mostly bilateral, network including the visual cortex, sensorimotor cortex, premotor cortex, posterior parietal cortex, and insular cortex. The network we identified in the OTI condition is consistent with a host of neuroimaging studies investigating neural correlates of observation of real-world hand movements. For example, observation of intransitive (non-object oriented) actions involving pictures or videos of real hands is associated with engagement of a distributed network involving the frontal, parietal, and temporal lobes (Decety, Grezes et al. 1997; Buccino, Binkofski et al. 2001; Grezes, Fonlupt et al. 2001; Suchan, Melde et al. 2008). In contrast, activation in the simple main effect of observe ellipses (OE) versus static virtual hands was predominantly localized to visual processing areas (occipito-temporal cortex), making it unlikely that activation in the OTI condition was attributed to low-level effects such as object shape, color, motion, or its position in the visual field. Activation in the OTI > OE contrast confirmed this finding. It has been suggested that the above mentioned frontal and parietal regions, particularly those involving the mirror-neuron system, may be part of a network subserving internal simulation of action which may resonate during intentional observation of movement (Rizzolatti and Luppino 2001; Gallese, Keysers et al. 2004; Kilner, Paulignan et al. 2004). Our data extend this hypothesis, suggesting that observation of virtual, but realistic, effectors may also engage similar neural substrates.

An earlier fMRI study investigated observation of grasp performed by high and low fidelity VR hands versus those performed by real hands (Perani, Fazio et al. 2001). The authors noted that observation of grasp performed by real hands was associated with stronger recruitment of the frontal and parietal cortices and that the degree of realness of the virtual hands had negligible effect on higher-order sensorimotor centers. Along these lines, activation in the left ventral premotor cortex, a presumptive mirror neuron site, has been shown to be more strongly recruited when participants observe grasp performed by a real versus a robotic (nonbiological) hand (Tai, Scherfler et al. 2004). However, in these paradigms, subjects 1) passively observed the actions performed by another agent, and 2) never engaged in practicing the observed action (with real-time feedback) themselves. Particularly, in Perani et al's study, bilateral precuneus and right inferior parietal lobule (BA39, 40) were recruited during observation of real but not virtual hand grasping movements (see Table 2 in (Perani, Fazio et al. 2001)). In our study, observation of virtual hand actions (with the intent to imitate the movement) paired with rehearsal of the observed action, likely led to recruitment of these higher-order sensorimotor centers during observation only (see OTI>OE in Table 1).

4.3.17 Time-varying Activation in the Insular Cortex

An additional component to interacting in VR pertains to the possibility that extended exposure to the virtual model is needed to develop a sense of control or ownership over the virtual representations of your own body. We tested this by performing a time-series analysis of the BOLD data. The analysis revealed a parametric increase in the BOLD signal in the left posterior insular cortex for the OTI condition. Other cortical regions that were recruited in the OTI or the OE conditions did not show such parametric increases. Note too that in the OTI condition, subjects did not make overt movements (see Results), but just observed with the intention to imitate immediately after. To our knowledge, this is the first evidence showing a time-variant change localized to the insular cortex driven by increased interaction with a virtual representation of one's hand. The increase in insular activation likely reflects the neural substrate underlying the emergence of a sensed relationship between self movement and the movement of the virtual hands that were controlled by the subject throughout the experiment. This thesis is supported by lesion and neuroimaging data implicating the insular cortex in awareness of actions performed by the self and others (see discussion in the above section). For example, several recent reports noted increased activation of the insula as subjects became increasingly aware of being in control of an action (Farrer and Frith 2002; Corradi-Dell'acqua, Ueno et al. 2008). Along these lines, we show a parametric increase during *observation* with the intent to imitate but not during the MOVE_h condition. The parametric increase in BOLD across the blocks is unlikely to be explained by any movement-related changes across the blocks since our analyses of movement kinematics (collected concurrently with fMRI by use of a data glove) did not reveal any significant changes in performance in the movement blocks nor any movement in the observation blocks. The parametric changes in BOLD likely reflects perceptuo-motor influences of interacting in VR. The exact source of this modulation of brain activity is the focus of our ongoing studies.

4.3.18 Control of a Virtual Representation of Your Own Hands

Subjects executed sequential finger movements with simultaneous feedback of their movement through VR hands (that they controlled) or through rotation of virtual ellipses (not actuated by subjects). Movement under both sensory feedback conditions led to a distributed activation in known networks recruited for sequential finger movement (Grafton, Arbib et al. 1996). To identify regions sensitive to feedback from VR hand models, we subtracted the VR ellipse contrast from the VR hands contrast. This subtraction revealed activation in the left precuneus, bilateral angular gyri, and left extrastriate body area. Our findings are consistent with recently hypothesized functions of these regions.

4.3.19 Contralateral Precuneus

For example, functional neuroimaging work in humans and unit recordings in non-human primates suggests that the parietal cortex is integral for sensorimotor integration, a process wherein visual and proprioceptive information is integrated with efferent copies of motor commands to generate an internal representation of the current state of the body. A number of related tasks that presumably require sensorimotor integration, such as motor imagery and the sense of degree of control of an action (i.e. sense of agency) are associated with activation of regions within the parietal cortex, particularly the precuneus in the case of imagery (Cavanna and Trimble 2006; Pellijeff, Bonilha et al. 2006; Vingerhoets) and the angular gyrus in the case of attribution of agency (Farrer, Frey et al. 2007 2003, 2007). Tracing studies, mapping the corticocortical connections of the precuneus, demonstrate that this region is reciprocally connected with higher-order centers in the superior and inferior parietal lobule, lateral and medial premotor areas, the prefrontal cortex, and cingulate cortex, further substantiating its role in sensorimotor integration.

4.3.10 Bilateral Angular Gyri

Tracing studies in monkeys demonstrate that area PG (the putative homologue of the angular gyrus in humans) is connected with higher-order sensorimotor centers including the rostral regions of the inferior parietal lobule, pre-SMA, and ventral premotor cortex (area F5b) (Gregoriou, Borra et al. 2006; Rozzi, Calzavara et al. 2006). Tractography in healthy humans, performed using diffusion-weighted tensor imaging, reveals similar findings, that the angular gyrus has strong connectivity with the ventral premotor cortex and the parahipocampal gyrus (which is implicated in perception of space) (Rushworth, Behrens et al. 2006). Cells in area PG (area 7a) have complex visual and somatosensory response properties suggesting that this region is involved in egocentric and allocentric space perception, particularly for guiding motor actions (Blum 1985; Blatt, Andersen et al. 1990; MacKay 1992; Yokochi, Tanaka et al. 2003), perhaps as part of the operation of the dorsal visual stream.

4.3.21 Extrastriate Body Area

The extrastriate body area (EBA), located in the occipito-temporal cortex at about the posterior inferior temporal sulcus/middle temporal gyrus (Peelen and Downing 2005; Spiridon, Fischl et al. 2006), near visual motion processing area MT (area V5) and a lateral occipital (area LO in which cells are selective for object form (Downing, Jiang et al. 2001; Downing, Wiggett et al. 2007)). A detailed review of EBA's role in perception is provided by (Peelen and Downing 2007). Human neuroimaging work reveals that the

EBA is selectively recruited when observing images of body parts (relative to images of faces or objects) and, like the angular gyrus and insular cortex, seems to be important for identifying the agent of the observed movement (David, Cohen et al. 2007). Transcranial magnetic stimulation-induced virtual lesions of EBA lead to transient decrement in performance on match-to-sample paradigms of images of body parts (Urgesi, Berlucchi et al. 2004). This body of literature allows us to suggest that the EBA activation in the VRhands>VRellipse contrast in our study indicates that increased activation in the EBA was specific to observation of moving virtual body parts.

4.3.22 General Conclusion

In our study, subjects' interactions in VR alternated between the conditions of observation of actions (performed by virtual hand models) to imitate, and the condition of actually controlling the VR hand models (whose motion was temporally and spatially congruent with the subject's own motion). A parsimonious explanation is that the VR hand models served as disembodied training tools in the former condition, and as embodied "extensions" of the subject's own body or as "pseudo-tools" in the latter condition. Our results suggest that the time-variant activation of the insula in the observation epochs may have reflected an improved ability to disembody the VR hands, while the recruitment of a network involving the precuneus, angular gyrus, and extrastriate body area for the execution condition may be attributable to the role of these regions in integrating visual feedback of the VR hand models with concurrent proprioceptive feedback and efferent copies of motor commands.

4.3.23 Supplement - Design of the System

The hardware components of our VR system may include, but are not limited to: 1) left and right Immersion CyberGloves used to measure 22 joint angles of the hand (Immersion 2006), 2) left and right 5DT Data Glove 16 MRI which uses MRI-compatible (fiberoptic) sensors to measure 16 joint angles of the hand; and 3) Ascension Flock of Birds 6 degrees of freedom sensors (Ascension Technology Corporation, Flock of Birds, http://www.ascension-tech.com) used to measure the position and orientation of the wrist and/or arm, 4) ShapeWrap and ShapeGlove MRI-compatible sensors (Measurand, Inc) used to measure hand and arm position and orientation, 5) CyberGrasp (Immersion Corp.) used to mechanically perturb finger motion, and 6) HapticMaster (FCS) which is a 3 degrees of freedom, force-controlled manipulandum to perturb arm motion, 6) a visual display of an interactive virtual environment. These environments have been designed using C++/OpenGl or Virtools (Dassault Systèmes, Virtools Dev 3.5, 2006: http://www.virtools.com). Examples of virtual environments are depicted herein. Movement of the hands depicted in the virtual environment is an exact representation of the movement of the subject's hands in real space. For example, in the Piano Trainer, movement of the keys of the virtual piano and appropriate musical sounds are defined by the interaction between the virtual finger and the virtual key using a collision detection algorithm. These and similar environments has been successfully used by our group for training patients post stroke (Adamovich 2005; Merians, Poizner et al. 2006; Adamovich, Qiu et al. 2007; Merians, Lewis et al. 2007).

RESEARCH AIM 3

5.1 Quality Virtual-Reality Visual Feedback Facilitates Neural Activation in the Motor Cortex and Secondary Sensorimotor Areas

A growing body of evidence supports bolstering sensory information to improve human performance. This appears to be true for healthy subjects in some circumstances and is particularly true in cases wherein one sensory skill is diminished, such as is the case for some patient populations including those who have suffered from stroke, and in aging. Recent theories of learning provide models to integrate selective experiences into VE's with successful track records for facilitating skill learning in healthy and patient-based populations. However, it remains unknown how visual sensory modulations implemented to exploit a rich computer based virtual environment might selectively affect the brain for a number of important applications. It is also not known how these forms of feedback can be optimally integrated into systems such as those that support training or rehabilitation of the hand to elicit the desired outcome.

The pervasiveness and accessible cost of virtual environments presents a perfect opportunity to investigate features wherein parametrically modulated sensory stimulus and feedback can be crafted to accommodate various techniques such as error-less and error-based experiences in ways not possible using natural world settings and is accompanied by an unprecedented degree of personalization providing liberal application of appropriate features to individuals and situations. Training systems that offer a suite of sensorimotor stimulus and feedback options can provide a platform to accommodate the sensory needs and learning style of an individual in health, age, or in disease. These VE systems might provide a unique opportunity for well defined parametrically adaptive modeling, sensory support and enhancement, error-less or error-based feedback, adaptable learning models, and various levels of task complexity. Therefore, this research is uniquely enabled and timely. By creating a safe environment wherein sensory experiences can be controlled, various mechanisms present in the human brain may be targeted. Some characteristics or level of sensory information (volume, brightness, color, gain, temporal shifts, frequency, close-to-normal, etc.) that are not present in the subject's world or that are not strong enough (sufficient in quality) as experienced by the subject might be subject to specific modifications, intentionally presented, enhanced, modulated, or re-presented through the VE, potentially leading to short term modulation of somatosensory cortical (SI) networks. Continuous support of SI networks might be effective in promoting long term reorganization of target areas and may be included in a training, or rehabilitation plan.

Modulation of visual input and feedback through VE might provide an ideal test case for sensory experiments. Visual sensory experiences may be manipulated independently of proprioception sensory experiences. Visual information provides a potent signal for reorganization of sensorimotor circuits and can override other afferent modalities in conditions of sensory conflict (Snijders, Holmes et al. 2007). When tactile information is limited as in the case of some patient groups, vision might modulate tactile performance (Serino, Farne et al. 2007). Particularly in cases when subjects have identified a goal, as in imitation or OTI, intention may additionally influence the expectation of the content of feedback experiences. A goal of the present research was to design and develop a flexible MRI compatible exercise system to investigate effective ways of using visual sensory experiences or illusions to optimize observation, imitation, feedback, and imagery and to identify methods to selectively modulate brain activation in a target action-observation and action-execution network.

Aim 3) For the third objective, sensory manipulations of the virtual hand (that are not achievable in the real world) were tested in functional imaging and behavioral studies wherein subjects interacted in a VE while receiving various visual feedback that was of either high, moderate, modest, or poor fidelity of the subjects' moving hand.

Behavioral and functional brain imaging experiments were conducted to test the capacity of the novel virtual environment system with virtual proxy hands controlled through the movement of the subject, to drive specific neural actuations in target brain regions. The vision of this research investigation is to begin to understand how virtual environments might support selective neuroplastic changes through facilitation and inhibition of the sensorimotor system as a novel form of therapy. An event-related functional magnetic resonance imaging experiment was chosen for this investigation because fMRI offers excellent spatial resolution and allows analysis of multiple distributed sensory and motor regions, including but not limited to motor cortex.

5.2 MRI Methods

Five healthy subjects performed sequential finger flexion movements with their dominant right hand (index through pinky fingers) as if they were pressing imaginary piano keys at a rate of 1 Hz. Subjects' finger motion was recorded with an MRI-compatible data glove (see Design and Methods section for details about the glove and

VR architecture) and the joint angles were transmitted in real time to a computer controlling the motion of a right-sided virtual hand. The virtual hand on the display was sized in proportion to the subjects' actual hand and its movement was calibrated to the user's hand before the experiment. Under optimally calibrated conditions, subjects reported that the virtual hand's motion corresponded perfectly to their actual motion. During each movement sequence, subjects' hand motion actuated motion of the virtual hand, which was projected to the participants via a screen in the MRI room. We parametrically manipulated the amount that the virtual hand's motion corresponded to the subjects' own motion from: 1) poor correspondence (incorrect virtual fingers move), 2) fair correspondence (virtual fingers move at a 25% amplitude relative to the subject's own movement), 3) fair+ correspondence (65%), to 4) perfect correspondence (100%). Each subject performed four sessions (40 trials/session). During each trial, subjects were required to evaluate the correspondence between movement of the virtual fingers and their own motion. After each trial, subjects rated the correspondence on a scale of 1-4 (with '4' indicating perfect correspondence) by using their left hand to press one of four buttons. Six functional runs were performed with 40 trials/run (240 trials total; 60 trials/concordance condition). All subjects completed an MRI screening questionnaire and consent approved by the imaging center and university IRB committee prior to participation. Magnetic resonance imaging was performed at NYU's Center for Brain Imaging (3-T Siemens Allegra head-only scanner). We acquired a T1-weighted ($1\times1\times1$ mm^3) 3D-MPRAGE pulse sequence structural image and T2*-weighted functional images (TR=2500 ms, TE=30 ms, FOV=192 cm, flip angle=90°, bandwidth=4112 Hz/px, echo-spacing=0.31 ms, 3x3x3 voxels, 46 slices). Preprocessing was done using

SPM5 (http://www.fil.ion.ucl.ac.uk/spm/). The first two volumes were discarded to account for field inhomogeneities. Each subject's functional volumes were realigned to the first volume, and the functional and structural images were then co-registered and spatially normalized to the Montreal Neurological Institute template. Condition-specific differences in the BOLD signal were analyzed with a general linear model approach for event-related fMRI using SPM5; activations were significant at a threshold.

5.3 Behavioral Study Methods

A study was conducted to investigate how quality of visual feedback affects brain activation during observation of virtual hand motion. Five healthy subjects performed sequential finger flexion movements with their dominant right hand (index through pinky fingers) as if they were pressing imaginary piano keys at a rate of 1 Hz. Control subjects were asked to rate the quality of visual feedback by determining how much they felt "in control" of the action of the virtual hand that they viewed. Subjects pressed one of four buttons to indicate their response. They determined whether the feedback was of either of poor, fair, fair plus, or perfect fidelity in relationship with the movement of one's own hand. The gain between the subject's actual movement and the virtual hand movement was parametrically manipulated:

1. poor correspondence (incorrect virtual fingers move),
2. fair correspondence (virtual fingers move at a 25% amplitude relative to the subject's own movement),
3. fair+ correspondence (65%),
4. perfect correspondence (100%).

Aim 3 – Outside the magnet

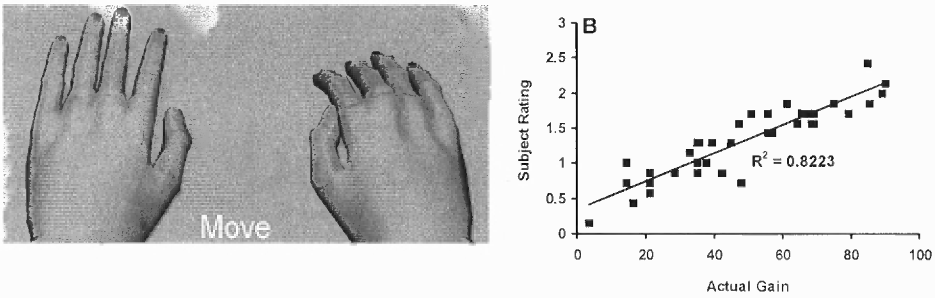


Figure 5.1 Aim 3 Pilot Data - Subject Rating - Control of Virtual Hand. The gain between the subject's actual movement and the virtual hand movement was systematically manipulated. Subjects rated the degree to which they were "in control of the virtual hand" by pressing one of four buttons.

Aim 3 identified *True* concordance between the subject's motion and feedback of the right virtual hand's (VH_R) motion parametrically varied from: 1) poor (incorrect VH_R fingers move), 2) fair (VH_R fingers move at a 30% amplitude relative to the subject's own movement), 3) fair+ (65%), to 4) good (100%). Following movement, subjects had 3 seconds to *judge* the concordance on a scale of 1-4 (by pressing a button with the left hand). Factors *true* and *judged concordance* (levels: poor, fair, fair+, good) were modeled with the BOLD signal as a 4x4 factorial design to delineate neural regions underlying implicit versus explicit attribution of agency. Six functional runs were performed with 40 trials/run (240 trials total; 60 trials/concordance condition). Each functional run lasted about 6.5 min.).

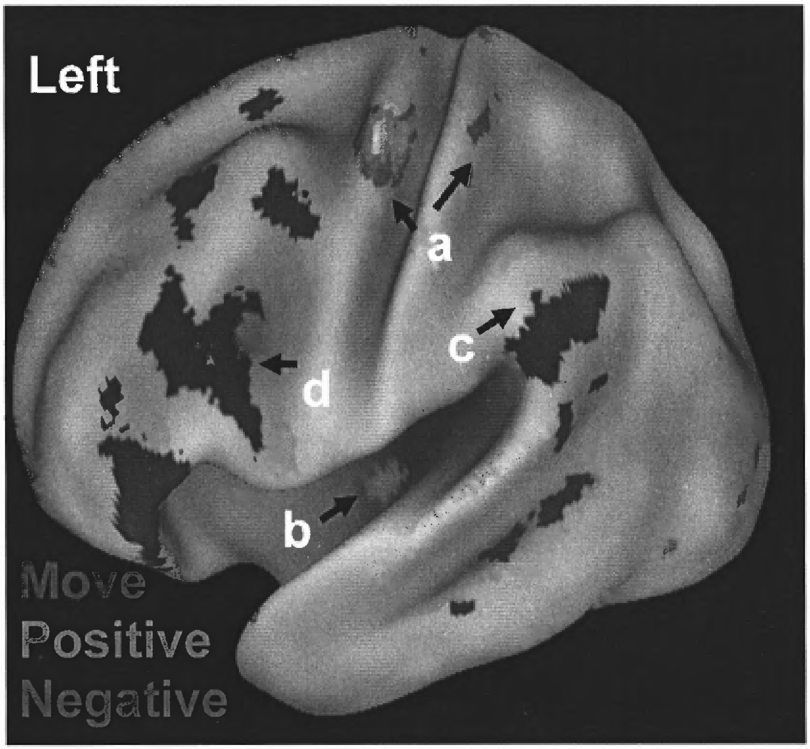


Figure 5.2 Quality-related Brain Activation. Regions showing significant BOLD activation in the Virtual Gain experiment. Contrasts are: move>rest (red); positive (green) correlation and negative (blue) correlation between BOLD and the correspondence of the virtual hand-to-real hand motion.

Each degree of congruence was modeled in a separate column in the design matrix. Contrasts for positive and negative correlations between BOLD signal and degree of congruence were made for each subject in a fixed-effects model using SPM5. Behavioral data were compared with brain studies for correlation of active neural pathways and associated subject judgment of concordance. Data acquisition and analysis as previously described.

The present research contributes to the field by demonstrating a new method for studying the effects of sensorimotor experiences in virtual environments using a flexible

MRI compatible technique to investigate human performance in computer interface task design and neural underpinnings of interactions in a modulated sensorimotor virtual environment while simultaneously recording kinematic measures of human performance and behavioral response, for analysis. Subjects in these studies were able to directly observe their own hands actuating virtual reality representations of their own hands in real time moving in concurrence with their own movements in an overlapping or 'where is' position for the first time within the MRI environment, to develop a relationship with these hands serving as a proxy for the subjects' own hands, and to then observe unexpected modulations of the behavior of the proxy hands in response to the subjects' actions when the subjects moved the right hand and saw the left hand move. Subjects participated in experiments where virtual reality avatars were used in imitation exercises in and outside the MRI environment, confirming consistency of the visual sensorimotor manipulation, and the perception of the subject when participating in the virtual activity. Once the subjects developed a relationship with the virtual proxy hands through training experience in virtual environments (previously these researchers demonstrated increased activation of the insula associated with a sense of agency during specific virtual proxy hand OTI training in virtual environments), the unexpected visual feedback was introduced, and was associated with the subject's own movement. Functional brain imaging captured brain network actuations while sensors in the MRI compatible gloves actuated virtual imagines, and measured all subject movement for the purpose of driving the error-based visual feedback kinematics, for analysis, and to monitor compliance.

5.4 Findings

Activations in the motor cortex hand region and the insula were positively correlated with the movement task and the associated visual feedback. However, the angular gyrus and premotor cortex activation was negatively correlated. Therefore, when the subject visual feedback was not in good correspondence with the perceived movement, the angular gyrus and the premotor cortex were recruited to a lesser degree than when the gain of the image of the virtual hands proxies was in perfect concordance with the subject's own movements. Activation of the insula, which was present during the visual feedback distortions is important to demonstrate that the visual feedback was recognized by the subject: the action represented the subject's own involvement with the scene. However, the lost quality of the visual feedback resulted in the reduced recruitment of important motor planning and action understanding regions of the brain. Error-based feedback appears to have a proportional affect upon the recruitment of motor planning and action observation regions of the brain. Error-based feedback appears to deny the brain of important sensorimotor stimulus associated with performance and might be a mechanism of learned disuse. Longer experiments may explore this possibility. Since the present experiment involved learning in the environment and then experiencing the unexpected error-based visual stimulus, it would be reasonable to conduct another study to determine habituation and the possibility of extinction of the effects of the negative feedback in the total absence of perfect correspondence, or in the case of the naïve user. Therefore, such an experiment might be conducted by implementing a novel design of the brain study wherein the OTI training is eliminated. The error-based technique might serve a role when a subject has had an injury, and movement is not expected for some time in one limb, and plasticity adaptation is expected to occur, such might be the case in learned disuse. Error-correcting visual feedback of the remaining limb might serve a short term purpose to reduce learned disuse until therapy may be initiated. This model of feedback might serve an important purpose to gain further understanding of how certain pathologies of the senses might affect the motor system over longer periods of time, such as during recovery from trauma or injury. Experiments with unexpected sensory feedback, not in concurrence with actual movement planning or execution, might provide models to study specific mechanisms of dysfunction. Following observation with intent to imitate, and also imitation with accurate visual feedback training, modulation of movement in an unexpected manner may be explored. These modulations can be presented following an OTI and at the movement initiation of the task. Such unexpected events can be perturbations (for example, a robot that moves the hand in an unexpected direction) in the MRI, while visual sensorimotor feedback provides good quality feedback of the planned move (incongruent to the actual movement) and might provide insights into the relationship between visual feedback and proprioception. The visual feedback provided might actually be created using kinematics recorded from the individual during previous rehearsals of the task. Therefore, there would be a strong signal of visual feedback from the subject's own motor profile while the subject experiences physical perturbation of the hand or fingers. Another interesting area for further research may engage subjects in reviewing their own movements from previous practice sessions to determine brain activations while watching one's own movement in subsequent episodes. Perhaps reviewing one's own motor program over the course of training might lead to some effect to benefit training or to provide support during recovery.

The behavioral portion of this study demonstrated that the visual sensory feedback precisely corresponded with the subject's perception of the quality of the visual feedback and how accurately the visual feedback represented his or her own hand movements. This portion of the study demonstrated that the subjects were aware of the quality changes in the visual feedback and that they were accurate in determining how close the visual presentation represented the movements they made.

In conclusion, VE is a promising tool for neuroscientific discovery, and for applications including but not limited to motor skills acquisition, exercise for training, and rehabilitation. A specific set of sensory experiences in virtual environments, visual stimulus for modeling and feedback mechanisms, can enable subjects to successfully participate in intensive computerized training paradigms. Parametrically modulated visual sensorimotor experience in virtual environments has been shown to recruit action-observation action execution-understanding brain networks in concordance with the quality (modulation of concurrence of subject's movement and the real time visual feedback embodied in the virtual hands – modifications of gain in poor, fair, good, or total correspondence with subject's movements, subject moves right and sees left hand move, etc.). There are several implications of these findings. Patients may be continually experiencing impoverished visual feedback of their hemiparetic limbs. The present research demonstrates that the impoverished, or error-based feedback represented by the virtual hands reduces activation of action observation and execution brain networks. This activation was modulated even in the presence of activation of the insula, known to be involved with recognition of one's involvement in the scene, or sense of agency. By implementing an increase in gain, with no other change in motor dynamics, activation in the target important brain regions was increased, while the insula remained relatively active throughout. As a therapy for patients suffering from hemiparesis, modulating the gain to improve visual experiences of feedback in concordance with intended movements might provide a therapy to support SI. Including such gain enhanced visual feedback provided through sensorimotor experience in virtual environment may also enable seriously disabled patients to participate in sensory therapies, or in passive therapies, by demonstrating enhanced gain at even minor efforts of the subjects. Perhaps by reviewing prior exercise sessions in the virtual environment, subjects may receive visual sensory support for recovery. Evidence shows that early therapies reduce loss of cortical representations. This and other sensorimotor experience in virtual environments may offer significant value to early intervention even when the patient is unable to move.

RESEARCH AIM 4

6.1 fMRI Analysis of Neural Mechanisms Underlying Training in a Virtual Environment: Activating Ipsilateral Cortical Motor Areas

Stroke patients who suffer hemiplegia with paralysis of a hand, may be unable to participate in rehabilitation exercises during the acute phase of injury, thereby making them vulnerable to loss of cortical representation. Virtual Environment (VE) therapy is proposed employing the virtual hands avatar for bimanual and unimanual somatosensory feedback to engage and actuate relevant motor cortical regions in the presence of hemiplegia and to promote plasticity-based neuro-functional changes promoting recovery of hand function. A functional MRI study on healthy controls investigated the possibility of inducing increased neural activations in primary, as well as secondary motor areas through virtual reality-based exercises of the hand. These areas are known to be important in effective motor output in stroke patients with impaired corticospinal systems. Specifically, the effect of viewing a virtual left hand avatar move when subject moves only his or her own right hand, was investigated. Increased activations were found in the motor related brain areas responsible for left hand movement during this novel rehabilitation protocol, right hand exercises in VE while viewing virtual left hand, when compared to viewing of virtual right hand avatar motion accompanying subject right hand movement. Findings indicate that increased activation of the ipsilateral motor cortex during hand exercise modulated by viewing the contralateral virtual reality hand avatar may be an improved strategy for rehabilitation during acute phase of stroke when the patient may be unable to participate in rehabilitation exercises. The presented protocol may create an improved plasticity context promoting recovery of hand function for rehabilitation and may increase evidence-based treatments available to patients who cannot move voluntarily including acute, and also sub-acute, and chronic stroke patients or those with motor related or traumatic brain injury.

6.1.1 Introduction

Virtual Environments (VE), flexible computer generated environments used to develop exercise protocols for motor skills acquisition and stroke rehabilitation, have been demonstrated to be effective in improving upper extremity motor function in adults with chronic stroke-related hemiparesis (Merians, Jack et al. 2002). Many acute stroke subjects cannot perform effective voluntary movement, and are unable to participate in rehabilitation exercises delaying important interventions. Delay in therapies may lead to loss of cortical representation.

6.1.2 Competition for Neural Territory

The prevailing paradigm for upper extremity rehabilitation describes the kinesiological need to develop proximal control and mobility of the shoulder prior to initiating training on the hand (Lennon, Baxter et al. 2001). This has been the accepted rehabilitation method for many years. An increasing number of human and animal studies (Nudo, Jenkins et al. 1990; Pascual-Leone, Grafman et al. 1994; Karni, Meyer et al. 1995; Hlustik, Solodkin et al. 2004) have reported that movement practice increases the area and density of motor cortex correlated with that movement, and that new patterns of representation emerge after intensive motor practice; with the possibility that this expansion of motor territory influences representations occupying adjacent territory (Hlustik, Solodkin et al. 2004) or ipsilateral territory (Small, Hlustik et al. 2002). It is not clear whether this expansion of cortical representations occurs through sharing of cortical tissue among representations (Kossut and Siucinska 1998) or through competition for cortical territory (Merzenich, Wright et al. 1996). The mechanism of expansion of cortical movement representations may also differ depending on whether plasticity occurs in an intact brain or after a cortical lesion (Pascual-Leone, Graman et al. 1994; Karni, Meyer et al. 1995; Nudo, Plautz et al. 2001) and on lesion location (Hamzei, Liepert et al. 2006). These findings prompt us to reconsider the rehabilitation strategy that encourages early shoulder activation post-stroke. In general there is better return of upper arm function post-stroke than of the hand (Lang, Wagner et al. 2006). Does early motor activity of the upper arm and shoulder hinder recovery of hand function because of cortical competition facilitated through intensive motor activity? Can early intervention for hand function be enhanced through the use of a virtual environment hands avatar and associated rehabilitation protocols?

Underlying mechanisms of action of VE therapies, particularly for the benefit of motor skills acquisition and for acute stroke subjects, have not been thoroughly investigated. Functional MRI compatible VE can be used to assess and track neural activation during exercises with somatosensory experience protocols that correspond with training in the rehabilitation exercises enabled in the virtual environment, including manipulated or altered virtual experiences (Brewer, Fagan et al. 2005) modeled to stimulate ‘mirror neurons’ (Rizzolatti and Craighero 2004) associated with motor facilitation (Fadiga 1995; Maeda, Kleiner-Fisman et al. 2002). Functional MRI may be used in conjunction with VE rehabilitation protocols to determine activation of primary and secondary motor systems important for effective motor output in stroke subjects with corticospinal system (CSS) impairment (Ward 2006; Ward, Newton et al. 2006). Stroke rehabilitation is moving into the realm of plasticity-mediated therapies (Stein 2004) related to the ability of the adult brain to re-map functions, shifting regions of motor control to adjacent tissue (Asanuma 1991; Jacobs and Donoghue 1991; Nudo 1996), or the contralateral hemisphere (Glees 1980; Fisher 1992; Sabatini, Toni et al. 1994) to take over functions of damaged cortical tissue. Activation of primary and secondary cortical motor regions in the absence of voluntary movement may improve the likelihood of recovery through mechanisms of plasticity. Properties of the mirror neuron system believed to exist in the human brain may explain the human ability to learn by imitation (Fadiga 1995; Maeda 2002; Patuzzo 2003). Recent concepts in neurorehabilitation inspire the interest in tapping into the properties of the mirror neuron system to stimulate primary and secondary motor systems and to create a context for plasticity of motor control rehabilitation through novel hand imitation and sensory feedback VE rehabilitation protocols.

Imitation exercises are more effective in activating pars opercularis of IFG during finger lifting than symbolic or spatial cues indicating importance of mirror neurons (Iacoboni 1999). Visual guidance can reduce cognitive burden in stroke subjects compared with self-guided tasks (Hanlon, Buffington et al. 2005). In rehabilitation, compliance can be difficult to confirm (Pomeroy, Clark et al. 2005). Intelligent VE can provide highly structured task presentation, imitation applications, visual guidance, and can monitor compliance, making VE an attractive choice for rehabilitation. Higher level functioning mediates motor skills learning by imitation (middle frontal gyrus for learning novel hand actions) (Buccino 2004). The hypothesis is that in the presence of VE protocols, a complex visual-neural stimulus can be achieved that engages mirror neurons for imitation, and secondary motor systems, known to be necessary for motor output in stroke patients while providing visual guidance, known to benefit stroke patients and older persons. Further, the hypothesis is that training and rehabilitation interactions in the VE might stimulate important cognitive networks. Another hypothesis is that training and rehabilitation of tasks should involve some protocols wherein interactions with elements are matched for observation and action (Mattar 2005). VE's are appropriate since it has been shown that performance improves for such task configurations. It has also been shown that presenting a first-person perspective for imitation, might stimulate more direct and stronger cognitive networks than third-person perspective. Viewing virtual hand movement during VE exercises might activate hand-relevant parts of the brain (right MT/V5, left and right anterior IPS, right precentral gyrus, and right inferior frontal sulcus (Wheaton, Abbott et al. 2004)), might promote engagement in feelings of ownership of the virtual hands (Ehrsson, Spence et al. 2004; Ehrsson, Wiech et al. 2007), understanding goals of the observed virtual action (Hamilton 2006), recognition of biological movement (Servos, et al. 2002) of the virtual hand in the scene, and sense of self-awareness and agency (Decety, Grezes et al. 1997; Decety, et al. 2006). Ultimately, this MRI compatible VE might enable analysis of the feedback and feed-forward realtime dynamics of the brain network associated with the interaction of visual recognition of actions and the control of actions (Hamilton and Grafton 2006). In the present research experiments were conducted to determine if it is possible to manipulate the activation of motor related regions by altering sensory feedback to engage activation in brain regions associated with successful movement of target body regions thereby providing an evidence-based rehabilitation protocol for motor skills acquisition and for acute stroke subjects who cannot generate effective voluntary movement. The inability to move compromises the stroke subject's ability to participate in rehabilitation and through properties of plasticity, makes them vulnerable to loss of cortical representation. Therefore, research was conducted in a functional MRI experiment using virtual environment hands avatars to alter the visual sensory experience during hand exercises in healthy control subjects.

6.1.3 Sensory Feedback of the Contralateral Hand Can Facilitate Ipsilateral Motor Networks

The present research explored whether providing feedback of the non-moving hand, contralateral to the moving hand, could facilitate motor networks in the ipsilateral hemisphere. Subjects performed sequential finger movements with their right hand while receiving one of four types of feedback of finger movement: 1) left VR hand motion, 2) right VR hand motion, 3) left blob motion, 4) right blob motion. Blobs were non-anthropomorphic shapes (matching the virtual hand in size, color, movement, and visual field position) thus controlling for these non-specific effects. Six functional runs were performed with 50 trials/run (300 trials total; 75 trials/concordance condition). The conditions were modeled according to a 2x2 factorial fixed-effects model.

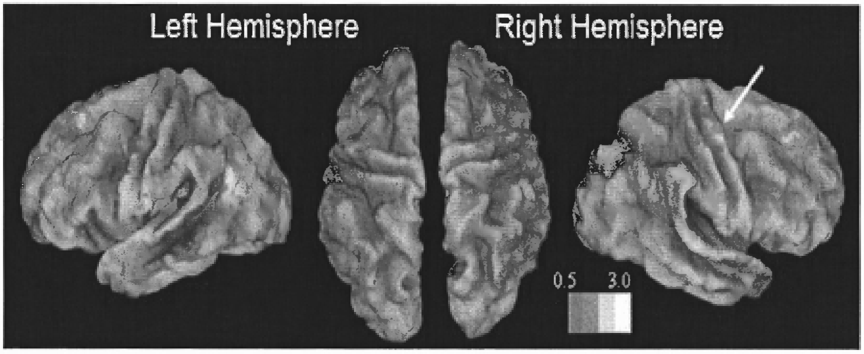


Figure 6.1 Ipsilateral Brain Activation Left-Right Therapy.

A representative subject performed a finger sequence with the RIGHT hand. The contrast shows activations that were significantly greater when viewing the corresponding finger motion of the LEFT > RIGHT virtual hand. Note that viewing the LEFT virtual hand led to significant activation of the primary motor cortex IPSILATERAL to the moving hand (i.e. contralateral to the observed virtual hand) (see arrow). the intention to imitate afterwards. Shown are BOLD correlation with block number; i.e., the development of activation in this condition. Significant BOLD activity (p<.01) is rendered on an inflated cortical surface template. Figure shows a representative subject's BOLD activation for actuating motion of the virtual left hand more than actuating the virtual right hand. Note that the only difference between these conditions is the feedback (left versus right hand) while the physical movement is always generated by the subject's own right hand. Left hand > right hand feedback produced significantly greater activation of the right sensorimotor cortex (i.e. the cortex ipsilateral to the physically moving hand). In other words, this simple sensory manipulation was sufficient to significantly facilitate lateralized activity in the cortex representing the physically static hand. This physiological response may explain a previously reported phenomenon in limb amputee patients, who feel attenuation of phantom limb pain when using a mirror reflection of their non-amputated limb to simulate their amputated limb (Ramachandran 2005). This type of sensory illusion has been hypothesized to have utility for stroke patients as well (Altschuler, Wisdom et al. 1999; Ramachandran, Altschuler et al. 1999). However, until now, the physiological mechanisms have not been explored. The present data suggest that these neuroplastic changes may occur at the level of the primary motor cortex and that VE may be an effective way of providing stroke patients in the acute phase, when the affected limb is immobile, with illusions of limb motion (actuated by their non-affected limb).

6.1.4 Materials and Methods

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). The scan was obtained while subjects were instructed to perform hand exercises. Images were processed using AFNI software.

All data were tested for the presence of any head motion induced signal changes using image registration algorithm. A synthesized box-car waveform corresponding to the stimulus presentation cycle was cross-correlated with all pixels on a pixel-by-pixel basis for each data set to identify the regions activated by the task. The correlation-coefficient threshold of 0.5, after a Bonferroni correction, corresponded to a statistical significance of $p < 0.001$. All pixels that passed this threshold were considered activated and belonging to the sensorimotor and its associated cortex.

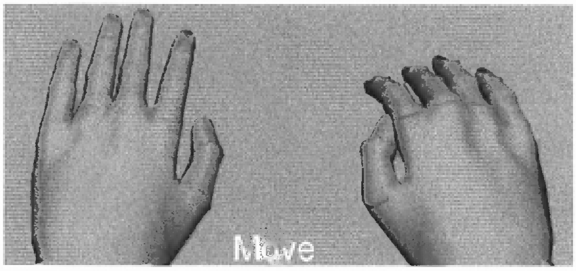


Figure 6.2 VE representation viewed by subject Condition 1: Move while watching moving hand.

In the trial experiment, each subject is presented with a task to perform in the MRI environment, and in analysis, changes relative to a control state are mapped. Five right-handed subjects, four healthy controls and one 70 year old woman who had a right hemispheric subcortical ischemic stroke 7 years ago participated in an imitation of hand movement protocol created in a three-dimensional VE. A 5DT MRI compatible VE glove was used on each subject's hands to control the VE animated hand, to correlate brain activation with finger articulation, and to confirm subject compliance with instructions.

Each subject is first asked to watch the virtual hand animation (opening and closing of the hand at about 1 Hz), while intending to imitate the action. In Condition 1, he is asked to reproduce the observed hand motion by moving his right hand while watching the moving representation of his hand on the screen. In Condition 2, the subject moved his right hand while looking at animated virtual hands displayed on the screen, however, the left hand moves in response to his or her right hand movement.

6.1.5 Results

When comparing Condition 1 with Condition 2, greater activation is seen in a number of regions associated with the sensorimotor control of the hand in Condition 1 while the subject sees the virtual left hand moving (see page 167). In addition to increased activation in the primary motor cortex, increased activation is observed in a number of sensorimotor areas including dorsal premotor and supplementary motor areas, as well as anterior cingulate cortex, anterior intraparietal cortex and superior temporal gyrus. Analysis of the hand kinematics demonstrated that this increase in brain activation was not associated with any significant increase in the amplitude or frequency of finger motion.

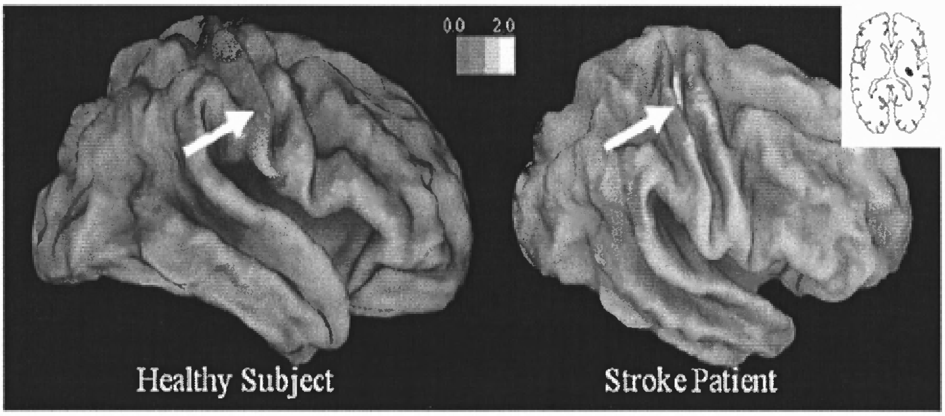


Figure 6.3 Left-Right Therapy Healthy Subject and Stroke Patient.

Most importantly, the recruitment of ipsilateral activation was also seen in the subject who had suffered a stroke. The shift in laterality of the activation associated with the Left-Right Therapy represents brain activation in the region of the brain affected by the stroke and also associated with the hemiparetic limb. If activation of important motor related brain networks is associated with recovery of motor function, then visual sensorimotor experience in virtual environments may serve an important role in establishing a therapeutic condition for hemiparetic patients.

RESEARCH AIM 5

Aim 5) For the fifth objective, visual feedback of seeing one's own hand or seeing a virtual hand was compared with the absence of seeing a hand during a sensorimotor experience. Unlike Research Aims 2-4 where we investigated effects of movement observation during simple finger sequencing, Research Aim 5 was utilizing more complex hand movements. This objective investigated whether seeing one's hand helps during imitation of novel hand gestures and whether seeing one's hand actuating a virtual hand helps during imitation of novel hand gestures.

Introduction

Open access architecture, public communications infrastructures, flexible software, actuators, and input devices have become highly functional and inexpensive offering options in monitoring, assessment, learning, tele-learning (Patton, Dawe et al. 2006), and healthcare applications like never before. Simple, yet sophisticated applications may be used to assist in transforming learning sessions and motor skills treatments or training from short term and episodic to a more comprehensive persistent model, ready to assist the individual in his or her everyday life challenges. Neuroscience research has extended the understanding of correlates associated with important experiences, skills, and behaviors of humans (Friston 2005). Brain mapping has provided a window into the complex brain activations associated with learning and a variety of important human functions (Grafton, Mazziotta et al. 1992). Virtual Environments allow designers to represent ecologically relevant experiences to which humans are sensitive, and in many convenient models (Jacobs, Pinto et al. 2004). Convergence of technologies (Patton 2006) and communications integrated with neuroscience is revolutionizing fields of education, training (Rizzo, Bowerly et al. 2006), and rehabilitation (Adamovich, Qiu et al. 2007). At the same time, these new technologies have provided the means to integrate delivery of neural therapies and also to provide for the real-time performance support during difficult or stressful tasks, for example, when patients are unable to participate in traditional rehabilitation due to extreme weakness or hemiparesis (Kwakkel, Meskers et al. 2008).

In addition to providing rehabilitation for patients, carefully crafted virtual environment platform features and applications based upon sound research principles may benefit a wide range of fields (Adamovich, Qiu et al. 2007) including primary neuroscience research, human computer interface design, the general education marketplace, and applications for specialized skills development for example, defense, surgery, and flight, and for cognitive prosthetics and psychotherapy. The VESLI technique and platform uniquely trains the brain through task design and sensory stimulation and feedback using targets identified by brain mapping – targets recruited through specific training protocols resulting in recruitment of important action observation and action execution neural networks including language and motor planning related Broca's area (Heiser, Iacoboni et al. 2003; Iacoboni 2005). VESLI provides personalized sensory augmentation and sensory stimulation enabled in virtual environments (Haggard, Christakou et al. 2007).

Many services may be offered through a system developed using such an architecture. One such service includes a Motor Skills Disease Management model following a patient through the logical health management cycle from initial stages and providing adaptive and pervasive long-term support and services in the clinic and in the community. Such a system may be introduced in a phased approach offering effective features to targeted clients during a particular phase of their treatment, such as those who have suffered from stroke or traumatic brain injury, and during the acute and sub-acute phase of care.

At present, there are few options available for rehabilitation for patients who are too weak or too severely disabled to participate in traditional therapy. Over time, additional features may be included on the platform making it multi-purpose; at that point, additional patient populations may be targeted increasing impact. Other patients who would benefit from such a platform offering personalized early intervention and long-term treatment and follow up performance support include but are not limited to those with traumatic brain injury, amputation, spinal injury, those with brain implants, prosthetics, Parkinson's Disease, Cerebral Palsy, or those for whom imitation experience is daunting, as it may be for people who suffer from social or communication issues such as Autism. Benefits gained in typical social interactions may be missed by some segments of the population. Traditional performance training and support targeting intensive, repetitive skills acquisition may also be offered on such a platform (Dobkin 1997). The platform provides for the delivery of dynamic and adaptable personalized augmented sensorimotor action-observation and action-execution, exercise, treatment, imitation, OTI, and training protocols in a compelling pervasive virtual environment.

The Motor Skills Management feature of VESLI wherein symptoms or performance indicators are measured and tracked, and protocols using predictive reinforcement formulated by experts, carefully crafted tasks (Kerzel, Hommel et al. 2001) and feedback, inform and assist the individual through protocol compliance. Sensorimotor and task accomplishment feedback is given in the promotion of learning and good health through a combination of behavioral instructions managed by the system and prescriptions (modifying the algorithms in exercise programs) based upon professionally designed protocols. Over time, additional features may be incorporated to provide extensive and feature rich services platforms for revolutionary interventions in a connected and pervasive computing environment.

Peripheral devices integrated into the system measure kinematics and provide input to programs enabling features and tracking performance. In the near future additional devices and applications enabled through an ad hoc wireless networks and internet connectivity will easily support data acquisition in a variety of locations and situations to measure and support everyday life in the home of a person who has motor skills, communications, social, or cognitive needs. Eventually, systems of this type with mixed real-world and virtual environment elements may provide enough features to individuals to enable them to obtain performance support and to maintain and manage significant portions of their own health and independence in the community for longer periods of time. Such applications may lead to improved quality of life for many people and less reliance on direct medical care that will lead to fewer emergency interventions, hospitalizations, and specialized care facility admissions. The present research incorporates an exercise system with visual sensory augmentation features demonstrated to recruit specific neural correlates associated with a sense of involvement or agency in actions viewed, and also the neural correlates of action observation and action execution, of body parts. VESLI was designed and developed as a motor skills acquisition training and research system. In the present behavioral experiments, interacting with visual sensory modulations and feedback were investigated in an observation and imitation protocol involving intransitive hand gestures.

The significance of the present research is to bring about understanding of the effects of sensory feedback on the neural correlates of simple finger imitation sequences, and understanding of high level task performance and to integrate that understanding into the virtual reality motor skills acquisition and training environment.

7.2 Platform and Services Approach

Early intervention and individualized therapies may optimize the potential for recovery from hemiparesis and other motor dysfunction. Because of the advent of computerized rehabilitation and neural-plastic approaches, platforms that offer the opportunity for the service provider or therapist to assess and prescribe a protocol early following injury (thereby reducing possible loss of cortical representation) and to offer customized or unique therapies for individuals are possible. Through brain mapping, connectivity mapping, evaluation of damage and understanding of retained functional abilities of patients, and knowledge of target networks, customized protocols may soon be established. With such a flexible computerized platform, the abilities and needs of the individual may be systematically and objectively identified. Progress may be easily tracked and reflected in iteratively updated treatment plans. The integrated system itself tests the abilities of the subject. The VE system also presents sensory conditions manipulated through computer programs that are not traditionally accessible in a clinic or home environment thus extending the impact of clinical care to include the VE practice environment where the individual can receive more intensive therapy important for plasticity based rehabilitation. Elements within the home may be integrated within the application as features in the system grow. This is important for people who cannot get out and for those who are limited in their ability to interact with their environment. For example, sensors installed in common household or workplace elements may be integrated into the system to monitor motor skills and activities and may be integrated into the learning paradigms increasing the influence on Activities of Daily Living. VESLI is a connected model for everyday motor skills support and for monitoring the patient performance and participation in Activities of Daily Living.

7.3 Profiles for Learning

The VESLI approach is to consider specific brain injury or learning need of an individual, identify target skills, remaining abilities, and their associated brain networks within the individual through skills or diagnostic evaluation and brain imaging. Then the plan is to introduce a learning paradigm through virtual environment and sensory feedback targeting activation of the specific brain correlates associated with target behavior. Even when the subject cannot perform the specific behavior as in the case of hemiplegic stroke patients, the VESLI system has been demonstrated in functional brain imaging experiments to engage neural correlates known to be associated with the desired behavior through task design (OTI) and enhanced visual sensory biofeedback. This extends the system reach to patients who are paralyzed and also to those who might be training for use of prosthesis. It also allows VESLI to include customers for whom mental imaging is the goal of the learning protocol, while demonstrating brain activations that are motor related when compared with research findings of brain networks associated with mental imaging.

The VESLI approach differs from traditional stroke therapy approaches that use statistically demonstrated therapies for each and every patient, only engage the patient after the acute stage of recovery, and can only engage the patient in therapies when they can actually perform a task. For hand therapies, the patient must have at least a minimal range of motion in order to participate in traditional therapies. For passive therapy or for visual sensory augmented therapy provided through VESLI, subjects may have severe paralysis and still participate.

Aim 5) For the fifth objective, visual feedback of seeing one's own hand or seeing a virtual hand was compared with the absence of seeing a hand during a sensorimotor experience. This objective investigated whether seeing one's hand helps during imitation of novel hand gestures and whether seeing one's hand actuating a virtual hand helps during imitation of novel hand gestures.

This objective further clarifies the biological model of the sensorimotor experience and helps in the understanding of the role of virtual sensory stimulation and feedback which includes seeing one's own hand movement, or seeing a virtual hand actuated by one's own hand, during action-observation action-execution (Buccino, Binkofski et al. 2004), OTI, and imitation of novel hand gestures (Arbib, Billard et al. 2000; Carmo and Rumiati 2009). Visual and auditory language learning activates target neural networks (Binkofski and Buccino 2004; Newman-Norlund, Frey et al. 2006). Since VESLI uses American Sign Language, subjects were screened for their understanding of English. Gestures were defined in Pictures and in Text. A variety of hand-shapes are included in

VESLI applications from among the 17 used in American Sign Language (Costello 2002) (not including finger spelling). Included hand signs range in motor skills difficulty and are assessed with the Chedoke-McMaster scale. The study includes signs ranging from Level 3 through 7. The study questions are as follows: (Chadwick-Dias, Investments et al.) Does viewing one's own hands facilitate imitating sign language hand gestures? Imitating Gestures with a Virtual Agent: Seeing One's Own Hand In Practice. Does seeing one's own hand during practice facilitate imitating gestures in a Virtual Environment? (4B) Does viewing computer-generated hand models actuated by one's own hands facilitate imitating sign language hand gestures? Imitating Gestures with a Virtual Agent and Virtual Self: Seeing One's Own Hand Actuate a Virtual Hand in Virtual Environment. Does seeing one's own hand actuate a Virtual Hand facilitate gesture imitation in a Virtual Environment? (4C) Does viewing text or picture, or viewing an agent (computer-generated human) in either first person perspective or third person perspective facilitate imitating sign language hand gestures? Imitating Gestures with a Virtual Agent: Imitating 3rd Person and 1st Person Virtual Agents Does 3PP or 1PP Virtual Agent Facilitate Imitating Gestures? Does seeing your hand affect the virtual hands (El-Shawarby, Ravhon et al.) effect imitating in 3PP or 1PP Virtual Agent Gesture Experience?

This study investigated the role of visual feedback in sensorimotor experience and neurorehabilitation. In particular, the study investigated whether viewing one's own hands (Poizner and Tallal 1987) will facilitate implicitly imitating intransitive sign language hand gestures (Hamzei, Dettmers et al. 2002). Virtual environment behavioral experiments were conducted in the lab where the subjects watched a virtual agent (computer-generated human) in either first person perspective or third person perspective (Jackson, Meltzoff et al. 2006). The agents demonstrated American Sign Language gestures (Corina and Knapp 2008), accompanied with either text or picture descriptions (Kahn, Rymer et al. 2004;Davachi 2004; Davachi 2006), and with an agent (computer-generated human) in either first person perspective or third person perspective (Corina and Knapp 2006). The study investigated how the above conditions might facilitate experiences in implicitly imitating intransitive complex sign language hand gestures (Jackson, Meltzoff et al. 2006). In addition, the effects of viewing one's own hands during the imitation process was compared with the effects of viewing computer-generated hand models actuated by the subject's own hands in real time. In future work, brain networks activated (initially during gesture study) when the subject successfully learns the gestures (tested in the memory task) will be mapped to understand needed networks for hand gesture imitation. The goal is to understand which neural networks are activated when successful behavior, imitation, OTI, exercise, takes place, and results in successful memory. Brain activations present in recall will also be investigated.

The present work may provide a basis for the development of cognitive and language tasks such as implicit intransitive gesture imitation within the conscious control of the subject, utilizing sensory manipulation and incorporated into motor task action-observation action-execution, OTI, imitation and learning paradigms for personalized complex motor skills acquisition and training, practice, and rehabilitation utilizing implicit learning and simplifying dexterous hand activities. Through visual sensory support, passive and active therapies might be realized, even therapies that might be used in early stages of stroke when patients are weak. Behavioral, clinical measures, and future fMRI studies may be used to determine relevant brain networks associated with each specific voluntary motor task imitation and learning paradigms. Further work may be conducted to include healthy and patient subjects who have suffered stroke, brain injury, or other condition such as autism resulting in motor dysfunction. Through the mapping of relevant brain networks associated with task performance and by understanding the effects of stroke or other injury on the brains of individuals, strategies might be developed to identify the cognitive and language tasks and sensory manipulation that may be appropriate for use in skills acquisition, training, and or rehabilitation of an individual. An important question for future research is to identify whether the task of selecting between definitions with picture or definitions with text selectively actuate important target brain regions associated with complex hand skills motor planning and execution and or complex hand skills acquisition.

It is hypothesized that subjects who have suffered stroke (with reduced proprioception sense) or other injury or condition might benefit more from viewing hands while performing the imitation or learning task (engaging cognitive networks) and will differ from healthy control subjects during these tasks. High level tasks can modulate motor skills. The present ASL intransitive gesture imitation research study includes only healthy controls. Future studies should include subjects who might selectively benefit more from bolstered or augmented visual feedback. In addition, future studies should include mapping dorsal and ventral visual processes in functional imaging and comparing patient populations with healthy controls in this processing.

Anatomic and functional studies of individuals, for example, subjects who have suffered from stroke, compared with required networks revealed in this research, might shed light on the potential effectiveness of these tasks in a rehabilitation strategy. Comparison of brain mapping with patient brain studies might reveal prognostic indicators. Future work may include correlating functional motor skills performance, and location and extent of lesion, for selecting stroke patients who might benefit from virtual reality therapies and specific tasks within those VE therapies as a means to stimulate neural plasticity – targeting brain regions associated with for example, implicit tasks such as imitating intransitive gestures. Further research in brain imaging and corresponding motor skills performance analysis before, during, and following rehabilitation activities might lead to a better understanding of optimal time to participate in such therapies and the learning processes that take place between sessions across the recovery interval. Individual neural networks such as secondary motor regions, recognition of biological motion (Servos, et al. 2002), body part (Wheaton, Abbott et al. 2004), self-other (Farrer and Frith 2002), activation of a sense of agency and self-involvement, and attenuation of some of these sensations will be investigated in the future as part of understanding how virtual experiences engage the brain. Work proposed may provide the basis for understanding the underlying mechanisms of action of important physical therapies.

Therapies involved include practice-induced neural plasticity associated with virtual reality physical therapies in hand and finger rehabilitation. Corresponding clinical effectiveness of these therapies are objectively measured and represent motor skills acquisition. Behavioral learning responses are also measured in the memory tasks of the present research. Faster response time in memory tasks is believed to result from transformation of cognitive processes into motor memory representations. This study will use response time in memory tasks as a proxy for motor learning and has been demonstrated to correspond with correctness of responses. In addition, kinematic measures will be used to characterize motor skills performance during gesture imitation, and is used to demonstrate compliance, but kinematics analysis is not within the scope of the present research. Future work would include additional functional brain imaging studies that track repetitive exercises to further understand the changes in brain activations throughout an individual rehabilitation session and between rehabilitation sessions. Future work will present kinematic analysis of gesture practice and performance.

For subjects suffering hemiplegia or other motor skills issues, initial functional connectivity in the brain and clinical motor skills associated will be investigated in the future. Mapping control subjects for connectivity, mapping the tasks, and comparing with patient connectivity might reveal important clues to impediments of recovery, and might lead to innovations in rehabilitation. Particularly, monitoring patients throughout intervention might reveal important information about mechanisms of recovery not yet completely understood. The present research establishes a model for research and might help to develop novel practice-induced plasticity computer-based virtual environment physical therapy programs optimized for sensorimotor experiences that selectively actuate target brain regions and that yield desired behavioral outcomes for skills development for healthy persons and for stroke and other patients suffering from brain injury-related motor dysfunction such as hemiplegia. The same research may result in important information about how to provide sensory support for specific groups and for specific tasks. These experiments combining virtual environments to augment sensory experiences might provide a suitable model for the more widespread use of functional MRI to identify prognostic indicators and therapy targets (in the brain) associated with motor skills recovery in stroke and other conditions.

The present research provides a flexible MRI compatible virtual environment and proof of concept human experiments through which a systematic series of experiments demonstrated an example of neurophysiologically driven sensorimotor experience that activates target brain networks; one application is to apply this research to develop a hand imitation rehabilitation strategy. In the future, as more subjects who have hemiparesis participate in such research studies, when taken together with the present findings, results might lead to greater understanding of the fundamental impact of injury upon the neural networks in proximity to the lesion and distant function, to the principal neural networks traditionally associated with the motor skills and dysfunction, and in various dispersed functions of the brain some of which might affect prognostic indicators and recovery strategies. This exciting new frontier of in vivo human brain behavior research assisted using MRI compatible virtual environments will reveal the fundamental and complex interactions of networks in the brain. Various strategies revealed through systematic study of sensory experiences will reveal tasks that can functionally stimulate target networks for example, those cognitive and sensory networks associated with motor function, to benefit recovery. The present model of research in the MRI compatible virtual environment training system establishes an effective means to transfer research findings readily into the clinical environment.

Knowledge gathered in this study of the sensory mechanisms leading to successful sensorimotor imitation in virtual environments, such as mirror or feedback modulated sensorimotor experiences, avatar model choice, 3rd person/1st person (Jackson, Meltzoff et al. 2006), text and picture support, implicit instructions, intransitive gestures (compared with transitive tool-based gestures), and the presence or absence of subject hands proxy, along with future work on understanding of neural connectivity available for rehabilitation in the injured brain (location and extent of damage), and an understanding of the dynamics associated with spontaneous and facilitated recovery, combined with the improved understanding of which patients will benefit from plasticity-mediated therapies, will bring about promising evidence based therapies. Many additional high level and cognitive tasks may be tested in the same platform in order to identify good tasks for learning and rehabilitation. Understanding the neural underpinnings of motor skills acquisition and motor skills memory formation will provide the potential for revolutionary training and rehabilitation options to be delivered through a comprehensive service platform using technologies such as the virtual environment and based upon theories of brain plasticity.

7.4 Experimental Design – Aim 5

Subjects were informed about the nature and goals of the experiment. They were instructed in their role and activities associated with participation. They provided informed consent in order to participate. The subjects were freely able to withdraw from the experiment at any time.

7.5 Summary of the Study Design

In a Learning Session, each subject was instructed to imitate hand gestures beneath a special two-way mirror in either a See Hands or Hidden Hands condition. The gestures were presented in close proximity to the subject's hands on the same mirror viewing surface using a laptop and a multi-media projector. In the Hidden Hands condition, the light behind the mirror was turned off. In the See Hands condition, the light behind the mirror was turned on, enabling the subject to see his or her own hand through the special two-way mirror while also viewing the avatar model demonstrating the gesture. The subjects were then asked to perform a Memory task to identify gestures as Familiar or New, provide Definition from two choices, and indicate source (Source Task) as Picture or Text recalled from the initial Learning Session. This method assures the memory is from the specific episode of learning the gesture. Since the words and pictures are familiar, the Source Task checks subject memory of this particular episode of hand gesture and definition, and not some generalized knowledge. Speed and accuracy in performing the Memory Task and the Source Task, remembering the Item and Source, and accurately rejecting new Lure signs is measured using a customized software package and data capture application within the VESLI System. Practice time and recall time for each question was limited and precisely administered through the custom software and included parameters. Time constraints assure that subjects do not perform at ceiling. Practice in the Virtual Hands condition was measured with the instrumented data glove (CyberGlove, Immersion Inc) and determined subject compliance with the gesture practice portion of the task. Analysis investigated whether Seeing the hands during practice contributed to performance of the Memory Task (Item and Source) for each sign practiced with Text or Picture descriptions. The special mirror used in this experiment has the advantage of providing an environment wherein a subject can see his or her own hand or a virtual hand moving in concordance with his or her own hand movement by virtue of the computer virtual experience. The virtual hand proxy was positioned in an overlapped ("where is") position with the subject's own hands. The special mirror also concealed the hands during the Control Condition of Hidden Hands in each of the experiments.

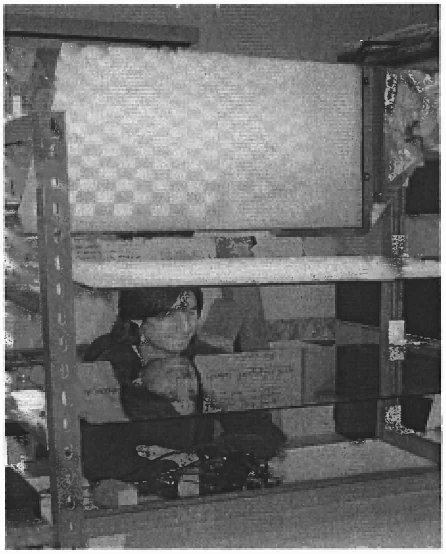


Figure 7.1 Custom built multimedia system with two-way mirror.

7.5.1 Position of the Virtual Agent, 1st Person Perspective versus 3rd Person Perspective

In a separate future study, these tasks may be repeated in the fMRI for brain mapping of neural correlates associated with viewing virtual hands, or imitating virtual agent in first or third person perspectives, using biologically driven avatars and linear programmed avatars. Neural correlates associated with kinematics and successful Memory Task will be identified.

7.5.2 Procedure

The Virtual Environment Sign Language Instruction (VESLI) System consists of: a laboratory Dell computer, Jack human avatar software, Virtools avatar, a multimedia projector, a database containing American Sign Language animation files, CyberGloves containing bend sensors, and a custom built multimedia two-way mirror display. Subjects were asked to sit in a chair close to the special two-way mirror and to view the animation of hand gestures performed by the virtual agent and displayed on the special mirror using a multi-media projector.

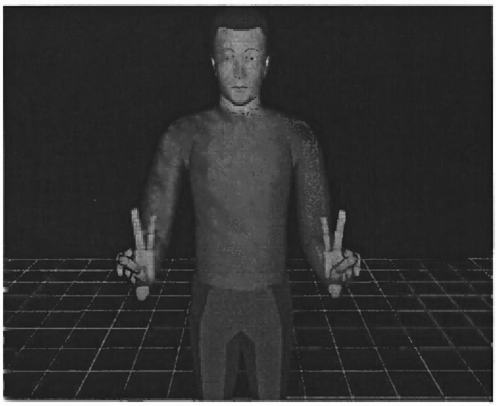


Figure 7.2 Virtual Agent 3rd Person Perspective presenting hand gesture for Lobster.

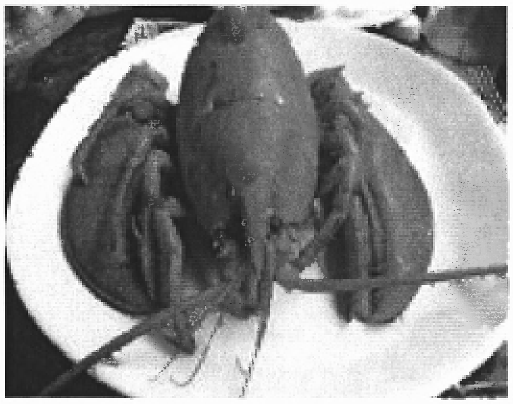


Figure 7.3 Example definition of hand gesture presented during Learning Session: picture of Lobster.

At the same time, definitions of the hand gestures were displayed in either text or pictures. Subjects viewed animations and were instructed to practice making the hand gestures while the definitions and avatar animation remained visible. Signs were pseudo-randomly ordered.

For half of the practice sessions, the subjects were able to view his or her own hands. For half of the sessions, the mirror light was off obscuring the subject's view of his or her hand. Hand gestures were presented by the Virtual Reality Agent during the Learning Session.

Figure 7.4 Example choices in Memory Session: Picture Cat.

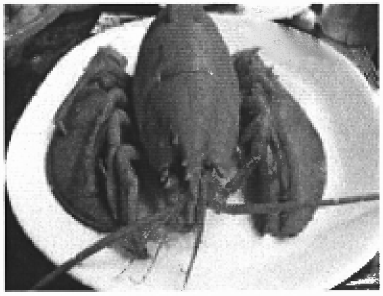


Figure 7.5 Example choices in Memory Session: Picture Lobster.

A Memory Session following the Learning Session tested the subject's ability to remember the hand gesture, the meaning of the hand gesture, selected from two choices, and the source definition format in the initial gesture presentation, text or picture. Eight of ten additional novel signs were presented during each of the Memory Sessions and served as Control Conditions for each of the two experiments. Subjects were instructed to reject signs they did not practice in the initial Learning Sessions. In experiment 2, the subject viewed a Virtual Reality hand in place of his or her own hand. The subject's own movement controlled the movement of the virtual hands during practice and visual feedback was error-less. In this experiment, subjects viewed the 1st person avatar demonstrate the signs. Again, Picture or Text descriptions were presented to the subjects. This study considered the neural mechanisms of action perception/execution and language/picture processing for clues about successful conditions for imitation and sensorimotor experiences in a virtual environment.

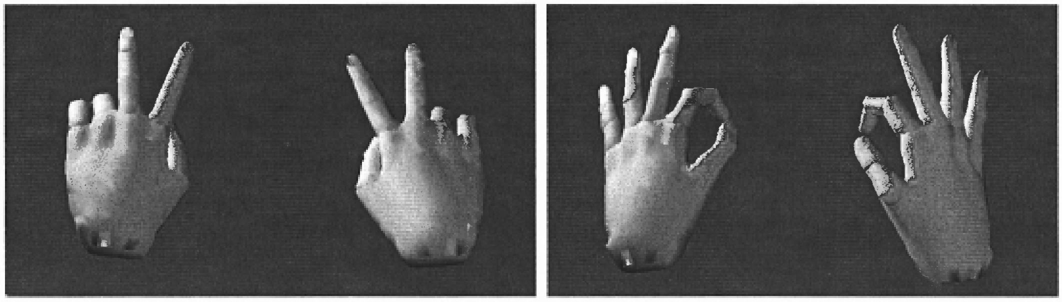


Figure 7.6 VR Lobster Sign (left panel) and VR Cat Sign (right panel).

In experiment 1, the view of the virtual agent was in the 3rd person perspective. In experiment 2, the view of the virtual agent was in the 1st person perspective. In experiment 1, subjects saw their own hands through the mirror, and in experiment 2, subjects viewed virtual hands displayed on the special mirror. In both experiments 1 and 2, subjects practiced half of the gestures with their 'own hands' obscured beneath the special mirror for a No Hands condition and serving as a control. Novel signs as Lures served as a Control Condition. Subjects were asked to participate in both experiments with breaks after each approximately twenty minute segment. Healthy control subjects who understand English, who are right-handed, and who are not proficient in American Sign Language or other formalized gesture systems participated in the experiments.

***Learning Session*:** Subject sees Virtual Agent demonstrate sign gestures, with corresponding picture (Wong, Bjarnason et al.), text (VA-T), of sign meaning.

Practice: Subject is asked to imitate the sign

- Condition Hidden Hand (HH) – Subject cannot see his or her own hand because light is off beneath the special mirror
- Condition See Hand (SH) – Subject can see his or her own hand because light is on beneath the special mirror

- Condition See Virtual Hand (El-Shawarby, Ravhon et al.) – Subject can see the Virtual Hand displayed in the same location as his or her own hand projected onto the special mirror

***Memory Session*:** Subject sees the Virtual Agent demonstrate signs, and is asked if he or she remembers having seen each sign. Several Lure signs have been added that have not been presented previously to the subject.

Response Coding: Correctly Remembered Item (I), Correctly Remembered Item and Source (IS), Not Remembered, Miss (M), False Alarm (FA), Novel Gesture (N).

***Meaning*:** Subject is asked to identify sign meaning with same or changed virtual.

- Condition 1A Same (S) or Changed (C) - Subject sees sign - selects one of two pictures as the Definition of the gesture.
- Condition 1B Same (S) or Changed (C) – Subject sees sign – selects one of two words as the Definition of the gesture.

***Source Identification*:** Subject is asked to remember learning condition, Picture, Text, or Novel.

Response Coding: VA-Picture (P), VA-Text (T), Novel (N)

7.5.3 Conditions

Experiment 1 – 3rd Person Perspective Agent Seen Hand versus Hidden Hand, 2 x 2

See Hand; Hidden Hand

Picture; Text

Experiment 2 - 3rd Person Perspective Agent See Virtual Hand versus Hidden Hand, 2 x 2

See Virtual Hand; Hidden Hand

Picture; Text

Experiment 1

Imitating Gesture with a Virtual Agent: Seeing One's Own Hand In Practice.

Does seeing one's own hand during practice facilitate imitating gestures in a Virtual Environment?

Learning session: Subjects watched an agent present thirty-two gesture & description pairs (descriptions: 16 pictures, 16 text). While each gesture was presented, subjects practiced the gesture. Practice: Subjects practiced each gesture – conditions randomized (8 pictures, 8 text with Hidden Hands; 8 pictures, 8 text with See Hands).

Memory, Meaning, & Source session: Subjects viewed all forty-two gestures to select Meaning of each gesture with voice from 21 picture pairs, and 21 text pairs [10 Novel gestures, 32 Familiar gestures; Source: 16 Same (pictures-text), 16 Different (pictures-text)]. Subjects used keyboard and identified, Definition, Familiar and Novel gestures. Hidden Hands served as a control condition. In the Memory session, Novel gestures served as a control condition. In the Memory session, source conditions (picture-text) were reversed for half of the gestures compared with learning session. Custom application timed, scored, and reported results.

7.6 Experiment 2

Imitating Gestures with a Virtual Agent and Virtual Self: Seeing One's Own Hand Actuate a Virtual Hand in Virtual Environment.

Does seeing one's own hand actuate a Virtual Hand facilitate imitating gestures in a Virtual Environment?

7.7 Procedure

Learning session: Subjects watched 1st Person Perspective agent present thirty-two gesture & description pairs (descriptions: 16 pictures, 16 text). While each gesture was presented, subjects practiced the gesture. Practice: Subjects practiced each gesture – conditions randomized (8 pictures, 8 text with Hidden Hands - HH; 8 pictures, 8 text in condition See Virtual Hands - VH).

Memory, Meaning, & Source session: Subjects viewed forty-two gestures (32 previously learned – Familiar; 10 new gestures - Novel). Subjects viewed each gesture in random conditions – 21 Text, 21 Picture. Subjects identified Definition, Familiar and Novel gestures with keyboard. Subjects selected Meaning of each gesture from picture pairs, and text pairs in randomized order and source same-source different (10 Novel gestures, 32 Familiar gestures). Hidden Hands served as a control condition. Novel gestures served as a control condition. Subjects used a keyboard to identify whether gesture was initially accompanied with a Picture or Text. Custom application timed, scored, and reported results.

7.8 Analysis

Subjects' responses and biometric data were captured using keyboard input, a customized software package for data recording and analysis, and CyberGloves with sensors. For Experiment 1, Virtual Agent condition was 3rd Person Perspective, with Text or Picture definitions of thirty two hand gestures from the American Sign Language dictionary. For Experiment 2, Virtual Agent condition was 1st Person Perspective. The retrieval conditions corresponding with responses of subjects include: Virtual Environment Plus See Hands, when the subject could See the proxy hands actuated by his or her hands in real time while learning the hand gesture; Virtual Environment Plus Hidden Hands, when the subject's hands were in darkness and visibility was prevented by the special two-way mirror. In Novel – Correctly Rejected, the subjects determined that a lure sign and definition was not studied during the Learning Session. The subjects were asked to remember the definitions of each of thirty-two hand gestures for each experiment previously studied by selecting one of two definitions presented either as Pictures or as Text or identifying the gesture as Novel (Control Condition). Ten additional signs were inserted into the Memory Sessions. Old Items were those that were presented during the Learning Session. The subject choices during the Memory Session included remembering that the hand gesture was presented with a picture or with a text definition (Item Plus Source), which was defined as a correct response, may have remembered the sign plus the definition (Item), an error, or may have forgotten the item entirely (Miss), another error type. Memory Conditions associated with subject responses are: Old – Item Plus Source (familiar and recollected), Item Only (familiar but not recollected), or Missed (less familiar or forgotten). For New items, the subjects may have made a Correct Rejection, realizing that the hand gesture presented during the Memory Session is actually a new gesture (Lure), or may have believed the hand gesture to be familiar, resulting in a False Alarm. Correct Item Plus Sources were analyzed based upon initial condition, See Hands, See Virtual Hands, or Hidden Hands, and Picture or Text, 3rd Person Agent or 3rd Person Agent, and were also analyzed based upon Memory Condition, Same (Picture Practice/Picture Memory, Text Practice/Text Memory) or Changed (Picture Practice/Text Memory, Text Practice/Picture Memory). Control errors were analyzed for Picture or Text effects. Motor responses and kinematics in imitation were analyzed from biometric data gathered using the CyberGloves for speed of response and hand shaping.

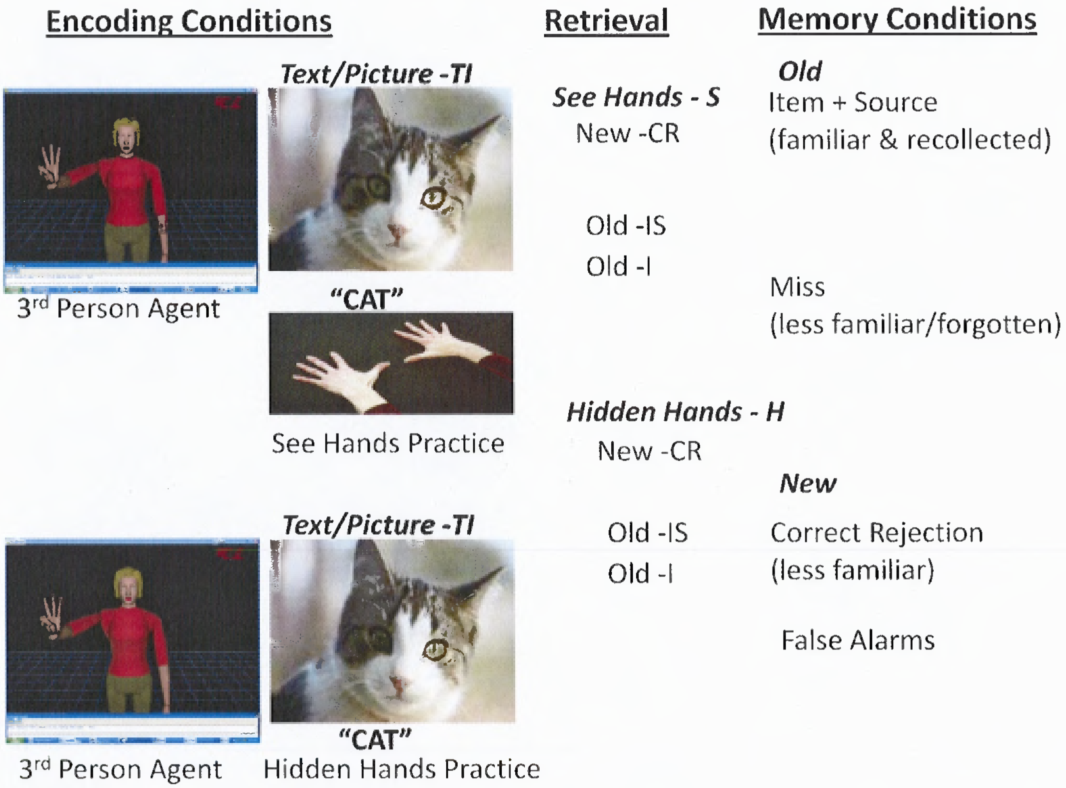


Figure 7.7 Experiment 1 – 3rd Person Perspective - Encoding, Retrieval, and Memory Conditions.

7.9 Data Analysis – Aim 5

VESLI study data were analyzed using three-way repeated measures ANOVA with the following factors:

Experiment 1

- Feedback (See Hands, No Hands), Definition (Picture, Text), and Recall (Same, Change).

Experiment 2

- Feedback (See Virtual Hands, No Hands), Definition (Picture, Text), and Recall (Same, Change).

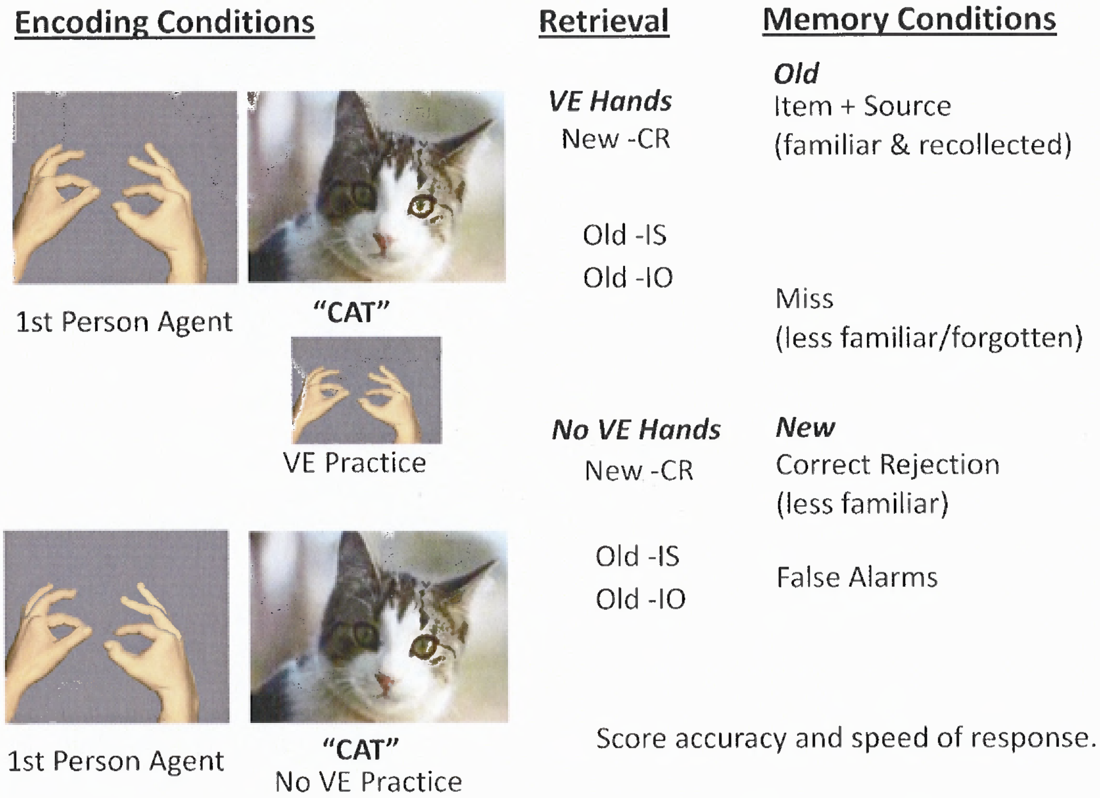


Figure 7.8 Experiment 2 – 1st Person Perspective - Encoding, Retrieval and Memory Conditions.

7.10 Experimental Results Aim 5

Significant findings in Experiment 1 include the following:

- For Average Response Time - Recall (Same, Change) – F (1, 9) = 5.8, p = .039.
- For Average Source Time – Definition (Picture, Text) – F (1, 9) = 14.28, p = .004.

Significant findings in Experiment 2 include the following:

- For Average Response Time – Definition (Picture, Text) – F (1, 9) = 31.7, p = .0003.
- For Average Response Time – Interaction of Feedback (See Virtual Hands, No Hands) and Recall (Same, Change) – F (1, 9) = 38.8, p = .0002.
- For Average Source Time – Definition (Picture, Text) – F (1, 9) = 6.96, p = .027.
- For Average Source Time – Interaction of Feedback (Hidden Hands, See Virtual Hands) and Recall (Same, Change) – F (1, 9) = 13.9, p = .0047.

In experiment one for Control Subjects, findings indicate that when practicing hand gestures in virtual environments, Picture Definitions improve performance of Memory. Average Response Time was faster in Picture than in Text: F (1,9) = 5.8, p = .039. The Average Source Time was faster in Picture than in Text: F (1,9) = 14.28, p = .004.

In experiment two for Control Subjects, Average Source Time was faster when the sign was defined as Picture: F (1,9) = 6.96, p = .027. The Average Response Time was faster when recall was the same as in the training conditions, in the presence of the Virtual Reality Hands Avatars: F (1,9) = 38.8, p = .0002. The Average Source Time was faster when signs were defined as Pictures during both training and recall. For Remembering hand gestures in virtual environments with a virtual hand representing one's own hands, there is an interaction of Feedback (Hidden Hands, See Virtual Hands) and the Recall condition (Same, Change).

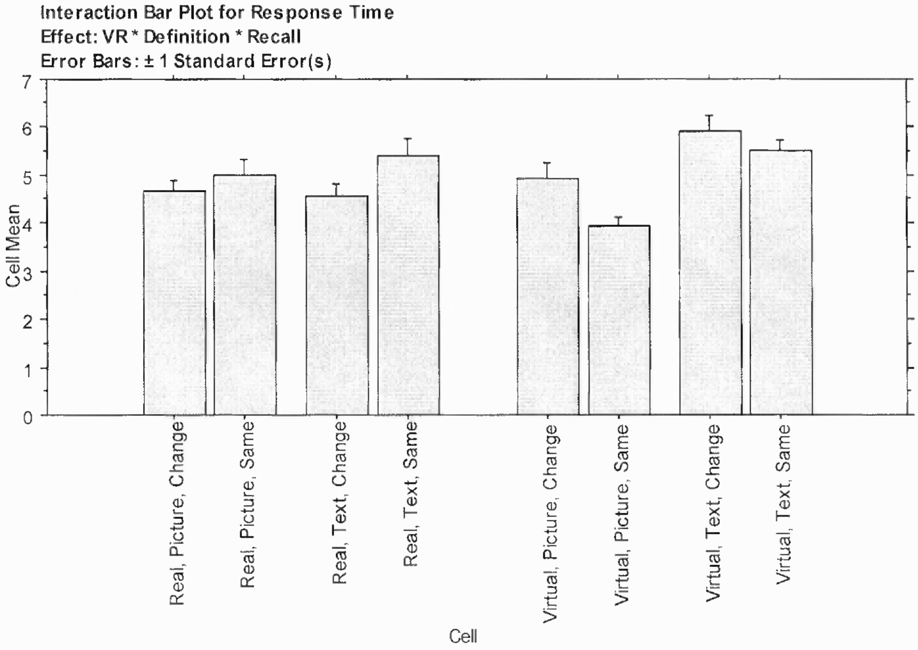


Figure 7.9 Interaction Bar Plot for Response Time Real Hands vs. Virtual Hands by Definition by Recall.

When comparing Real Hands with Virtual Reality Hands Avatars, there was an effect of the Virtual Reality Hands. Control Subjects performed best when using Virtual Reality Hands Avatars to replace their own hands in practice when the definitions were presented as Pictures and recall conditions matched the practice conditions, whereas when Text definitions were used in practice and then Picture definitions were used in recall, Control Subjects response times were longest of among all conditions. Individual subjects were evaluated to identify personal Memory style for practicing hand gestures. The VESLI system is helpful to identify individual strengths and possibly to improve performance.

Future research can investigate sensorimotor conditions improving memory for individuals and for patients. The VESLI system provides significant flexibility in the user interface. The therapist or teacher can easily create a list of gestures and practice conditions that match the patient's style to provide a training experience. Future studies can also be implemented in the MRI environment to map neural correlates of successful gesture memory with and without viewing one's own hand actuating the proxy, with picture or text descriptions, with 1st and 3rd person avatar models. In that experimental condition, the relationship between the student and the teacher can be investigated. Further research proposes to study subjects who have suffered from stroke or other brain injuries or conditions of motor dysfunction to determine if viewing hands or viewing virtual hands in a virtual environment will help individuals imitate and learn hand gestures.

The VESLI system can be used to investigate the differential neural mechanisms of grasping objects, transitive gestures, and imitating intransitive gestures. VESLI can provide an exercise system for the hand and arm, hand alone, hand and arm separately, for unilateral exercise, and for bilateral exercise. VESLI is suitable for Mirror Virtual Therapy (MVT), to present tasks of varying levels of difficulty, and with means to measure and track kinematics and performance over time.

CHAPTER 8

DISCUSSION

Observation and imitation are among the most powerful and influential aspects of human skill learning. Since neural networks for observation and execution show a large degree of overlap (Iacoboni 1999 ; Buccino 2004) and kinematic analysis demonstrates that movement observation facilitates movement (Castiello 2003; Edwards, Humphreys et al. 2003) , individuals may benefit from observation of embodied actions/effectors during the motor skills acquisition or during the acutely immobile phase following stroke. Viewing hands (Wheaton, David F. Abbott et al. 2004) and viewing body parts (Dechent and Frahm 2003) in the real world actuates characteristic brain networks. Physical therapy may induce brain plasticity in subacute and also chronic stroke subjects (Johansen-Berg, Rushworth et al. 2002; Calautti and Baron 2003; You 2005) and has been demonstrated to be effective when implemented early following stroke (Nudo, Wise et al. 1996) however, many patients might be too weak to participate. Significant evidence of support exists for the use of features in VE to promote motor skills acquisition (Merians, Jack et al. 2002; Adamovich 2004; Merians, Poizner et al. 2006) and facilitate voluntary motor production. It may be possible to provide ecological models, by representing real world scenarios in a wide variety of tasks and sensory experience in VE using flexibility of programming, lower cost platforms, and personalization enabled by technology (Carignan and Krebs 2006) for customized, attended, massed, intense, and repetitive training and to deliver support (Reinkensmeyer, Pang et al. 2002) including robotics and haptics. Vision and associated mechanisms impose a strong influence on motor learning (Buccino 2004) , can extinguish effects of other senses (Azanon and Haggard 2009), compensate diminished senses, and may be modulated independently of proprioception. Through vision, the mirror neuron system might provide some support to the motor learning process, the acquisition and/or modification of movement (Shumway-Cook 2007) , through a number of mechanisms; action observation alone may be sufficient to induce a motor memory in M1 similar to physical practice (Stefan, Cohen et al. 2005) , and can accelerate functional recovery following stroke (Celnik, Webster et al. 2008) . Perhaps vision augmentation in VE may help to avoid learned non-use (Taub, Uswatte et al. 2006) , improve encounters wherein individuals must perform tasks without perfect visual feedback (Plautz, Milliken et al. 2000) , or without required intensity and repetition (Taub, Uswatte et al. 2002) credited with preventing loss of function, and cortical representation, for implicit learning models (Boyd and Winstein 2006), and for abstract goal formulation, and provide activities in which patients with limited function can participate while targeting specific neural networks including Broca's area with language and motor function (Binkofski and Buccino 2004). Complexity of rehabilitation tasks may present challenges (Rushworth, Nixon et al. 1997; Rushworth, Nixon et al. 1998 #5631) particularly to patients . There is inspiration for visual guidance to support performance through a number of mechanisms as in visual social models to facilitate movement through modeling the task, directly (explicitly) or indirectly (implicitly) communicating the parameters or the intentions of action (Becchio, Adenzato et al. 2006; Pierno, Becchio et al. 2006; Becchio, Sartori et al. 2008) , simplifying tasks by reducing complexity, and through reduction of cognitive burden (Hanlon, Buffington et al. 2005) . To afford subjects the opportunity to embody movement providing afferent information to an affected function that they can observe

(Plautz, Milliken et al. 2000) to stimulate recovery (Wilson 1998) to participate in experience-dependent (Dobkin 2000), that match intention with feedback, realistic representations of human hands in VE that can be actuated in real time by the actor's hands were developed. Viewing mirror image of limbs during training has already been shown to facilitate learning in the untrained limb (Dionne and Henriques 2008) in healthy controls and has been hypothesized to be helpful in patients of stroke and in reducing pain in amputees (Altschuler, Wisdom et al. 1999; Ramachandran, Altschuler et al. 1999) and might be an ideal vision augmentation therapy supported by VE and computer generated non-human models may be adopted for that purpose (Press, Gillmeister et al. 2007). Until the present research, it was unclear whether viewing virtual hands avatars in a VE will actuate action-observation action-execution brain networks as will real-world observation. The present research explored effectiveness of visual sensorimotor experience in VE to go beyond providing interesting activities for subjective benefits associated with motivation and the like; sensorimotor experience modulated in VE's activated differential neural pathways associated with action-observation action-execution of real world experience (Buccino, Solodkin et al. 2006). Behavioral, kinematics, and neural brain mapping in VE together reveal not only the 'what' is happening, but also the 'why'.

In the future, resting state connectivity (Biswal, Yetkin et al. 1995) and mapping anti-correlated brain regions, as well as longer term studies, before during, and following training or treatments may capture effects not observed in a single imitation study episode, and will also lend insight to between episode effects of training, implicit learning processes, brain states in correctly remembering the hand gestures, and or the nature of recovery, relapse, or recidivism, which are important research topics.

Although it may be difficult to apply findings of basic research to practice, in addition to providing a means to study underlying neural mechanisms of interacting in the VE, the model presented herein provides a translational recipe to incorporate the effective mechanisms in a training system. Functional brain imaging has successfully differentiated mechanisms underlying motor skills in an unambiguous manner and remains an important method for mapping neural underpinnings of human behavior and experience whereas behavioral studies may not. Interpretation of findings in functional brain studies of patients might be difficult and may not result in understanding all mechanisms of recovery or dysfunction. Tasks thought to be functionally similar actually involve different cortical networks, for example, in inhibition of over learned and imitative response tendencies (Brass, Derrfuss et al. 2005) . Emerging evidence shows that interactive VE's may be a promising tool for studying sensorimotor processes and for a wide variety of applications including exemplars or paths for rehabilitation and essential discovery of neuroscience such as mechanisms of recovery which at present, may be unclear. Activation of neural pathways in the brain over time has been associated with plasticity-based changes in various brain networks and changes in neural programs affect processes of recovery (Heller and Goodwin 1987) over time (Boroojerdi, Ziemann et al. 2001). VE's can be used to trigger supportive visual feedback in response to minimal efforts (Agnew and Wise 2008) and may be particularly helpful when the patient has impoverished movements. Systematic comprehensive exploration of training mechanisms with healthy and patient populations may be performed in the new model presented herein with exceptional control over features and with the goal to increase access to hand and finger therapies (Begliomini, Wall et al. 2007) to avoid loss of quality of life and reduce loss of cortical representation suffered by stroke patients for example, and to strategically position the patient for a more effective recovery, perhaps through mechanisms of plasticity (Boroojerdi, Ziemann et al. 2001). A long term vision is to identify the essential elements of the VE sensorimotor experience that may selectively modulate neural reorganization for applications including training, education, basic neuroscience, rehabilitation of patients with neural dysfunction (August 2006; Lewis 2006) and to extend access and reduce costs of treatment.

VE's provide engaging, motivating, interactive, customizable flexible applications utilizing a variety of therapeutic techniques, and have been recently shown effective in improving upper extremity motor function in adults with chronic stroke-related hemiparesis (Merians, Jack et al. 2002). VE can support diminished senses, task structure, or cognitive processes.

For the first time, a VE training system and an MR-compatible version of the VE were used to study the neural networks involved in observation, observation with intent to imitate (OTI) with 1st person perspective and 3rd person perspective virtual teachers, and imitation of complex hand movements with complex 1st person virtual proxy representing the subject's hands, moving synchronously with his or her own movement, with unimanual, bilateral or symmetric action. VE's are found to embody specific qualities of sensory experience that can selectively modulate activation in target brain regions in healthy and in a person with specific motor dysfunction. Loss of hand function is directly related to loss of quality of life and participation in activities of daily living.

Indeed, many of the key elements associated with the dexterous hand motor repertoire enable an engaging and fulfilling lifestyle. Appropriate intervention may be provided to those who are weak in the Virtual Environment Sign Language Instruction System.

Laterality changes, associated with plasticity, were measured in the regions of interest (ROI's) in the present study as subjects responded to sensorimotor modulation – Moving the right hand and Seeing the left hand move, the Left-Right therapy or Mirror Virtual Therapy (MVT). Even in the stroke subject, laterality shifts were observed during this experiment, providing some inspiration that the VESLI methods may be useful in inducing plasticity through activation of target neural networks. The novel Left-Right Therapy or MVT, of the present research made novel rehabilitation practical using VE visual sensory feedback, and therefore may provide an important training and therapy device for motor skills acquisition and rehabilitation. Discovered in the present research, intensity of activation was correlated with viewing changes in gain between actual hand movement and the temporally synchronized movement of the 1st person proxy. Also found in the present research, following the initial training period, subjects experienced activation associated with the sense of agency facilitating activation of secondary motor areas of the brain during observation with intent to imitate (OTI), and also with imitation. The subjects appeared to be able to accept the virtual hands as proxies for their own complex hand and finger actions. It appears from the present research that the ability to accept the virtual hands proxy further enabled modulation of visual sensory experiences to selectively recruit brain activations that were at once similar to real world experience, and also not possible for some users, for example patients with disabled upper extremities. There are important implications of these findings for research on skills acquisition and training using VE's. Technology improvements in engineering and neuroscience portend the fruitful and optimistic future wherein comprehensive translational gains may be made to extend evidence-based rehabilitation options for serious conditions such as stroke.

Aims of the present research including but were not limited to Aim 2) exercise and experience in VE with visual feedback of a concurrently moving virtual hands proxy demonstrated to result in a relationship over time in OTI, and imitation, including a sense of agency, and resulting in actuation of motor-related brain networks, Aim 3) modulated quality of feedback which influences brain activations, and Aim 4) move hand and view unexpected visual feedback such as Left-Right Therapy, or MVT wherein specific simple visual modulations were investigated and found to relateralize brain activations. The accuracy or quality of visual feedback may be altered or modulated. Objects may be incorporated with or may replace gestures in practice and exercise for reach to grasp and hand pre-shaping experiences. Therapy models can follow various protocols: hand and arm together (HAT) or hand alone (HA), or hand and arm separately (HAS). Future studies can investigate more of the complex combinations of these conditions.

More work is needed to translate the findings in studies to practice, to clarify details of protocols, task design, properties of sensory variables, and doses (Celnik and Cohen 2004). Such research is not simple, however it may be systematically approached using the model presented in the present research.

Various neural mechanisms might be accessed through sensorimotor experience in VE. Direct task training appears to be important in yielding results from rehabilitation when compared with impairment focused approaches, such as strength training

(Kwakkel, van Peppen et al. 2004; Van Peppen, Kwakkel et al. 2004; Smidt, de Vet et al. 2005). Indeed sensory experience due to incoming information along with appropriate task design (Merzenich, Wright et al. 1996), perhaps provided within a virtual environment (Adamovich, Merians et al. 2004; Adamovich 2007), might lead to an ideal platform for implicit learning (Boyd and Winstein 2001) and intensive (Kwakkel, van Peppen et al. 2004) exercise and practice (Liepert 2000; Liepert, Graef et al. 2000) with carefully managed increasing task complexity and employing motivating factors to promote sensory-enriched (Byl, Roderick et al. 2003) task-oriented (Richards, Malouin et al. 2004) experience-dependent changes (Nudo 1997) in synaptic and functional connectivity across multiple sessions (Press, Casement et al. 2005), and could promote plastic reorganization (Robertson and Murre, 1999; Taub, Uswatte, and Elbert, 2002) . It may be possible through technology to provide significant personalization, motivation, attention attractors, engaging and beneficial sensorimotor experiences.

Although it is known that rehabilitation improves the outcome of patients who have suffered from stroke (Jorgensen, Kammersgaard et al. 1999) , many individuals may be too paralyzed to participate, however, they may be capable of participating in some passive and modest activity. VE experience with sensory augmentation provides afferent information to an affected function to stimulate recovery (Wilson 1998). Patients may be impaired in planning and guiding of hand shape consequently suffering great demands on visual processing, and putting them at a further disadvantage. Approximately 5 to 20% of stroke survivors who have initial upper limb impairment regain full use of the limb while about thirty to 66 percent regain no functional use of the upper limb at six months

(Sunderland, Tinson et al. 1992; Nakayama, Jorgensen et al. 1994) and about half of all stroke survivors are left with severe problems (Lawrence, Coshall et al. 2001) .

Successful repetitive task specific methods of improving functional skills of the fingers and hand following stroke (French, Thomas et al. 2007) are needed . Hand related therapies typically focus on tool use (transitive) and reach to grasp tasks, further complicating the exercise. Early sensory evoked potentials recording predicts the degree of motor recovery in the upper limb (Kusoffsky, Wadell et al. 1982) . Visual sensory augmentation may serve to improve performance in persons with a sensory deficit (Serino, Farne et al. 2007) indicating a likely means to improve conditions for patients. Somatosensory deficits in patients are typically related to lesions in the primary somatosensory cortex (SI) (Wikstrom, Roine et al. 2000). Loss of body sensations occurs in approximately fifty percent of stroke patients (Feigenson and McCarthy 1977; Feigenson, McDowell et al. 1977) affecting patients' ability to manipulate and use objects, to feel stimuli, and can lead to a complete nonuse of upper limb even when the limb shows normal function and limiting functional recovery of skills of everyday living (Carey, Kimberley et al. 2002). It is difficult to predict what recovery may be possible for patients suffering the effects of stroke and in one recent case study of a stroke subject recovery was limited to re-emergence of activation in the somatosensory cortices (Carey, Kimberley et al. 2002) while recovery of somatosensory skills preceded neural changes observed . Perceptual and functional training methods were compared and were found to yield similar results in stroke patients implicated in perceptual deficits (Edmans, Webster et al. 2000).

Visual enhancement of touch has been shown to illicit changes in SI activity in healthy subjects (Fiorio and Haggard 2005). Many stroke subjects suffer sensory deficit whereas tactile sense is improved through visual sensory enhancement when viewing the body (Kennett, Taylor-Clarke et al. 2001; Press, Taylor-Clarke et al. 2004) that persists following the visual stimulus (Taylor-Clarke, Kennett et al. 2004), and that this improvement is not due to attention (Haggard, Christakou et al. 2007).

Visual input results in a strong influence over the brain and often overrides other afferent modalities, for example when a sensory conflict is intentionally introduced (Snijders, Holmes et al. 2007). The individual's view of his or her own paretic arm may be obscured in VE to eliminate the dysfunctional visual scene. In the present research, activations of the insular cortex developed over time through a sequence of interactions with the virtual hands in the system (see Aim 2), (Lewis 2006), indicating that a protocol involving observation (Altschuler 2005; Buccino 2006; Celnik, Hummel et al. 2007; Celnik, Webster et al. 2008), imagery (Butler and Page 2006), observation with intent to imitate, and then executing the imitation sequence was successful in establishing a sense of agency or a sense of ownership (Ehrsson, Spence et al. 2004), perhaps resulting in accepting the virtual hands as a proxy for his or her own hands and perhaps interacting with them in relationship to his or her own body schema (Berlucchi and Aglioti 1997), or perhaps accepting them as tools or extensions of the body (Maravita and Iriki 2004; Farne, Dematte et al. 2005), or projecting his or her own action to the avatar outside his or her body (Corradi-Dell'acqua, Ueno et al. 2008). Humans can readily adapt to many transpositions and configurations presented in peripersonal space. Once the virtual hands have been accepted as a proxy for one's own hands (Caria, Veit et al.), capabilities of the

VE are transformed to provide a wide range of practical training activities. These capabilities exceed those available in the real world, wherein the subject is faced with a dysfunctional limb, pathological sensory experiences, reduced tactile senses, and a diminished ability to participate in the traditional therapies requiring intense repetitive close-to-normal movements. In this case the virtual world is providing sensory augmentation to the individual. A role of therapy is to provide afferent information to an affected function to stimulate recovery (Wilson 1998). In addition, the present functional MRI studies demonstrated activation of brain regions associated with viewing the hand (Wheaton, David F. Abbott et al. 2004), important in exercise and learning body-related skills. Within a rehabilitation situation, there may be a benefit to being able to view body parts (Dechent, 2003) when practicing or mentally modeling skills. Objects in space can have an impact on all the sensory systems (Craig and Rollman 1999) and arranging an appropriate experience with regard to objects within the space will likely differentially affect neural activations.

A variety of neural mechanisms may become facilitated within the therapy environment to affect a training or rehabilitation model and characteristics should be evaluated systematically to understand the duration of effects, attenuation and extinction, with populations, so that effective protocols for exercise and therapy may become more clearly understood. VE's can be used to present complex multimodal sensory information to the user and have been used in military training, entertainment simulations, surgical training, training in spatial awareness and more recently as a therapeutic intervention for phobias (Buccino 2004; Wheaton, David F. Abbott et al. 2004) and may become important in the future for delivery of various services including rehabilitation. In the present study, within the VE, once the insular cortex was actuated through initial experience, additional training in observation and imitation resulted in activation of the secondary motor regions in the individuals. These brain regions are implicated in successful recovery of stroke patients. Protocol in addition to visual sensory augmentation appears to be influential in recruiting the target activations. The extrastriate body area (EBA) responds when a subject views the body in its entirety more than when viewing parts and may be related to viewing one's own body parts (Astafiev, Stanley et al. 2004; Arzy, Thut et al. 2006), differentiating them from others(David, Cohen et al. 2007; Saxena, Ng et al. 2007), and moving them (Astafiev, Stanley et al. 2005). In the present research, functional MRI experiments demonstrated involvement of the EBA when subjects viewed movement of the virtual hand moving concurrently with his or her own hand (see Aim 2) (Adamovich et al., 2009) . One conclusion of the involvement of the EBA in the present study condition may be that interacting with the virtual hands presented in the visual sensorimotor experience in VE's may indeed recruit similar brain networks to those involved with the real world, including secondary motor regions associated with movement recovery in stroke (August, Lewis et al. 2006).

Significant evidence of support exists for the use of features in VE's to promote motor skills acquisition (Merians, Jack et al. 2002; Adamovich 2004; Merians, Poizner et al. 2006) and facilitate voluntary motor production (Morganti, Gaggioli et al. 2003). It is known that action-observation and action-execution activate the same brain networks (Iacoboni 1999 ; Buccino 2004), and kinematic analysis demonstrates that movement observation facilitates movement (Castiello 2003; Edwards, Humphreys et al. 2003), another benefit of visual augmentation. At the same time, some patients with damaged action observation systems did not demonstrate the same facilitation. Careful investigation is needed to uncover some of the mechanisms in brain injury that prevent recovery.

Through this unique research model, distinctive mechanisms of VE might come to be better understood – neurorehabilitation strategies and various mechanisms which might be used to stimulate plasticity-based changes in the human brain (Lewis 2006). A basic principle of rehabilitation is to provide afferent information to an affected function to stimulate recovery (Wilson 1998). VE's and associated technologies may provide a flexible training and rehabilitation tool that can be used to exploit the nervous systems' capacity for sensorimotor adaptation throughout one's life and thus provide plasticity-mediated therapies even when patients may experience changes in learning styles due to injury or fatigue.

There is potential for applications within the VE to perform a major function in the evaluation of patients, measuring kinematics, in standardizing therapies, tracking progress, and in training therapists (Riener and Burgkart 2001). High level and cognitive tasks under conscious control may initiate motor behavior. However, sensory feedback that accompanies motor movement may be difficult to achieve following brain injury. In the absence of the production of close-to-perfect performance, intense repetitive practice, with the rewards of matching intention with feedback, and implicit learning is difficult to achieve, providing a natural role for sensorimotor experience managed using VE technology. Physical therapy programs have focused on neurological recovery including neurodevelopmental technique, proprioceptive neuromuscular facilitation, sensorimotor integrative treatment, etc. although trials have failed to demonstrate benefit over compensatory therapies (Stein 2004) and do not meet the needs of severely impaired individuals.

Proliferation of lower cost augmentative technologies, modern communication networks, distributed service platforms, and models such as telerehabilitation hold great promise to transform options (Carignan and Krebs 2006) and deliver much needed support to persons with motor dysfunction (Reinkensmeyer, Pang et al. 2002), among other chronic conditions. Such a configuration can enable progress in research as well as delivery of services including sensorimotor learning in VE. Patients may be unlikely to use dysfunctional limbs potentially resulting in learned non-use (Taub, Uswatte et al. 2006). In the clinic and in the community, augmentative technologies may enable attractive solutions. For example, when patients are too weak or paralyzed, therapists may assist the patient in moving whereas with technology, passive therapies, and sensory support through VE's might play an important role. Robots may provide assistance to bridge the impairments of patients improving access and increasing options for patients with more seriously disabling conditions (Hogan and Krebs 2004; Krebs, Volpe et al. 2007; Lunenburger, Colombo et al. 2007). Robotically-facilitated repetitive movement training might be an effective stimulus for normalizing upper extremity motor control in persons with moderate to severe impairments who have difficulty performing unassisted movements (Patton and Mussa-Ivaldi 2004; Lum, Burgar et al. 2006) while haptic devices provide force feedback of realistic sensory experiences. An important feature of the robots is their ability to measure the kinematic and dynamic properties of a subject's movements and provide the assistive force necessary for the subject to perform the activity, with the robot adjusting the assistance and transitioning to resistance as the subject's abilities expand (Lum, Burgar et al. 2006). Auditory or visual cuing, such as external pacing in repetitive syncopated training can provide support for motor therapy (Ackerley, Stinear et al. 2007) delivered in VE. Mental imagery, sometimes used to assist the patient formulate new motor programs may be delivered through VE to augment cognitive deficits; and imagery may represent a complex cognitive task (Cabeza and Nyberg 2000) particularly when one must imagine objects that are not present. Compliance cannot readily be assessed. Patients with conditions such as apraxia might benefit from task simplification since complexities impair execution of the motor skill.

With the mirror therapy, Left-Right Therapy or MVT, sensory feedback (vision), and mental imagery (where the patient learns to mentally visualize motor programs), or mental practice (an exercise of viewing or imagining movement is experienced, with or without the patient actually performing the exercise with the paretic limb) (Butler and Page 2006) may be presented in VE. The present research investigated the neural correlates of Left-Right Therapy, or Mirror Virtual Therapy (MVT) and found that when the sensation of agency was present following training in the virtual environment, in both the healthy control subjects and also in the patient who suffered from stroke, increased brain activation was present ipsilateral to the moving hand and fingers as a consequence of subjects viewing the Left virtual hand avatar moving concurrently with the subject's right natural hand and fingers movement. The brain activation seen was related to the non-moving hand. The visual sensory modulation was successful in recruiting additional motor related brain networks associated with the target brain region. In the case of the patient, the actuated brain region was located within the hemisphere of the stroke injury.

Robotic devices provide exercise and assistance performing tasks and may be helpful (Volpe, Krebs et al. 2001) for the patient with hemiparesis. Early robotic devices train unilateral gross motor movements (Krebs, Hogan et al. 1998; Kahn, Lum et al. 2006), elbow and shoulder (Fasoli, Krebs et al. 2003), and a few upper extremity devices train bilateral motion (Lum, Burgar et al. 2006). None of these systems allows three dimensional arm movements with haptic assistance. Robotics for wrist and hand rehabilitation is much less developed (Daly, Hogan et al. 2005) and systems for training the hand and arms together are non-existent.

Virtual reality simulations when interfaced with robots, movement tracking and sensing glove systems can provide an engaging, motivating environment where the motion of the limb displayed in the virtual world in the first person perspective is a replication of the motion produced in the real world by the subject. The first person agent (egocentric) provides a proxy to replace the subject's own limb wherein the movement viewed may be an exact representation of the subject's own movement, or it may be modified to provide sensory feedback that enhances the subject's movements through mirror image, or it may represent change in the gain of the subject's own movements, or it may represent inconsistent, unexpected, and erroneous movement. In addition to investigating mirror movement visual feedback, the present research investigated changing gain or creating random finger movement feedback displayed by the virtual hands avatar in response to the subject moving his or her hand. Neural correlates were found to be less actuated in the conditions of incongruent visual feedback (see Aim 3).

VE/robotic systems for rehabilitation with various kinematic and performance measurement and adaptive features can be used to present sensory augmented therapies, monitor the specificity and frequency of visual and auditory feedback, provide imitation models, and virtual proxies, mirror therapies through use of a teacher model or the subject's own ipsilateral motor program (Merians 2007), can present goals and feedback to the subject, and can provide adaptive learning algorithms and graded assistive or resistive forces (Adamovich, Qinyin et al. 2007) that can be objectively and systematically manipulated to create personalized experience.

Research evidence implies that a rehabilitation practice environment that compensates for inadequacies in problem solving strategies related to goals of the movement might offer an accommodation for those who have prefrontal lesions thought to interfere with awareness of deficits as well as the ability to apply compensatory strategies for them (Stuss, Binns et al. 2002) . The VESLI system seems to be ideally suited to accommodating these important issues and the same level of accommodation might be very difficult in the real world. In a traditional rehabilitation environment, several challenged skills may be necessarily tapped in the hemiparetic patient. The individual will almost always be required to perform motor skills without perfect feedback of a well-functioning limb, with compromised sensations, with compromised memory skills, or while attempting mental imaging of the movement and or gazing at the ceiling. Establishing an imitation model reduces the anxiety, embarrassment, and concern about mental imaging compliance. Reach to grasp necessarily complicates task design by incorporating hand shaping and complex three dimension location and positioning reaching problems. The individual will almost always be required to abstract the goal or position to a target location and or follow instructions, often verbal, which challenge cognitive skills following a lesion. Patients perform better in implicit learning tasks than in explicit tasks. VESLI transforms all these complexities providing an intransitive, direct imitation model with low demand on memory, interpolation, or interpretation. In sensorimotor experience in VE's, individuals may receive visual sensory augmentation representing the instructions for imitation, and also representing the 1st person feedback of virtual limbs performing the task. VESLI therapy might be well-suited to patients to have difficulties formulating abstract goals and performing without perfect visual feedback. The latter condition has not been easy to investigate until the creating of the present system wherein individuals may be studied for their response to seeing dysfunctional visual feedback of their limb, compared with very good concordance of visual feedback based upon the Left-Right Therapy or the MVF. If the healthy controls are any indication, there is reduced recruitment of activation in conditions of lower quality visual support. There may indeed be particular groups of patients who will benefit more from the visual support of a VE sensorimotor experience due to the nature of their dysfunction.

Response to explicit information following stroke was uniformly negative regardless of task or lesion location with stroke groups showing an interference effect of explicit information while healthy controls did not. The interference effect of explicit information experienced by the stroke subjects was not task dependent and indicates that explicit information delivered before task practice may not be as useful for learning as discovering the solution to the motor task with practice alone and in the experiment, the effect held regardless of the task being learned (Boyd and Winstein 2006). Performance was found to remain stable with implicit motor learning and encouraged cognitively efficient motor control more so than explicit motor learning when time constraints called for a complex decision made at the same time as performance of a motor task (Masters, Lo et al. 2008).

Perhaps some of the differences observed in performance between populations of healthy controls and patient groups may be partially explained by the differential involvement of brain networks in action understanding, goal formation, and action execution and in light of the nature of the injury. Individuals may have unique injuries leading to disruptions of somewhat different brain networks. At the same time, behavior is not a source of reliable evidence regarding the location and extent of a brain injury. Evidence exists for differential involvement of ventral premotor, parietal, and temporal regions in action understanding. It has been proposed that fronto-parietal and visual areas involved in action understanding mediate a cascade of visual-motor processes at different levels of action description including a range from exact movement copies to those of abstract action goals achieved with different movement styles (Lestou, Pollick et al. 2008). Stages of learning processes necessarily actuate differential networks in the brain of healthy controls and patient groups wherein immediate and final goals in action planning actuate differential brain network and yet require similar movements. Preparatory activity resulted in activation bilaterally along the frontal gyrus and in the left inferior parietal cortex while in the Immediate Goal activity involved occipito-parietal and occipito-temporal cortex. Tasks can be performed at different levels engaging different fronto-parietal circuits when planning the same action modulated by the emphasis on either selecting a sequence of movements or selecting movements spatially compatible given object properties (Grol, Majdandzic et al. 2007).

Together, these findings inspire a quest to identify task and sensory conditions that facilitate movement in patients. The findings in the present study, demonstrating visual augmentation for rehabilitation exercises together with evidence from literature, inspire further brain mapping and connectivity studies in individuals. In addition, the findings inspire investigation to further the understanding of mechanisms leading to improved movement facilitation through rehabilitation. Visual information alone can influence motor programs as well as multimodal sensory experiences (Kennett, Taylor-Clarke et al. 2001). Visual errors can influence motor cortical areas during motor learning (Muellbacher, Ziemann et al. 2001; Muellbacher, Richards et al. 2002; Richardson, Overduin et al. 2006; Bray, Shimojo et al. 2007; Hadipour-Niktarash, Lee et al. 2007) and the present research demonstrates that an absence of visual feedback regarding movement of the hand results in significantly less brain activation than moving and seeing the virtual hand avatar move in congruence with the subjects' movement.

Active and rewarded practice is the means through which one learns to integrate feedback in motor learning. Vision might modulate tactile performance when tactile information is limited as in the case of some patient groups such as patients who have suffered stroke and who have a deficit in the tactile modality (Serino, Farne et al. 2007). Combined sensory input improves performance when each one individually fails to do so as in the case of elders.

Perception of hand and fingers appears to take differential mechanisms. Whereas identification of fingers is somatotopic, identification of hands seems to use a general body schema which is influenced by external spatial location (Haggard, Kitadono et al. 2006) and may hold implications for methods of exercising hands and fingers in patients.

Meanwhile, results of experiments suggest that identification of fingers occurs in a somatotopic representation or finger schema. The effect of sensory stimulation (Taylor-Clarke, Jacobsen et al. 2004; Taylor-Clarke, Kennett et al. 2004) outlasts the visual sensory experience and occurs when concurrent visual information regarding the stimulated body part is presented (Haggard, Taylor-Clarke et al. 2003) and has been attributed to backward projections from multisensory brain areas (Macaluso, Frith et al. 2000; Bremmer, Schlack et al. 2001; Macaluso, Frith et al. 2005) probably in the parietal lobe (Ro, Wallace et al. 2004) perhaps head centered within the ventral intraparietal area (Fogassi, Gallese et al. 1996; Duhamel, Colby et al. 1998) with a representation of peripersonal space (Graziano, Yap et al. 1994). In addition, recent evidence supports the presence of direct projections between different primary sensory areas (Schroeder and Foxe 2005; Ghazanfar and Schroeder 2006). Even at the very basic levels, multiple sensory integration appears to be taking place.

In a recent study, visual enhancement effects were found to be inversely related to a baseline measure of tactile acuity indicating that visual enhancement helped more when subjects presented poor tactile abilities (Serino, Farne et al. 2007) and might be useful to improve performance of patients. This effect is believed to be compatible with the inverse effectiveness rule (Stein, Jiang et al. 2001; Stein, Wallace et al. 2002; Stanford, Quessy et al. 2005; Rowland, Quessy et al. 2007) and appears to super-additively enhance performance.

The human brain may be capable of sophisticated levels of integration among sensory regions, utilizing additional information presented to one modality when deficits of other modalities or regions are present. Even in the case of healthy controls, manipulation of sensory experiences, even without providing additional information about the stimulus, was effective in improving performance. Serino and colleagues hypothesized that where some residual function is present, vision might serve to enhance tactile spatial resolution and make it more functionally useful (Serino, Farne et al. 2007). This is an interesting area for investigation and might shed some light on important mechanisms that if used in VE, might assist in creating an environment for learning and rehabilitation through modulation of tasks and sensory information. By creating a safe environment wherein sensory and task experiences can be controlled, various mechanisms present in the human brain may be targeted. Since the system can simultaneously monitor performance of the patient, performance may continually be known. Variability in performance throughout sensory and task manipulation may yield effective input for algorithms to update the rehabilitation application and to selectively present appropriate tasks and customized sensory augmented stimulus for the individual patient.

In a recent review article (McCombe Waller and Whitall 2008), it is posited that bilateral arm training might be a necessary adjunct to unilateral training. Bilateral skills are common in the real world and are therefore, likely to be a necessary and natural part of rehabilitation. Bilateral re-training may be strategically important benefiting more through bilateral not unilateral training. Bilateral training may help unilateral skill recovery through alternative putative mechanisms. VESLI visual sensory augmentation features enable Left-Right Therapy, or Mirror Virtual Therapy (MVT), symmetrical limb exercises, unimanual, and bilateral experiences. Bilateral exercises might access neuronal programs through inter-hemispheric disinhibition. More research is needed to determine the function of disinhibition in rehabilitation. Researchers (Floel, Hummel et al. 2008) demonstrated reduced interhemispheric inhibition with anesthesia to explore potential mechanisms of CIMT therapy and (Butefisch, Wessling et al. 2008) observed decreased short interval cortical inhibition in some stroke subjects, which appears to be a promising mechanism for rehabilitation.

Findings in a recent study (Romei, Thut et al. 2009) suggest a contralateral (right) M1 involvement in retrieval and transformation of motor information during left-hand reproduction of previously acquired right-hand motor-skills. Modulatory interactions of an inhibitory nature were observed from the dominant (left) to the non-dominant M1 in the same transfer-condition. These results provide evidence that M1 is essential to intrinsic movement-based skill-learning and not extrinsic spatial aspects of learning the motor skill. The authors present insight on models of motor-learning and hemispheric specialization, suggesting involvement of interhemispheric inhibition. It seems possible that separating the spatial location-based component of a hand and arm task would reduce complexity of the task, and increase availability of simpler exercises for rehabilitation. BATRAC (Whitall, McCombe Waller et al. 2000) demonstrates successful training of the arm in chronic stroke using bilateral exercises. The present research demonstrates implementation of observation with intent to imitate, activating secondary motor regions (see Aim 2), and bilateral exercises enabled in virtual environment visual sensory augmentation and Left-Right Therapy (see Aim 4). The mirror virtual therapy (MVT) and Left-Right Therapy seem ideal for the purpose of rehabilitating severely paralyzed individuals and have demonstrated to have promoted desired brain activations likely to be helpful in plasticity-based therapy and to promote recovery from stroke.

In a recent study of learning a bilateral task with visual feedback, new bilateral learning overshadowed the influence of the intrinsic patterns. Learning was also greatly affected by augmented feedback: dynamic, on-line pursuit tracking information was more effective in transfer than static, terminal feedback with implications of these findings upon theoretical constructs in motor learning (Hurley and Lee 2006). In another study involving both younger and older adults, both groups benefitted from concurrent visual feedback; however the older adults gained more from the concurrent feedback than the younger adults, relative to terminal feedback conditions suggesting that when learning bimanual coordination patterns, older adults are more sensitive to the structure of the practice conditions. The effect was seen particularly with relationship to the availability of concurrent visual information. This greater sensitivity to the learning environment may reflect a diminished capacity for inhibitory control and a decreased ability to focus attention on the salient aspects of learning the task and providing some evidence for controlled visual sensory environments for learning motor tasks, with concurrent visual feedback benefiting all participants but providing particular benefit to older adults (Wishart, Lee et al. 2002). Findings influence design considerations for systems to be used with aging populations and lead one to investigate visual sensory upper limb rehabilitation, making a strong case for VESLI techniques.

Bilaterally identical movements are believed to involve both hemispheres in an identical way. This theory is consistent with the findings that unimanual practice alone did not improve the hemiplegic upper limb's movement in those who were incompletely recovered as in recent research where it was hypothesized that enhanced ipsilateral CM activity is not helpful in recovery (Turton, Wroe et al. 1996). In their study, however, median Motricity Index for well-recovered group changed from 66 to 96 while the poorly-recovered group was statistically noteworthy, according to analysis conducted by Mudie, et al. Netz et al. using unilateral sustained grasp to observe ipsilateral disinhibition also found this was not positively correlated with recovery(Mudie and Matyas 2000); Netz, 1997). These studies, however, do not report initial stroke loss and therefore, results are difficult to interpret. Therapies for patients who cannot move a limb are not simple to execute. Virtual reality may provide one practical means to explore bilateral therapies with and without robot assistance. Bilateral exercises enabled through virtual environments might facilitate study of the effectiveness of this type of therapy and other theories about motor skills acquisition in patients suffering from more severe stroke injuries, and may help in the pursuit to understand the nature of interhemispheric disinhibition and any role it might play in skill acquisition.

In the case of the present experiment modulating the gain of the viewed virtual reality hand proxies, subjects' brain activations responded proportionately to the change in gain of the visual feedback (how similar or dissimilar it was to the subjects' own movement) demonstrating another virtual environment enabled sensorimotor experience valuable for visual therapy.

Activation responses observed in the present studies illustrates a learning period where the subject becomes familiar with the virtual hand proxies, and then ultimately recognizes the agent of action is him or herself. Following this training period, the brain activation remains even in the condition of observation with intent to imitate (OTI). The virtual environment sensory experiences, presented in this protocol, become a powerful tool to selectively actuate human brain regions associated with motor skills and motor skills planning. This activation persists even in cases when the subjects are not moving their own hands. Following the training period when the subject experiences the sense of agency, this important motor-related activation is present even in cases when the subject is experiencing Left-Right therapy, an illusion wherein the virtual hand proxy responds to the subject's own movement with a visual manipulation – the proxy provides a view of the concurrent movement of the hand opposite to the subject's own hand movement.

There is indirect evidence that there is a correspondence between visual sensory experience, such as observation with intent to imitate, and performing the action. There is also an important role in rehabilitation and learning in imagining motor action (Grezes, Fonlupt et al. 2001). Recent research reveals that the field of neuroscience is on the cusp of a new age wherein evidence-based and technology supported flexible highly personalized training can support sensorimotor learning, perhaps offering significant value over and above traditional therapy.

The VESLI system contributes to the field a model and exercise system to provide visual sensorimotor experience in virtual environments for research and for training. Technology supported passive or minimally active therapy extends the possible interventions available to severely impaired patients and contributes to translational research. VESLI follows this new model (Morganti, Gaggioli et al. 2003).

SENSORIMOTOR EXPERIENCE IN VIRTUAL ENVIRONMENTS

9.1 Overall Outcomes

A pivitol role that technology can play is to provide for some experience or skill absent in the individual student, or patient and to allow for the systematic testing of controversial treatment interventions associated with behavioral, kinematic, and neural mapping. Through highly flexible personalized technology systems providing performance augmentation and enhanced task structure including visual sensorimotor experience in VE, training and rehabilitation may become possible even for inexperienced, very weak, or severely impaired patients so that they may practice intensely and repetitively not previously possible with traditional real-world methods. Through VE visual sensory support, and compliance monitoring (Pomeroy, Clark et al. 2005) . Sensory augmentation introduces important visual stimulus and feedback for observation, mental imaging, observation with intent to imitate, OTI, and action execution, with computer generated virtual hands representing movement where no close-to-perfect example previously existed, for example, for those studying dexterous motor tasks or for patients who have suffered stroke or paralysis, and altogether making visual sensorimotor experience in VE a good options to accommodate individuals.

Studies involving humans observing computer generated, recorded movements, or static poses representing human movement provide some insight into the design of the VESLI system which has a laboratory version and a functional imaging component compatible with the MRI environment so that kinematic, behavior, and neural activations may be correlated and so that solutions may be easily transferred from the MRI experimental environment to the training environment. Kinematic data used to activate movement viewed in VESLI is generated from recorded human movement. Humans can discern biological movements of humans compared with animals (Pinto and Shiffrar 2009), by gender, and by individual (Agnew and Wise 2008), and is differentiated from linear motion even with only a few points of light (Servos, et al. 2002) , or when random dots in a background drift in a direction opposite to the points of light of human walking (Fujimoto 2003) and activating premotor cortex (Saygin, Wilson et al. 2004). There appears to be a design advantage for recording and displaying the avatar proxy representation using human recorded data for visual sensory experience and to embody tasks that might be considered appropriate for imitation and practice. An individual may adopt a representation created from his or her own or another human's motor program more readily than a linear computer based program. A program based upon a person's own body schema and sensorimotor experiences may help to re-set or reinforce many of his or her own movement characteristics since they may match copies of motor memories already present in some form, a topic for future research.

Properties of the mirror neuron system believed to exist in the human brain may explain the human ability to learn by imitation (Fadiga 1995; Maeda 2002; Patuzzo 2003) and tapping those properties might serve to stimulate insular cortex, and consequently, secondary motor systems and plasticity of motor control. VE exercise may help to shift attention from external space based body schema of the hand, to somatosensory perspective of the individual fingers thereby enabling bolstering sensory systems in motor learning. Imitation exercises mediated by higher level functioning (middle frontal gyrus for learning novel hand actions) (Buccino, Vogt et al. 2004), are more effective (in activating pars opercularis of IFG during finger lifting) than symbolic or spatial cues (Iacoboni 1999) , and may provide performance support compared with self-guided tasks (Hanlon, Buffington et al. 2005) simplifying tasks .

In the presence of VE protocols, a complex visuo-neuro stimulus can be achieved that engages mirror neurons for sensorimotor imitation. Through experience visual feedback in VE engages insular cortex (August) , and secondary motor systems (August) known to be necessary for motor output in stroke patients. Task design stimulates important cognitive networks. Since patients may still be in control of cognitive networks, and may have lost motor skills, higher level tasks that necessarily recruit brain regions associated with movement and movement planning, or movement understanding appear to be good targets for plasticity based learning, or to prevent loss of cortical representation following injury.

Training in a VE that is matched for observation and action (Wheaton, David F. Abbott et al. 2004) may provide an advantage since research shows that performance improves for such task configurations and since first-person perspective, might stimulate more direct and stronger cognitive networks than third-person perspective (Jackson, Meltzoff et al. 2006) in imitation, and reduce complexity of the task. Viewing the virtual hand movement might activate hand-relevant parts of the brain (right MT/V5, left and right anterior IPS, right precentral gyrus, and right inferior frontal sulcus (Wheaton, David F. Abbott et al. 2004)), might promote engagement in feelings of ownership of the virtual hand (Ehrsson, Spence et al. 2004; Ehrsson, Wiech et al. 2007) , understanding goals of the observed virtual action within the task (Hamilton and Grafton

2006) , recognition of biological movement (Servos, et al. 2002) of the virtual hand in the scene, and sense of self-awareness and agency (Decety, aDepartment of Psychology et al. 2006; Jackson, Meltzoff et al. 2006). To systematically verify the neural underpinnings and behavior and features useful to sway the balance of sensory experiences, even when individuals may be experiencing compromised senses, the novel MRI compatible VE model enables parametric modulation task and sensory experience for analysis of real-time dynamics of brain networks associated with interaction of recognition and control of actions (Hamilton, 2006) in health, ageing, and disease, associated effects, and to investigate attenuation and extinction over time. A new research and practice proof of concept model has been demonstrated, and in addition, new findings applicable to sensory training in VE's for hands and fingers have also been demonstrated. Specific modulations in the visual aspects of the VE yielded predictable outcomes in brain activation patterns in healthy controls and patients as well. Future work would involve a deeper understanding of the integration of those and additional sensory experience, and attenuation and extinction of those effects in complex tasks over time. Further work would involve mapping neural networks and functional connectivity networks (neuroanatomic underpinnings) of healthy controls and subjects who have suffered from injury; these subjects would be evaluated before, during, and following therapy experiences to develop prognostic indicators and to identify appropriate therapies for individuals and to understand the complex dynamics of recovery.

Because of the compatibility of the fMRI research system with the motor skills acquisition and rehabilitation training system, visual sensory modulation features found to be effective in the functional MRI environment in actuating desired brain networks may easily be translated into the motor skills acquisition and rehabilitation training system and may be translated from research to practice. Importantly, the new model for research demonstrated in the present work represents a significant contribution to translational neuroscience. Significantly, this research has demonstrated a new model for neuroscientific discovery – providing experiments for the first time using views of complex hand and finger models in the MRI environment, and behavioral data associated with avatar imitation exercises using personalized hand proxies. This research has also provided much needed objective data regarding successful imitation in the VE using virtual hands proxies, and also providing the map of human brain networks actuated when interacting with sensorimotor experience in VE's, to lay groundwork for the optimization of application designs including interventions that target important motor learning networks of the brain especially significant for revolutionary plasticity-based therapies involving the repetitive practice and acquisition of motor skills. This information will be relevant whether the rehabilitation is performed using more traditional means or whether it is delivered through newer technology. Findings are also relevant to the research of health and ageing, developmental, and issues of motor skills dysfunction. A new model for further research in this field has been provided herein. In addition, as technology opportunities extend to include virtual reality in wider applications, a clear understanding of the effects of certain virtual reality experiences on the human brain and behavior will inform design and human factors in a number of fields.

Technology embodying careful task design and optimization of strategies with a means to deliver the intensity of practice required for modifying neural architecture and function has the potential to change the way therapists deliver rehabilitation. Increasing access to therapy through technology can make a significant impact on the number of individuals who can participate and the amount of therapy they can receive, the duration of access to the therapies, the associated costs, and holds the potential to provide continual support over time.

Particularly relevant is the ability, through VE's, to improve rehabilitation methods available to weak or seriously impaired patients, for example, those with hemiparesis from stroke, or those with paralysis from brain or spinal cord injury and who may not be able to participate in traditional therapies. With passive and sensory augmented exercises such as those investigated herein, there may be good reason to believe visual sensorimotor experience in VE's can provide an effective therapeutic experience: compelling enough to engage a sense of agency, increasing activation in appropriate motor-related brain regions during observation with intent to imitate, activating secondary motor regions associated with recovery of motor skills in patients with corticospinal injury, activating ipsilateral brain regions through visual modulation alone, even in a stroke patient, even when the contralateral limb is not moving, and modulation of brain activation based upon quality of visual feedback that might possibly be helpful in activating action-observation action-execution brain networks while viewing scenes compatible with action intention, with a potential to bolster sensory experience in individuals especially applicable to those with altered natural sensory conditions and to simplify tasks. This present research findings may be directly translated from research to the application design in the specific case of training for skills acquisition, practice, or rehabilitation of motor skills, particularly for the hand.

This system is capable of measuring the complex span of hand-finger movements and simultaneously streaming this kinematic data to control the motion of representations of human hands in virtual environments and a plethora of features and services. This novel system also records experimental and behavioral responses for tracking and analysis. Results of the present research demonstrate that in addition to providing an initial proof of concept, the virtual environment rehabilitation system allows for the systematic testing of controversial treatment interventions

This research demonstrated the suitability of sensorimotor experience in virtual environments to support observation, observation with intent to imitate, and exercise of complex intransitive hand gestures, and simple hand gestures. The present research also demonstrated that an exercise and training environment practical for research and training can be replicated in an MRI compatible instantiation for the purposes of mapping neural correlates of sensorimotor experience in virtual environments pertaining to virtual hands avatars, observation, observation with intent to imitate, and exercise, accomplishing Aim 1. The present research also demonstrated a specific manner of modulation of visual and task related sensory experiences within the virtual reality system for selectively activating networks associated with moving hands and fingers including tasks that may also be integrated into rehabilitation situations for remediating hand function (Aims 2 through 4). The findings in Aim 1 trough 5 advance our understanding of the behavioral (Aim 3, and Aim 5) and neurophysiological mechanisms (Aims 2, 3, and 4) underlying interventions such as sensorimotor experiences delivered using virtual environments with potential for a wide array of applications including but not limited to neuroscience, training, rehabilitation and education. Importantly this research has demonstrated a new model for neuroscientific discovery – providing experiments for the first time using complex hand and finger models in the MRI environment, and behavioral data associated with avatar imitation exercises using personalized hand proxies. This research has also provided much needed objective data regarding human brain networks actuated when interacting with sensorimotor experiences in a virtual environment, to lay groundwork for the optimization of application designs including therapeutic interventions that target important motor learning networks of the brain especially significant for revolutionary plasticity-based therapies involving the practice and acquisition of motor skills. This information will be relevant whether the rehabilitation is performed using more traditional means or whether it is delivered through newer technology. Findings are also relevant to the research of healthy, developmental, and dysfunctional motor issues. A model for further research in this field has been provided herein. In addition, as technology opportunities extend to include virtual reality in wider applications, a clear understanding of the effects of certain virtual reality experiences on the human brain and behavior will inform design and human factors in a number of fields.

Careful task design and optimizing rehabilitation strategies with a means to deliver the intensity of practice required for modifying neural architecture and function has the potential to change the way therapists deliver rehabilitation. Increasing access to therapy through technology can make a significant impact on the number of people who can participate and the amount of therapy they can receive, and the duration of access to the therapies. Particularly relevant is the ability, through virtual environments, to improve rehabilitation methods available to seriously impaired patients, for example, those with hemiparesis from stroke, or those with paralysis from brain or spinal cord injury. With passive and sensory augmented exercises, the brain imaging findings from this research demonstrates that there may be good reason to believe virtual environments can provide a therapeutic experience: activating secondary motor regions (associated with recovery of motor skills), and activating ipsilateral brain regions, possibly helpful in activating action observation and action execution brain networks.

This present research findings illustrate targets activated by specific sensory experiences in virtual reality that may be directly applied to applications design in virtual environments and in the specific case of training for skills acquisition, practice, or rehabilitation of motor skills, particularly for the hand.

9.2 Conclusion

Emerging evidence shows that interactive virtual environments (VE's) may be a promising tool for studying sensorimotor processes and for a wide variety of applications including rehabilitation. Activation of neural pathways in the brain over time has been associated with plasticity-based changes in various brain networks. A long term vision is to identify the essential elements of the VE sensorimotor experience that may selectively modulate neural reorganization for a number of applications including rehabilitation of patients with neural dysfunction. However, the potential of VE's to recruit action observation-execution neural networks is largely unknown. Virtual Environment Sign Language Instructor (VESLI), an accurate and reliable MRI-compatible interactive computerized virtual environment for training and research purposes, was designed and developed. VESLI provides an imitation-based gesture learning system with a third and first person avatar that may be used as a model or as a proxy for the subjects' own hands during training and research. For the first time, a functional MRI-compatible virtual reality system (VR) has been developed to provide training and also a window into studying brain-behavior interactions. This system is capable of measuring the complex span of hand-finger movements and simultaneously streaming this kinematic data to control the motion of representations of human hands in virtual environments and a plethora of features and services. This novel system also records experimental and behavioral responses for tracking and analysis.

Results of the present research demonstrate that in addition to providing an initial proof of concept, the virtual environment rehabilitation system allows for the systematic testing of controversial treatment interventions accomplishing Aim 1. Consistent with Aim 1, experiments demonstrated that the VESLI system may be used in the intended modes to provide 1st and or 3rd person avatar models for imitation and exercise, a first person agent to create the visual modulation of subject hand movement intended in direct imitation, bilateral and mirror movement, and modulated visual feedback such as gain changes to test effects in experiments. Of course, other sensorial modulation may be included such as auditory and haptic in the laboratory and in the MRI environment. This system may be used to provide protocols for learning and therapy, to conduct data collection for applications to enable features, for subject monitoring, kinematic analysis, status, evaluation, clinical notes, and tracking. The element of VESLI tested in the MRI, the virtual hands in 1st person perspective, functioned as designed and was used in the present research to investigate underpinnings of sensorimotor experiences in virtual environments.

In a blocked fMRI design, thirteen healthy subjects observed, with the intent to imitate (OTI), finger sequences performed by the virtual hand avatar seen in 1st person perspective and animated by pre-recorded kinematic data to investigate Aim 2. Following this, subjects imitated the observed sequence while viewing the virtual hand avatar animated by their own movement in real-time. These blocks were interleaved with rest periods during which subjects viewed static virtual hand avatars and control trials in which the avatars were replaced with a moving non-anthropomorphic object. There are three main findings. First, both observation with intent to imitate and imitation with real-time virtual avatar feedback, were associated with activation in a distributed frontoparietal network typically recruited for observation and execution of real-world actions. Second, a time-variant increase in activation in the left insular cortex was noted for observation with intent to imitate actions performed by the virtual avatar. Third, imitation with virtual avatar feedback (relative to the control condition) was associated with a localized recruitment of the angular gyrus, precuneus, and extrastriate body area, regions which are (along with insular cortex) associated with the sense of agency. Data suggest that the virtual hand avatars may have served as disembodied training tools in the observation condition and as embodied "extensions" of the subject's own body (pseudo-tools) in the imitation (Iriki 2006). Once again, the present research establishes a unique relationship between sensorimotor experiences in virtual environments and selective actuation of brain networks. Furthermore, the research demonstrates that a specific protocol involving a period of training in the virtual environments, and that protocol was implicated in the corresponding increase in a specific target network associated with a sense of agency, recorded in the functional brain imaging data.

In order to understand the impact of seeing unexpected visual feedback when moving in virtual environments, Aim 3 endeavored to investigate this compelling condition using a behavioral and a corresponding functional imaging study. In the behavioral experiment, the affect of simple unexpected visual feedback perturbations, that involved parametrically modulated changes in the visual feedback represented by the ordinarily synchronized virtual hand avatars serving as a proxy for the subject's own hands was investigated. In the experiment, subjects moved his or her hands and saw first person avatar hands in virtual reality that moved either in perfect correspondence, in moderate, fair, or poor correspondence with his or her own movement, represented in the visual feedback by the proxy virtual hands. Subjects were accurately able to describe the level of correspondence between the movement depicted by the virtual hands and his or her own movement. In the MRI, neural activations varied with the correspondence of the visual feedback, confirming that modulation of the visual feedback, a sensorimotor experience, was reflected in the level of actuation in the target brain regions. The data confirm that virtual environments provide a unique opportunity to selectively stimulate neural activations not possible in the real world. Meanwhile, brain region activation associated with agency, the sensation that one is engaged in the scene and responsible for the movement, remained active throughout. In addition, the physical movements produced by the subjects remained consistent and therefore, the modulation of the gain in visual feedback is implicated for the change in brain network activation and not change in motor task compliance. These experimental findings may provide some insight into the neural conditions patients experience when faced with dysfunctional limb visual feedback.

For Aim 4, functional imaging experiment investigated brain activations associated with virtual mirror movement. In the experiment, subjects moved one hand

and visual feedback was manipulated: the subjects saw the contralateral hand move in real time. Brain activations were observed that were associated with moving the contralateral hand, although the subjects were not moving the contralateral hand at all. Again, findings demonstrate that opportunities presented through modulations in sensorimotor experiences in virtual environments selectively actuate target brain activations.

Behavioral experiments of Aim 5 used VESLI to investigate visual sensorimotor stimulus conditions affecting imitation of hand gestures in virtual reality. The system worked very well to provide a practice and an experimental environment. Findings indicate that control subjects remembered hand gestures better when imitation training involves picture definition of gestures and when recall testing employs text definitions. Control subjects could remember the hand gestures using the VESLI system when they had studied in any of the three viewing conditions: viewing his or her own natural hands, viewing his or her own hands actuating virtual hands in real time, or while the view of his or her own hands during practice was obscured within the virtual reality training system. Control subjects could remember the hand gestures while imitating a virtual reality teaching agent employing both avatar perspectives of either the third person or first person. When real hands are replaced by virtual hands avatars in control subjects, the initial practice condition of Picture with a memory condition of Picture definition yielded the best results in terms of memory and time. It is believed that patients with varying cognitive and motor issues will benefit from access to a variety of imitation models in VESLI, and that personal learning style may be accommodated by the VESLI training system. Flexibility of the virtual environment enables personalization. An agent model and a definition style may be selected that matches an individual's style based upon performance of that individual on the instrument used in these experiments. To illustrate this point, individuals were evaluated for their performance in the various protocols included in the study.

The present research contributes to the field by demonstrating a new method for studying the effects of sensorimotor experience in virtual environments using a flexible MRI compatible technique to investigate human performance in computer interface task design and neural underpinnings of interactions in a modulated sensorimotor virtual environment. The data presented advances the field through understanding the brain-behavior interactions when performing actions in VE for in a number of diverse fields and for diverse applications with implications in the development of observation- and imitation-based VE rehabilitation paradigms. The results of this research provide the foundation for a new model to describe parametric modulation of sensorimotor experiences and corresponding neural underpinnings in virtual environments.

Rehabilitation of the upper extremity is difficult. It has been reported that 75%-95% of patients post stroke learn to walk again, but 55% have continuing problems with upper extremity function (Mayo, Wood-Dauphinee et al. 1999) and as many as 77.4% experiencing weakness of the upper limb (Lawrence, Coshall et al. 2001). The complexity of sensorimotor control required for hand function as well as the wide range of recovery of manipulative abilities makes rehabilitation of the hand even more challenging. Walking drives the integration of both the affected and unaffected limbs, while functional activities performed with the upper extremity may be completed with one limb, therefore allowing the individual to transfer a task to the remaining good limb and neglect the affected side reducing potential exposure to exercise through daily activities. By offering more practical exercises for those who have severe hemiparesis, based upon principles of plasticity, and enabled using virtual environments, support may be provided to intervene and potentially avoid this damaging spiral.

Early virtual environment system designs demonstrated positive outcomes with the solutions most appropriate for patients with mild impairments. Newer systems, such as the novel VESLI system presented herein, may readily combine movement tracking, virtual environment therapeutic activities and gaming simulations and extend potential exercise models. Parametrically modulated sensorimotor experience and robotics, easily integrated into the system, appears to be a viable means to extend virtual exercises so that patients with more significant impairments may benefit from upper extremity therapies. Notably, visual sensory modulations such as virtual mirror therapies and modification of gains (improving visual feedback during exercise), possible in the novel virtual environment, might provide a safe exercise environment even to those patients unable to move, severely weakened, or those who can move using robots or prosthetics. Benefits include the ability to provide practical personalized therapies early following brain injury, and to offer a means to avoid loss of cortical representation. The haptic mechanisms incorporated into recent virtual environments such as the spring assistance, the damping to stabilize trajectories and the adaptable anti-gravity assistance allowed patients with greater impairments to successfully participate in activities in which they could not previously partake and to receive additional sensory stimulation to important brain areas. In addition, virtual reality therapy systems have shown promise in improving performance of upper limb in patients who suffered stroke. Therefore, it is reasonable to investigate combining the vision and haptic features in a new hand and arm system in the future.

The newest systems provide great flexibility in an easy to use package, and therefore, therapists can easily tailor interventions to address the specific needs of each patient or patient group, and collect group data to learn more about the nature of effective therapies and the progression of disease states. In recent system testing of the novel hand and arm therapies, patients reported that they enjoyed the virtual environment activities through which the therapies were delivered, and that they were challenged by the intervention.

The novel VESLI system addressed another important aspect of interventional therapies for the hand which is to provide visual sensory augmentation to promote observation, mental imaging, observation and imitation therapies, imitating intransitive gestures as exercise, and using a virtual hands proxy to replace one's own hands in exercise, thereby reducing exposure to dysfunctional limb. VESLI hand exercises specifically map the relationship between training parameters and functional outcomes. The classifications of Chedoke-McMaster used to classify skills levels in patient populations are incorporated into VESLI. When therapists plan hand gesture activities, they can select a level of difficulty and the corresponding inventory of hand gestures will be accessed by VESLI. In this manner, the exercises provided to the patients have membership in the clinical measures and reflect real world abilities.

Another innovation in the VESLI system is the introduction of imitating intransitive language hand gestures to the rehabilitation of hand dexterity. Many rehabilitation activities involve reach and grasp activities and target goals such as tools.

Tasks are designed to use implicit learning strategies to improve skills acquisition. VESLI hand gesture system is organized around a language task and omits tools as a primary means to establish a goal for the reach and grasp. The language based gestures represent intransitive hand exercises instead of predominantly transitive hand exercises typically associated with tools and tool pantomime. There is a tradition of evaluating patients using gesture imitation with implications pertaining to symptoms of apraxia. Intransitive gestures appear to be easier for healthy subjects and also for patients to imitate, relying on different brain networks from tool based gestures where it is assumed that one can easily imagine the tool. In the case of a patient with an injury, this imagery of the tool may actually present a difficult problem.

It is widely believed that language, preparation for hand movement, and hand gestures share a common brain network, and that this network has different properties from the grasping tools brain network. VESLI provides an entirely new model for hand therapy and rehabilitation through parametrically modulated sensorimotor experience in a virtual environment. The scale of a system effective in rehabilitating complex motor skills of the hand has not been demonstrated. It is quite possible that extensive practice of an intense nature may be required in order to effectively recover hand function following a brain injury. It is also possible that training, unsupervised training, consolidation breaks, and follow-up testing might help to identify how much training an individual will require to achieve optimal recovery. VESLI offers all these capabilities by virtue of the programmable system and individualized features. It is widely known that very little attention is presently paid to rehabilitation of these important quality of life skills. It is also possible that strength training and exercise with tools alone may lack important references in the higher level, complex hand behavior-related brain networks required for satisfactory recovery associated with quality of life. With virtual environments, greater flexibility enables therapies that address these needs. VESLI offers a never tired imitation and practice model for complex hand exercises drawing upon intransitive gestures, and sensorimotor experience in virtual environments, demonstrated in behavior and brain studies to have properties conducive to skills acquisition.

In addition to their use in assisting to provide more intense therapy of longer duration, Brewer (Haggbloom and Brewer 1989) suggests that robotics have the potential to address the challenge of conducting clinically relevant research. An example of this is the comparison of training the hand and arm separately (HAS) to training them together (HAT) (Adamovich, Fluet et al. 2008). It is a point of controversy whether training the upper extremity as an integrated unit leads to better outcomes than training the proximal and distal components separately. The current prevailing paradigm for upper extremity rehabilitation describes the need to develop proximal control and mobility prior to initiating training of the hand. During recovery from a lesion the hand and arm are thought to compete with each other for neural territory. Therefore, training proximal control first or along with distal control may actually have deleterious effects on the neuroplasticity and functional recovery of the hand. However, neural control mechanisms of arm transport and hand-object interaction are interdependent. Therefore, complex multisegmental motor training is thought to be more beneficial for skill retention. Particularly important is the need to investigate rehabilitation methods that increase the likelihood that hand function will be improved and that cortical mechanisms of plasticity leading to lost representations will be avoided. Additional research is needed to understand these issues.

Very little research is focused upon the plight of persons suffering from motor dysfunctions of the hand. VESLI can assist in comprehensively describing a new model for rehabilitation, testing the model, and can enable the personalized rehabilitation exercises.

Disambiguating cues when related to the speech (Skipper, Goldin-Meadow et al. 2009) may provide an additional potential avenue of therapeutic intervention to induce neural activation and inspire the imitation hand gestures in VESLI, simultaneous implicit instructions and disambiguating language cues. There might be an advantage in VESLI design in creating a language around the gestures, and reinforcing the language cues as a means to disambiguate motor configurations. Since the subjects or patients are not necessarily fluent in American Sign Language, the task of learning the meaning of the gestures and the act of differentiating among the gestures becomes part of the therapy itself.

To provide accommodation and personalization, the model avatar may be presented in first person or third person perspective. Some people might be more capable of imitating the hand gestures when a first person model is used, thus removing transformation issues and reducing cognitive burden (Karniel and Mussa-Ivaldi 2002). The present brain imaging research demonstrates that after some training, the subjects accepted the VESLI hands, indicated by increase in activation of regions of the brain associated with agency (Iriki, Tanaka et al. 1996). The VESLI proxy hand model takes the place of the subject's own hands and thereby offers an excellent opportunity to provide close-to-normal visual feedback. This visual feedback is optimally delivered through the virtual environment technology.

Some studies have previously indicated that neural processing is not the same when observing real actions and when observing virtual actions suggesting that observing virtual models of human arms could have significantly less facilitation effect when compared to video clips of real arm motion (Perani 2001). In the present experiments when subjects viewed the movement of the virtual hands, with the intention of imitating that action (OTI), the pre-motor and posterior parietal areas were activated. Furthermore, this activation was observed in both healthy subjects and in one subject post-stroke, that when the left virtual hand was actuated by the subject's physical movement of their right hand this selectively facilitated activity in the cortex ipsilateral to the real moving hand (contralateral to the moving virtual hand). This finding demonstrates an important new tool for therapy relying on VE to bring new experiences not easily rendered in the real world.

In an example of sensory augmentation, a person with tactile deficits may be presented with augmented visual stimulus to improve performance in tactile discrimination, even when there is no additional information about the tactile stimulation provided through the visual augmentation. This inspires exploration of sensory augmentation to supplement losses associated with brain injury.

A significant range of experiences is made possible through virtual environments and not necessarily through the natural world. For example, virtual environments may be used for intense and repetitive exercise selectively designed to facilitate activation of precise brain networks, including frontoparietal networks associated with action observation and action understanding. In addition, as the present research demonstrates, sensory experiences modulated in a virtual environment may recruit brain regions associated with movement even when the subject cannot move his or her own body part voluntarily.

A hypothesis of the present research is that viewing a virtual hand corresponding to the patient's affected side and animated by movement of the patient's unaffected hand could selectively facilitate the motor areas in the affected hemisphere. This sensory modulation takes advantage of the capabilities of a virtual environment to induce activation through observation. The system enables visual sensorimotor perturbations to target specific brain networks. Preliminary optimistic findings with a patient who suffered stroke suggest that this visual manipulation in VE should be further explored to determine effectiveness in facilitating sensorimotor areas and plasticity in a lesioned hemisphere. Various sensory modalities should be explored. Various tasks and complexities of conditions should be explored.

Virtual environments are believed to be a promising tool for human computer interaction in a variety of fields. VE is particularly promising as a tool to augment rehabilitation of motor dysfunction and other conditions.

From previous studies, it is known that adding haptic control mechanisms to the system enabled patient subjects with greater impairments to successfully participate in intensive computerized training paradigms. In the present research, training of an intransitive gesture was investigated. Teacher avatar models and personal proxies were investigated (Jackson, Meltzoff et al. 2005). Language and motor related tasks were investigated (Binkofski and Buccino 2004). Results indicate that various novel tasks may be implemented in virtual environments offering a wide variety of appropriate tasks for training and rehabilitation. Further research should investigate effects of additional task designs and dosages of practice in virtual environments with a variety of augmented sensory stimulation.

Finally, the present research tested the underlying mechanism of interacting within a virtual environment using brain imaging. It was found that the value of training in a virtual environment is not just limited to its ability to provide an intensive practice environment but that specially-designed VE's can be used to selectively activate important brain regions. Activation of these important brain regions may help stimulate skill acquisition or plasticity of brain functions. One important region activated by visual sensory modulation in virtual environments is a frontoparietal action-observation and action-execution network. The findings in the present research open a doorway to a potential suite of tools for clinicians treating patients with a variety of neuropathologies.

9.3 Recommendations for Future Research

Modern flexible VE systems offer a wide range of sensory experience, require a less sophisticated level of development skills than previous versions, and are programmable to the degree that they can accommodate requirements of individuals for personalization. They can even provide accommodations for patients who have neurological disorders making them attractive for rehabilitation. MRI compatible VE systems make significant and important investigations into the nature of human neuroscience, motor control, and associated behavior possible. MRI compatible VE systems enable research that can extend existing neuroscience knowledge, provide translational applications, and can bridge knowledge gained in animal model and human motor control research.

Exercise, training, and rehabilitation treatment interventions can exploit recent technological advances in computing, biological signal processing, robotics and haptics. Integrated solutions are poised to transform the nature of applications available to the community through connectivity to extensive resources via communications channels such as wireless, the web, private and public networks, and databases. The relative ease of access to such technology advances enables a vast array of products and services in many domains with compelling levels of sophistication, personalization, consistency, and transparency never before possible.

A better understanding of the underlying neurological principles and theories of sensory experience and task design manageable through parametrically modulated sensorimotor experiences in VE may inform tools and protocols available for basic neuroscience research and various applications. In particular, implications of this research may serve an important role in motor skills acquisition, training, and in the rehabilitation of hand motor skills. Very little research is focused upon the plight of persons suffering from motor dysfunctions of the hand. There appears to be evidence for optimism that future research can yield fruitful protocols for new therapeutic interventions.

Of key importance for future rehabilitation applications is the fact that visual sensory input can help patients with brain injury. In the present study, a flexible architecture was employed in VESLI so features employing visual sensory stimulation and feedback could be varied to optimize the number of visual conditions for exercise and testing.

There is a need to map brain areas involved in various tasks, and specific effects on performance of practicing tasks in parametrically modulated virtual environments, and the potential differential ways the engaged neural network may be affected in health and injury. Future research should identify and investigate additional potential networks to target for basic neuroscientific discovery, for motor skills acquisition, training, rehabilitation and to understand the complexities of successful skills acquisition or learning in healthy and in patient populations. Future research should also investigate confounding multidimensional influences preventing recovery of skills.

It is important to consider the fact that healthy subjects may achieve a high level of performance with or without visual augmentation and support. Whereas, some patients may find visual sensorimotor augmentation provides needed performance support for a number of important applications from mechanisms relating to specific visual sensory experience including but not limited to embodiment of movement of limbs, disambiguation of instructions, and OTI of implicit teacher models. Future research can help to define the specific benefits of such sensory interventions in VE.

Many high level tasks within conscious control and capable of being rendered in a VE with potential for recruiting underlying function (the target of a training or rehabilitation experience), may be systematically investigated using the model developed herein. For example, socially simultaneous hand movement, as in 'patty cake' hand games, possibly requiring understanding of intention and synchronization, might result in activating differential networks related through action-observation action-execution. Additional examples, obvious to those skilled in the art, will become clear.

Visual sensorimotor experience in a functional MRI compatible virtual environment provides a unique opportunity to use synthetic computer-generated virtual hands avatars to embody the motor behavior of an individual in action-observation and action-execution tasks, and to examine neural correlates, kinematics, and behaviors associated with the experience. Evidence-based plasticity oriented therapies in VE show potential to provide effective exercise conditions for rehabilitation of motor dysfunction of the hand. Improved hand function can increase quality of life. Indeed, many of the key elements associated with the dexterous hand motor repertoire enable an engaging and fulfilling lifestyle.

APPENDIX A

NEURAL CORRELATES OF FMRI EXPERIMENT AIM 2

Tables A.1 and A.2 show brain regions activated during fMRI study of Aim 2.

Table A.1 Regions in MNI space showing significant activation for the main contrasts of interest. Data are thresholded at p<0.001 at the cluster level, uncorrected, and a voxel extent of k=10. *IPL*, inferior parietal lobule, *IPS*, intraparietal sulcus, *ITG*, inferior temporal gyrus, *MTG*, middle temporal gyrus, *STG*, superior temporal gyrus, *MFG*, middle frontal gyrus, *SFG*, superior frontal gyrus, *SFS*, superior frontal sulcus.

	Side	*x,y,z {mm}*	K	t-value	z-value	p(FDR)	p(unc)
OTI > WATCH_e							
Precuneus, IPS, SPL, IPL, angular gyrus, postcentral gyrs, central sulcus	R	*16 -68 50*	7595	14.4	5.64	0.001	0.000
Central sulcus, anterior-posteior bank	R	*66 -14 24*	66	6.14	3.97	0.002	0.000
Lateral parieto-occipital	L	*-34 -80 18*	273	7.97	4.5	0.001	0.000
	R	*44 -74 12*	2848	12.87	5.43	0.001	0.000
Anterior insula	L	*-32 14 10*	40	6.63	4.13	0.002	0.000
	L	*-40 18 0*	41	5.77	3.84	0.003	0.000
	R	*38 18 2*	1783	10.5	5.05	0.001	0.000
Frontal pole	L	*-28 64 6*	24	5.8	3.85	0.003	0.000
Caudal SFG, precentral gyrus	L	*-20 -4 62*	712	7.86	4.47	0.002	0.000
Rostral SFS, SFG, MFG	R	*34 4 56*	2522	9.3	4.81	0.001	0.000
Rostral MFG	L	*-58 10 34*	121	8.1	4.53	0.001	0.000
	R	*46 44 26*	376	10	4.95	0.001	0.000
Pars orbitalis	L	*-44 52 14*	59	6.02	3.92	0.003	0.000

Pars opercularis, precentral gyrus	L	*-62 4 18*	58	6.33	4.03	0.002	0.000
	R	*46 20 26*	285	9.56	4.86	0.001	0.000
left occipital pole	L	*-26 -104 -2*	1005	8.84	4.71	0.001	0.000
ITG	R	*26 -32 -2*	87	6.19	3.98	0.002	0.000
	R	*38 -20 -10*	51	9.45	4.84	0.001	0.000
Rostral lateral sulcus	L	*-64 -34 22*	28	5.97	3.91	0.003	0.000
	L	*-50 -36 26*	73	5.82	3.86	0.003	0.000
Cerebellar vermis	R	*6 -62 -34*	65	6.84	4.19	0.002	0.000
Intermediate inferior cerebellum	L	*-20 -74 -48*	156	6.78	4.17	0.002	0.000
	L	*-34 -62 -34*	41	4.98	3.53	0.005	0.000
	R	*40 -58 -44*	193	6.79	4.17	0.002	0.000
Posterior putamen	R	*20 0 20*	79	8.18	4.55	0.001	0.000
Caudate	L	*-14 20 -4*	125	8.05	4.52	0.001	0.000
MOVE_h > MOVE_e							
IPL, angular gyrus	L	*-26 -70 32*	88	6.29	4.02	0.239	0.000
	R	*38 -68 38*	124	7.25	4.31	0.239	0.000
Precuneus	R	*18 -62 46*	53	4.89	3.49	0.239	0.000
Occipital pole	L	*-26 -86 -4*	122	5.19	3.62	0.239	0.000
	R	*26 -86 -6*	253	6.77	4.17	0.239	0.000
ITG, intermediate	R	*58 -54 -14*	56	6.34	4.03	0.239	0.000
	R	*40 -68 -12*	40	4.96	3.52	0.239	0.000
WATCH_e > OTI							
Cuneus, calcarine sulcus	L	*-12 -94 20*	97	7	4.24	0.511	0.000
Cuneus	R	*18 -80 24*	10	5	3.54	0.541	0.000
Inferior occipital	R	*6 -62 0*	110	6.8	4.18	0.511	0.000
MOVE_e > MOVE_h							
Corpus callosum	L	*-10 -16 32*	112	12.33	5.35	0.009	0.000
Cuneus	L	*-10 -88 34*	331	6.85	4.19	0.075	0.000
Frontal pole	L	*-16 58 14*	94	8.9	4.72	0.049	0.000

STG, rostral	R	*62 4 -6*	21	5.44	3.71	0.096	0.000
SFS, intermediate	L	*-20 20 50*	54	7.11	4.27	0.075	0.000
MFG, rostral	R	*22 46 16*	68	6.15	3.97	0.075	0.000
MFG, precentral sulcus	R	*34 -6 38*	76	7.73	4.44	0.075	0.000
Pars orbitalis	L	*-36 56 -4*	37	5.62	3.78	0.091	0.000
OTI block 4>3>2>1							
Posterior-intermediate insula	L	*-46 -16 14*	163	9.04	4.75	0.066	0.000

Table A.2 Regions in MNI space showing significant activation for the secondary contrasts of interest not reported in Table 1. Data are thresholded at p<0.001 at the cluster level, uncorrected, and a voxel extent of k=10. *IPL*, inferior parietal lobule, *IPS*, intraparietal sulcus, *ITG*, inferior temporal gyrus, *MTG*, middle temporal gyrus, *STG*, superior temporal gyrus, *MFG*, middle frontal gyrus, *SFG*, superior frontal gyrus, *SFS*, superior frontal sulcus.

	Side	*x,y,z {mm}*	K	t-value	z-value	p(FDR)	p(unc)
OTI > REST							
Anterior insula	R	*34 20 -4*	350	10.07	4.96	0.005	0.000
	L	*-34 20 2*	50	7.93	4.49	0.005	0.000
IPL, angular gyrus	L	*-44 -32 44*	2686	9.31	4.81	0.005	0.000
IPL, postcentral gyrus	L	*-66 -16 20*	23	5.48	3.73	0.005	0.000
Precuneus, IPS, IPL	R	*14 -76 56*	3893	8.92	4.73	0.005	0.000
Caudal SFS	L	*-24 2 50*	158	7.55	4.39	0.005	0.000
MFG, precentral sulcus/gyrus	L	*-52 12 38*	382	6.8	4.18	0.005	0.000
Pars orbitalis	R	*46 50 -10*	261	8.09	4.53	0.005	0.000
	L	*-46 46 -16*	34	6.16	3.97	0.005	0.000
	L	*-26 64 4*	25	5.06	3.56	0.006	0.000
Pars triangularis	L	*-48 28 12*	12	7.02	4.24	0.005	0.000
Pars opercularis, precentral gyrus	R	*66 -12 34*	122	6.68	4.14	0.005	0.000
	R	*52 18 22*	1975	7.2	4.29	0.005	0.000
	L	*-54 18 4*	39	5.43	3.71	0.005	0.000
ITG	R	*26 -16 -28*	114	6.31	4.02	0.005	0.000
ITG	R	*38 -24 -12*	48	6.1	3.95	0.005	0.000
Anterior cingulate	R	*18 22 42*	65	6.96	4.23	0.005	0.000
	L	*-8 30 38*	35	6.15	3.97	0.005	0.000

	L	*-8 12 60*	145	6.03	3.93	0.005	0.000
Putamen	L	*-24 16 12*	20	5.34	3.68	0.005	0.000
Dentate	R	*24 -60 -38*	23	5.03	3.55	0.006	0.000
Occipito-parietal	L	*-26 -72 22*	154	4.99	3.53	0.006	0.000
Occipital-temporal	R	*46 -68 2*	4701	7.7	4.43	0.005	0.000
Calcarine sulcus	L	*-26 -102 -4*	2729	6.9	4.21	0.005	0.000
WATCH_e > REST							
Inferior occipito-temporal	R	*48 -68 2*	1218	7.96	4.5	0.068	0.000
	L	*-44 -70 -16*	644	8.06	4.52	0.068	0.000
Occipital pole	R	*20 -96 10*	284	6.07	3.94	0.068	0.000
Occipital pole	L	*-8 -104 -4*	35	7.4	4.35	0.068	0.000
	L	*-22 -96 6*	84	5.11	3.58	0.068	0.000
Caudal IPS	R	*36 -44 54*	10	4.38	3.26	0.068	0.001
	L	*-36 -46 38*	17	6.29	4.02	0.068	0.000
	L	*-34 -44 48*	34	5.01	3.54	0.068	0.000
Anterior intermediate cerebellum	L	*-38 -48 -28*	203	6.2	3.98	0.068	0.000
MTG	L	*-54 -66 16*	15	5.25	3.64	0.068	0.000
MFG, intermediate	L	*-44 14 52*	16	4.69	3.41	0.068	0.000
Anterior cingulate	L	*-8 40 40*	16	4.57	3.35	0.068	0.000
MOVE_h > REST							
Intermediate cerebellum, dentate	R	*28 -38 -50*	1260	7.39	4.35	0.01	0.000
SFG, precentral gyrus	L	*-22 -4 74*	4045	6.76	4.16	0.01	0.000
	R	*16 2 58*	303	6.78	4.17	0.01	0.000
Occipito-temporal	R	*44 -66 -10*	1856	6.18	3.98	0.01	0.000
Posterior insula	L	*-44 -8 4*	732	6.08	3.94	0.01	0.000
Intermediate insula	R	*50 6 4*	1185	6.06	3.94	0.01	0.000
Anterior, intermediate cingulate	L	*-6 4 48*	638	5.94	3.90	0.01	0.000
Central sulcus, pre/post-central gyri	R	*46 -26 32*	1572	5.73	3.82	0.01	0.000
Precuneus	R	*16 -70 52*	103	5.70	3.81	0.01	0.000
Lateral inferior	L	*-46 -74 -*	1007	5.51	3.74	0.01	0.000

occipital		*20*					
IPL, angular gyrus	R	*32 -70 22*	53	5.30	3.66	0.01	0.000
Intermediate putamen	R	*24 -2 6*	52	5.26	3.64	0.01	0.000
Pars opercularis	R	*56 6 42*	20	4.61	3.37	0.01	0.000
Occipital pole	L	*-26 -86 -4*	96	4.54	3.34	0.01	0.000
MOVE_e > REST							
Intermediate insula, frontoparietal operculum, central sulcus, pre/postcentral gyrus	L	*-58 -2 2*	8268	8.05	4.52	0.006	0.000
Central sulcus, pre/poscentral gyrus	R	*56 -20 44*	2614	7.97	4.5	0.006	0.000
Anterior-posterior insula	R	*54 16 -6*	2687	7.66	4.42	0.006	0.000
Inferior occipital-temporal	R	*44 -64 0*	543	6.76	4.16	0.006	0.000
Inferior lateral temporal lobe	L	*-38 -76 -18*	482	6.09	3.95	0.006	0.000
Intermediate, superior cerebellum	R	*44 -56 -40*	653	5.9	3.88	0.006	0.000
	L	*-27 -70 -38*	434	5.92	3.89	0.006	0.000
Precuneus	L	*-14 -54 54*	63	5.59	3.77	0.006	0.000
Caudal MFG	L	*-56 2 44*	19	5.56	3.76	0.006	0.000
Anterior insula	L	*-32 18 4*	59	5.52	3.74	0.006	0.000
Intermediate putamen	R	*18 2 12*	70	5.33	3.67	0.006	0.000
Rostral SFS	R	*22 50 20*	36	4.96	3.52	0.007	0.000

APPENDIX B

VESLI STATISTICS EXPERIMENTS 1 AND 2

Figure B.1 to B.19 show statistical analysis of the two VESLI Experiments.

ANOVA Table for Average Response Time 1

	DF	Sum of Squares	Mean Square	F-Value	P-Value	Lambda	Power
Subject	9	36.853	4.095				
Feedback	1	.779	.779	.895	.3688	.895	.131
Feedback * Subject	9	7.833	.870				
Definition	1	.361	.361	.196	.6683	.196	.068
Definition * Subject	9	16.557	1.840				
Recall	1	6.720	6.720	5.780	.0396	5.780	.570
Recall * Subject	9	10.464	1.163				
Feedback * Definition	1	1.760	1.760	2.353	.1594	2.353	.268
Feedback * Definition * Subject	9	6.734	.748				
Feedback * Recall	1	.311	.311	.189	.6742	.189	.067
Feedback * Recall * Subject	9	14.846	1.650				
Definition * Recall	1	1.265	1.265	.862	.3773	.862	.128
Definition * Recall * Subject	9	13.199	1.467				
Feedback * Definition * Recall	1	.007	.007	.003	.9586	.003	.050
Feedback * Definition * Recall * Subject	9	20.754	2.306				

Figure B.1 ANOVA Table for Average Response Time Experiment 1.

Means Table for Average Response Time 1
Effect: Recall

	Count	Mean	Std. Dev.	Std. Err.
Change	40	4.620	1.038	.164
Same	40	5.200	1.517	.240

Figure B.2 ART Effect: Recall Experiment 1.

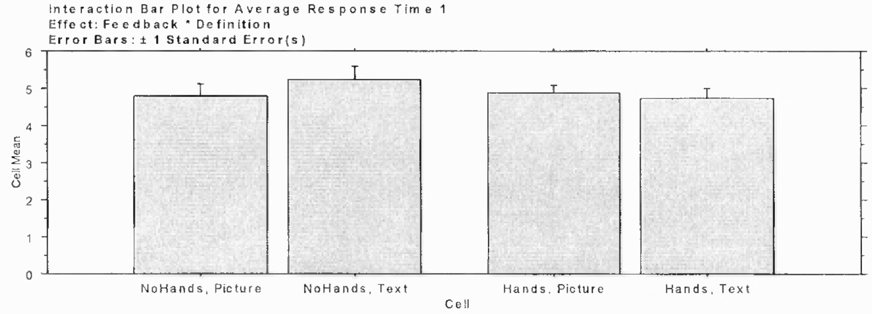


Figure B.3 ART Feedback * Definition Experiment 1.

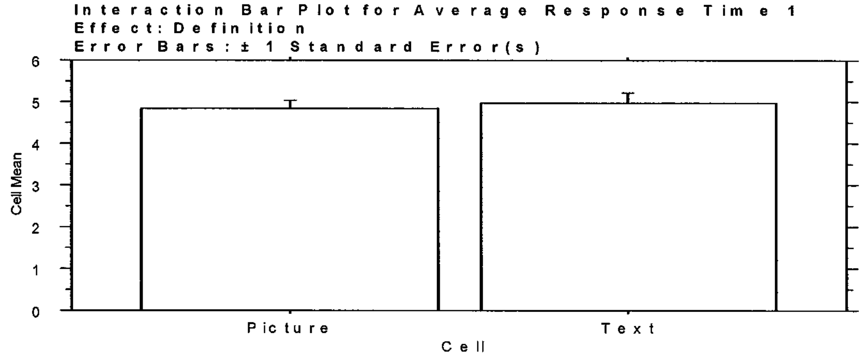


Figure B.4 ART Effect Definition Experiment 1.

ANOVA Table for Average Source Time 1

	DF	Sum of Squares	Mean Square	F-Value	P-Value	Lambda	Power
Subject	9	15.981	1.776				
Feedback	1	.729	.729	.814	.3905	.814	.124
Feedback * Subject	9	8.060	.896				
Definition	1	9.418	9.418	14.283	.0044	14.283	.930
Definition * Subject	9	5.935	.659				
Recall	1	.003	.003	.003	.9587	.003	.050
Recall * Subject	9	10.772	1.197				
Feedback * Definition	1	1.920	1.920	1.512	.2500	1.512	.189
Feedback * Definition * Subject	9	11.428	1.270				
Feedback * Recall	1	.458	.458	.630	.4477	.630	.107
Feedback * Recall * Subject	9	6.546	.727				
Definition * Recall	1	1.271	1.271	1.062	.3297	1.062	.146
Definition * Recall * Subject	9	10.774	1.197				
Feedback * Definition * Recall	1	3.403E-4	3.403E-4	.001	.9791	.001	.050
Feedback * Definition * Recall * Subject	9	4.240	.471				

Figure B.5 ANOVA Table Average Source Time Experiment 1.

Means Table for Average Source Time 1
Effect: Definition

	Count	Mean	Std. Dev.	Std. Err.
Picture	40	2.418	.858	.136
Text	40	3.105	1.126	.178

Figure B.6 AST Effect Definition Experiment 1.

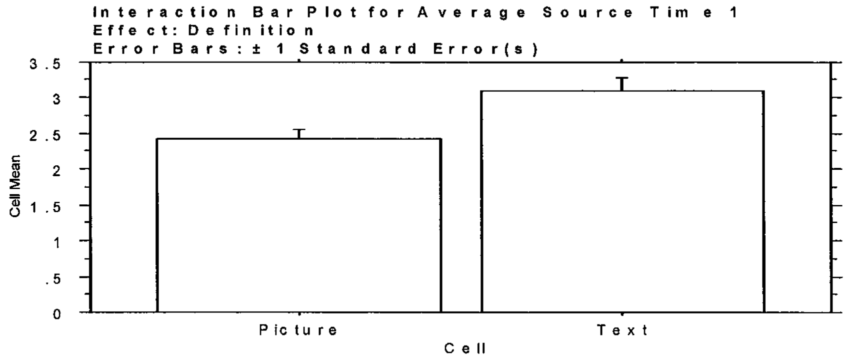


Figure B.7 AST Effect Definition Experiment 1.

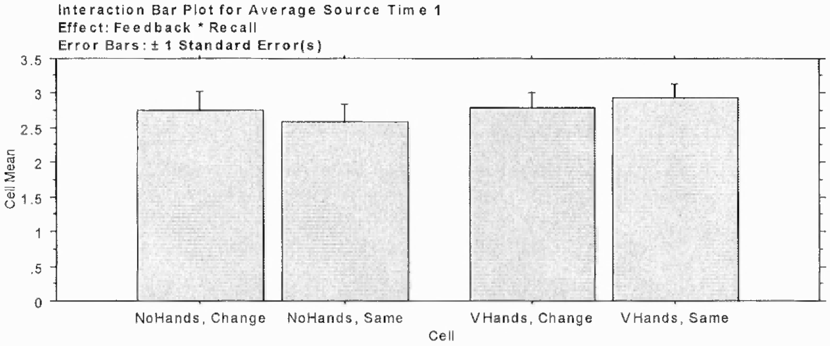


Figure B.8 AST Effect Feedback * Recall Experiment 1.

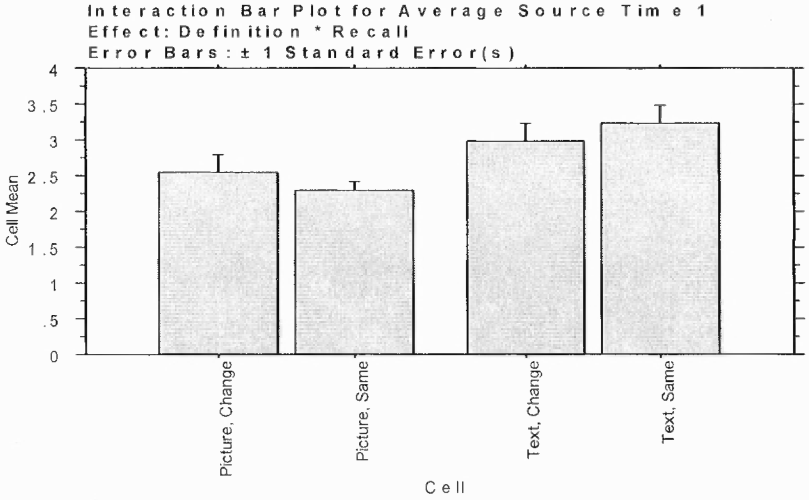
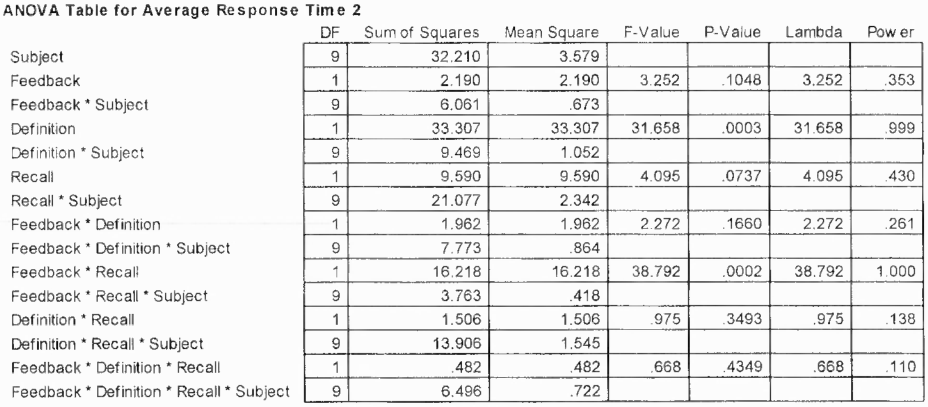


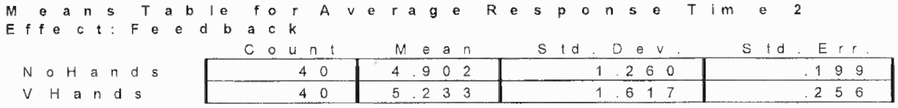
Figure B.9 AST Effect Definition * Recall Experiment 1.



ANOVA Table for Average Response Time 2

	DF	Sum of Squares	Mean Square	F-Value	P-Value	Lambda	Power
Subject	9	32.210	3.579				
Feedback	1	2.190	2.190	3.252	.1048	3.252	.353
Feedback * Subject	9	6.061	.673				
Definition	1	33.307	33.307	31.658	.0003	31.658	.999
Definition * Subject	9	9.469	1.052				
Recall	1	9.590	9.590	4.095	.0737	4.095	.430
Recall * Subject	9	21.077	2.342				
Feedback * Definition	1	1.962	1.962	2.272	.1660	2.272	.261
Feedback * Definition * Subject	9	7.773	.864				
Feedback * Recall	1	16.218	16.218	38.792	.0002	38.792	1.000
Feedback * Recall * Subject	9	3.763	.418				
Definition * Recall	1	1.506	1.506	.975	.3493	.975	.138
Definition * Recall * Subject	9	13.906	1.545				
Feedback * Definition * Recall	1	.482	.482	.668	.4349	.668	.110
Feedback * Definition * Recall * Subject	9	6.496	.722				

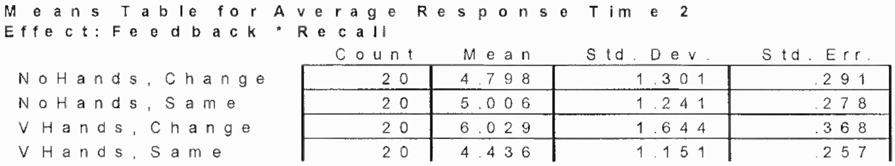
Figure B.10 ANOVA Table for Average Response Time Experiment 2.



Means Table for Average Response Time 2
Effect: Feedback

	Count	Mean	Std. Dev.	Std. Err.
NoHands	40	4.902	1.260	.199
VHands	40	5.233	1.617	.256

Figure B.11 ART Effect Feedback Experiment 2.



Means Table for Average Response Time 2
Effect: Feedback * Recall

	Count	Mean	Std. Dev.	Std. Err.
NoHands, Change	20	4.798	1.301	.291
NoHands, Same	20	5.006	1.241	.278
VHands, Change	20	6.029	1.644	.368
VHands, Same	20	4.436	1.151	.257

Figure B.12 ART Effect Feedback * Recall Experiment 2.

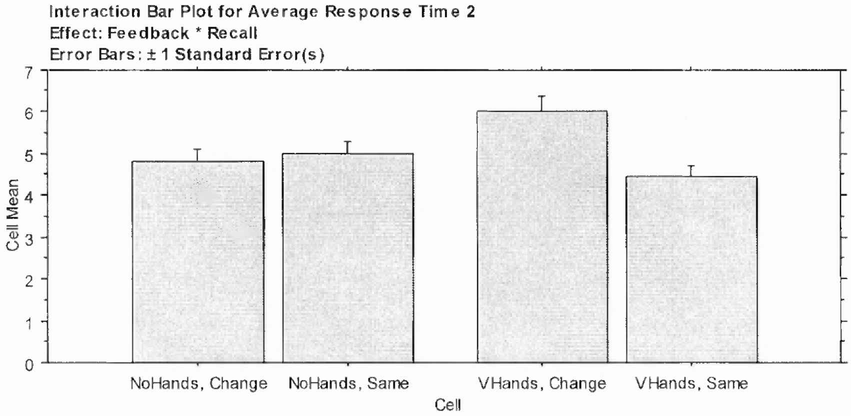


Figure B.13 ART Effect Feedback * Recall Experiment 2.

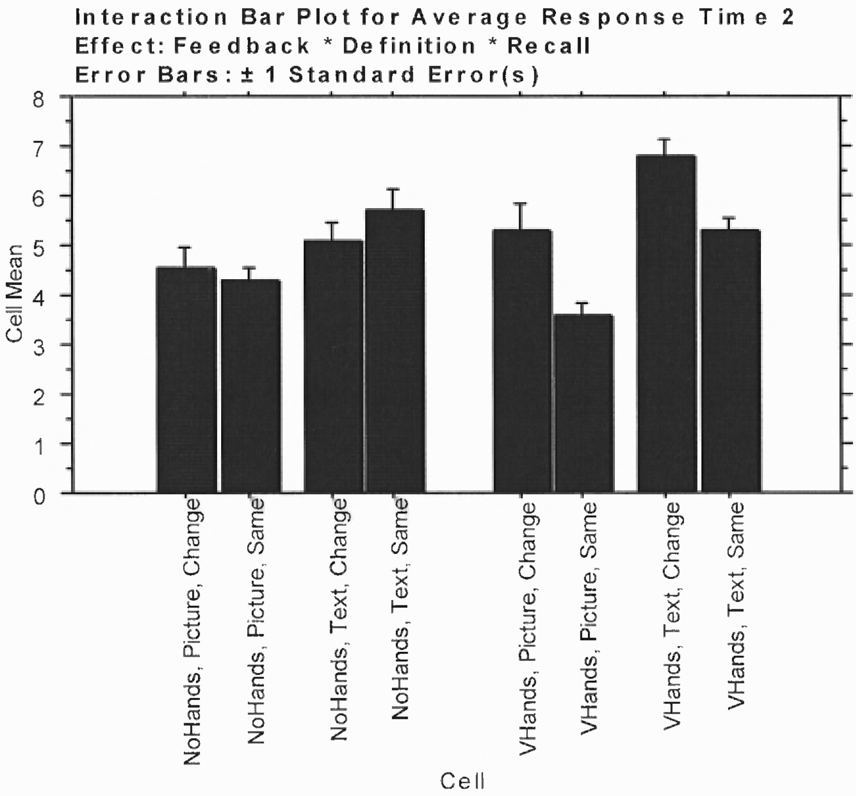
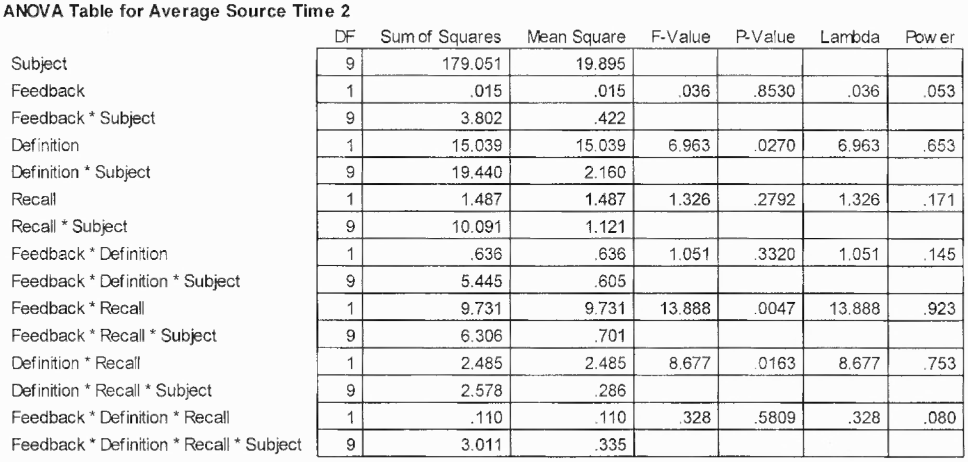


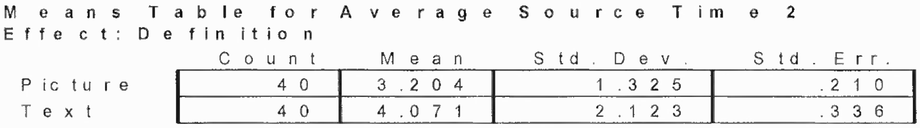
Figure B.14 ART Effect Feedback * Definition * Recall Experiment 2.



ANOVA Table for Average Source Time 2

	DF	Sum of Squares	Mean Square	F-Value	P-Value	Lambda	Power
Subject	9	179.051	19.895				
Feedback	1	.015	.015	.036	.8530	.036	.053
Feedback * Subject	9	3.802	.422				
Definition	1	15.039	15.039	6.963	.0270	6.963	.653
Definition * Subject	9	19.440	2.160				
Recall	1	1.487	1.487	1.326	.2792	1.326	.171
Recall * Subject	9	10.091	1.121				
Feedback * Definition	1	.636	.636	1.051	.3320	1.051	.145
Feedback * Definition * Subject	9	5.445	.605				
Feedback * Recall	1	9.731	9.731	13.888	.0047	13.888	.923
Feedback * Recall * Subject	9	6.306	.701				
Definition * Recall	1	2.485	2.485	8.677	.0163	8.677	.753
Definition * Recall * Subject	9	2.578	.286				
Feedback * Definition * Recall	1	.110	.110	.328	.5809	.328	.080
Feedback * Definition * Recall * Subject	9	3.011	.335				

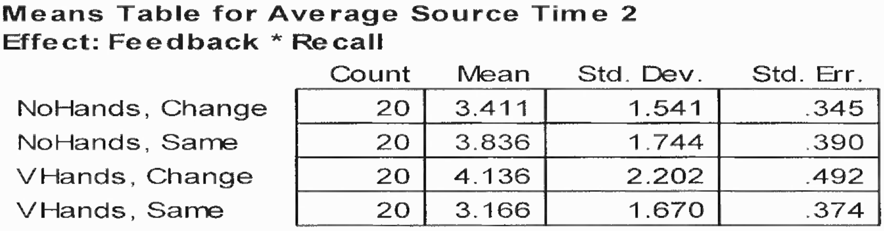
Figure B.15 ANOVA Table for Average Source Time Experiment 2.



Means Table for Average Source Time 2
Effect: Definition

	Count	Mean	Std. Dev.	Std. Err.
Picture	40	3.204	1.325	.210
Text	40	4.071	2.123	.336

Figure B.16 AST Effect Definition Experiment 2.



Means Table for Average Source Time 2
Effect: Feedback * Recall

	Count	Mean	Std. Dev.	Std. Err.
NoHands, Change	20	3.411	1.541	.345
NoHands, Same	20	3.836	1.744	.390
VHands, Change	20	4.136	2.202	.492
VHands, Same	20	3.166	1.670	.374

Figure B.17 AST Effect Feedback * Recall Experiment 2.

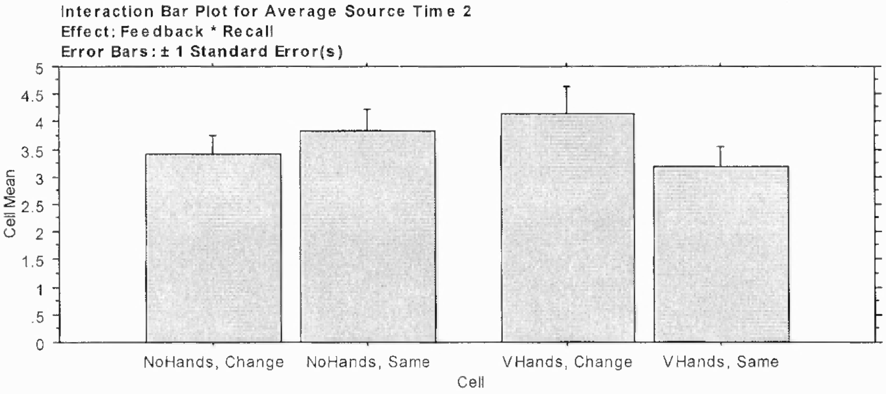


Figure B.18 AST Effect Feedback * Recall Experiment 2.

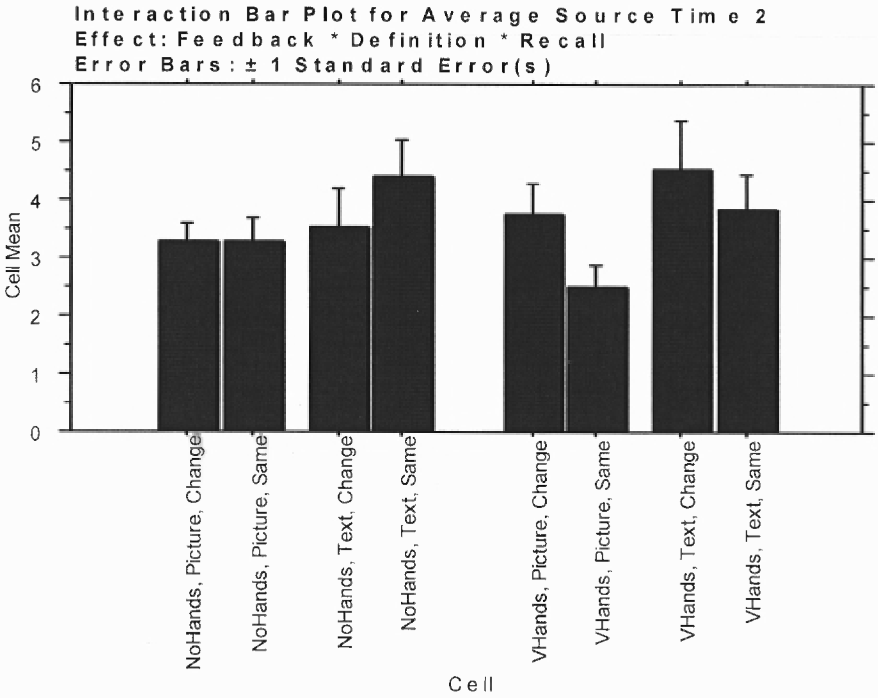
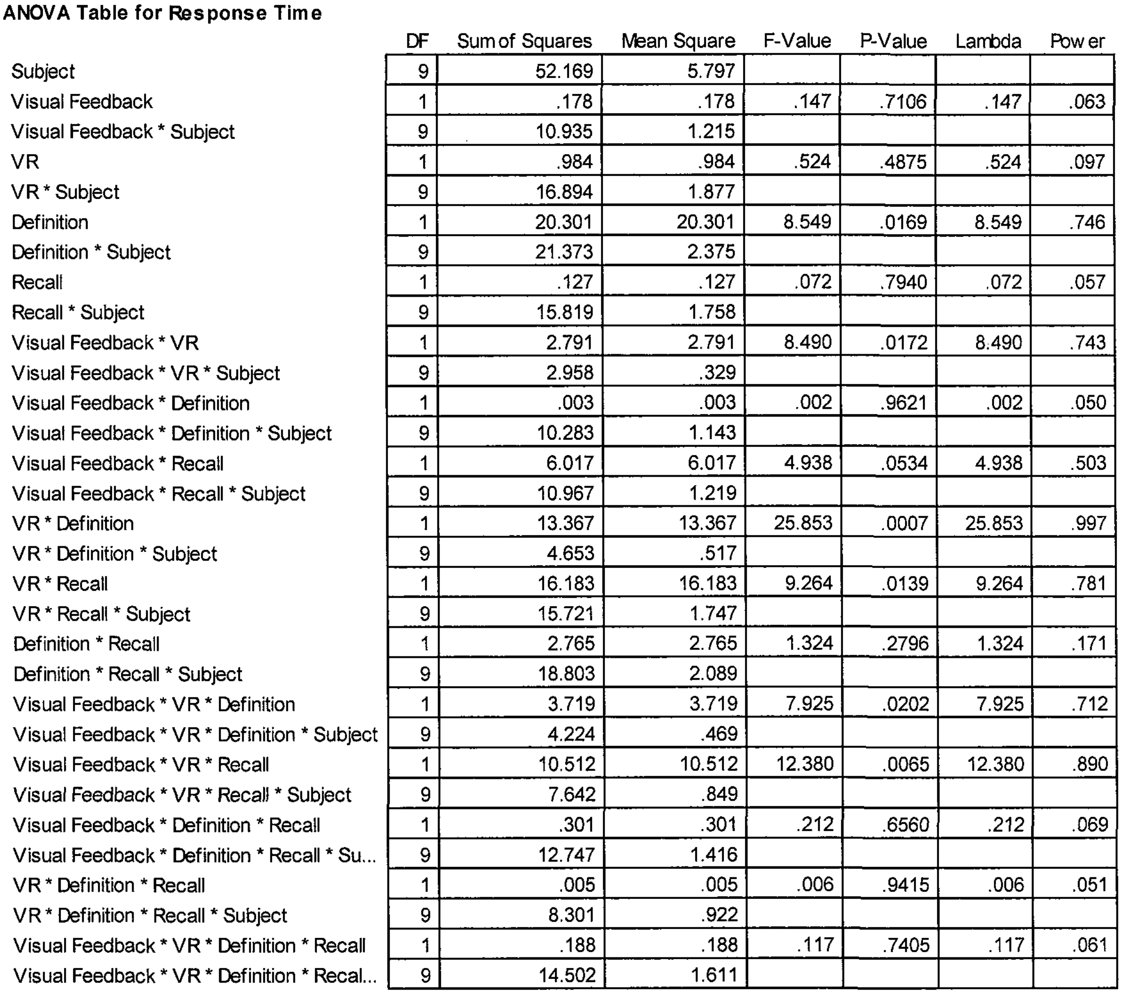


Figure B.19 AST Effect Feedback * Definition * Recall Experiment 2.

APPENDIX C

VESLI SUMMARY STATISTICS

Figures C.1 through C.17 show statistics of VESLI experiments comparing Viewing Natural Hands and Viewing Virtual Hands with Hidden Hands as a control condition.



ANOVA Table for Response Time

	DF	Sum of Squares	Mean Square	F-Value	P-Value	Lambda	Power
Subject	9	52.169	5.797				
Visual Feedback	1	.178	.178	.147	.7106	.147	.063
Visual Feedback * Subject	9	10.935	1.215				
VR	1	.984	.984	.524	.4875	.524	.097
VR * Subject	9	16.894	1.877				
Definition	1	20.301	20.301	8.549	.0169	8.549	.746
Definition * Subject	9	21.373	2.375				
Recall	1	.127	.127	.072	.7940	.072	.057
Recall * Subject	9	15.819	1.758				
Visual Feedback * VR	1	2.791	2.791	8.490	.0172	8.490	.743
Visual Feedback * VR * Subject	9	2.958	.329				
Visual Feedback * Definition	1	.003	.003	.002	.9621	.002	.050
Visual Feedback * Definition * Subject	9	10.283	1.143				
Visual Feedback * Recall	1	6.017	6.017	4.938	.0534	4.938	.503
Visual Feedback * Recall * Subject	9	10.967	1.219				
VR * Definition	1	13.367	13.367	25.853	.0007	25.853	.997
VR * Definition * Subject	9	4.653	.517				
VR * Recall	1	16.183	16.183	9.264	.0139	9.264	.781
VR * Recall * Subject	9	15.721	1.747				
Definition * Recall	1	2.765	2.765	1.324	.2796	1.324	.171
Definition * Recall * Subject	9	18.803	2.089				
Visual Feedback * VR * Definition	1	3.719	3.719	7.925	.0202	7.925	.712
Visual Feedback * VR * Definition * Subject	9	4.224	.469				
Visual Feedback * VR * Recall	1	10.512	10.512	12.380	.0065	12.380	.890
Visual Feedback * VR * Recall * Subject	9	7.642	.849				
Visual Feedback * Definition * Recall	1	.301	.301	.212	.6560	.212	.069
Visual Feedback * Definition * Recall * Su...	9	12.747	1.416				
VR * Definition * Recall	1	.005	.005	.006	.9415	.006	.051
VR * Definition * Recall * Subject	9	8.301	.922				
Visual Feedback * VR * Definition * Recall	1	.188	.188	.117	.7405	.117	.061
Visual Feedback * VR * Definition * Recal...	9	14.502	1.611				

Figure C.1 ANOVA Table for Response Time.

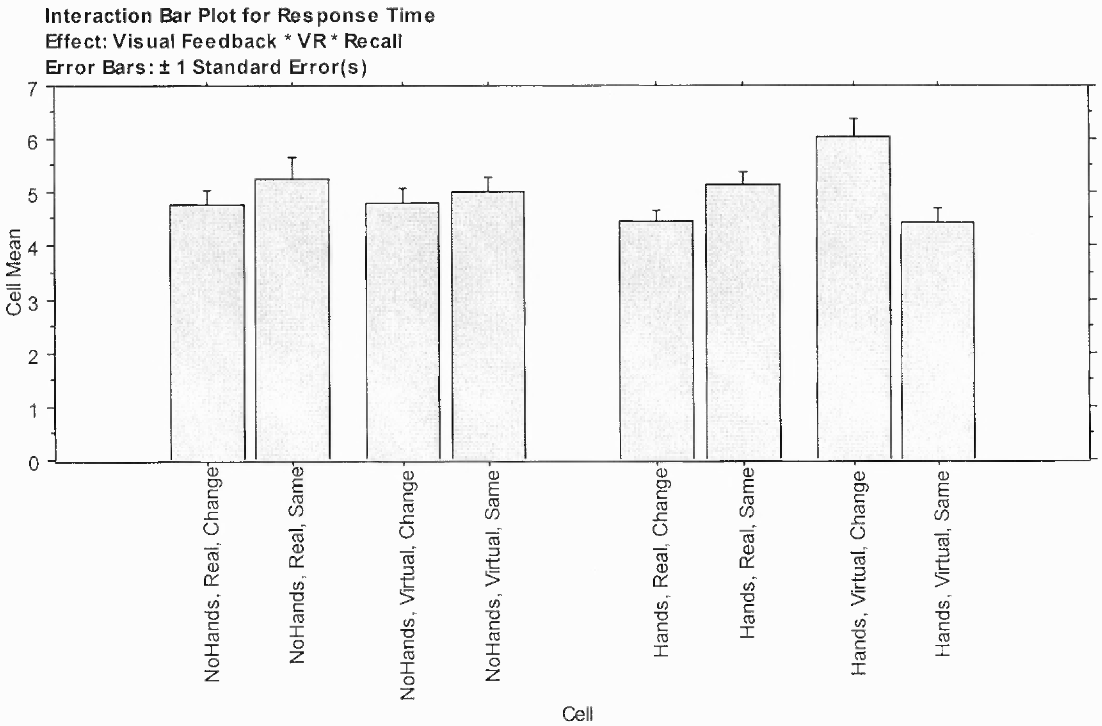


Figure C.2 RT Effect: Visual Feedback * VR Recall.

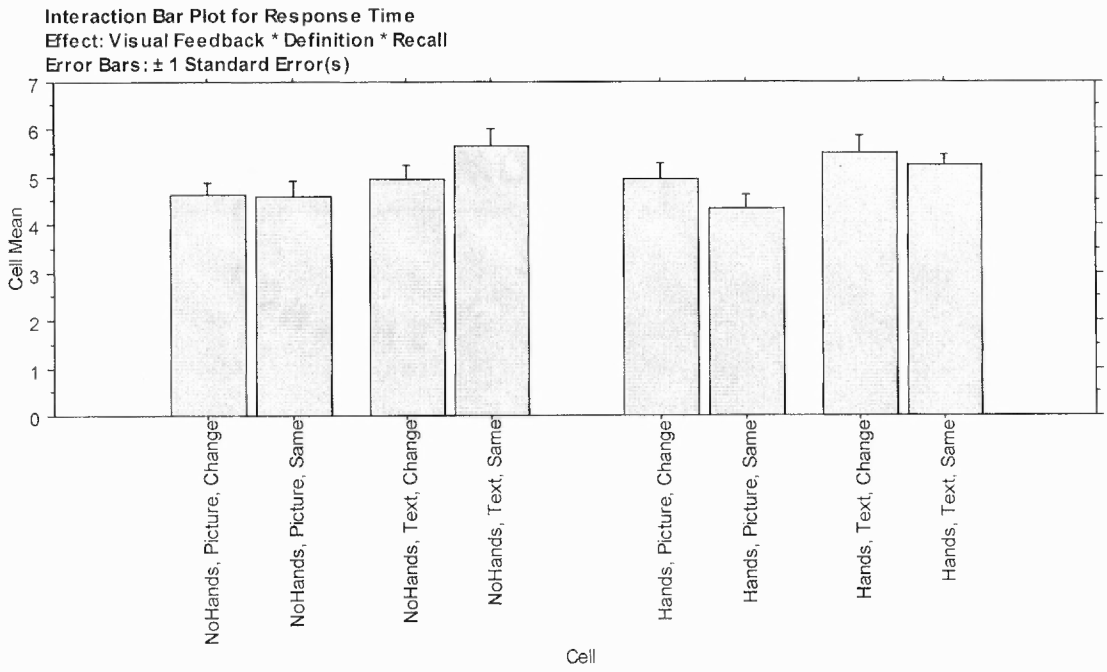


Figure C.3 RT Effect: Visual Feedback * Definition * Recall.

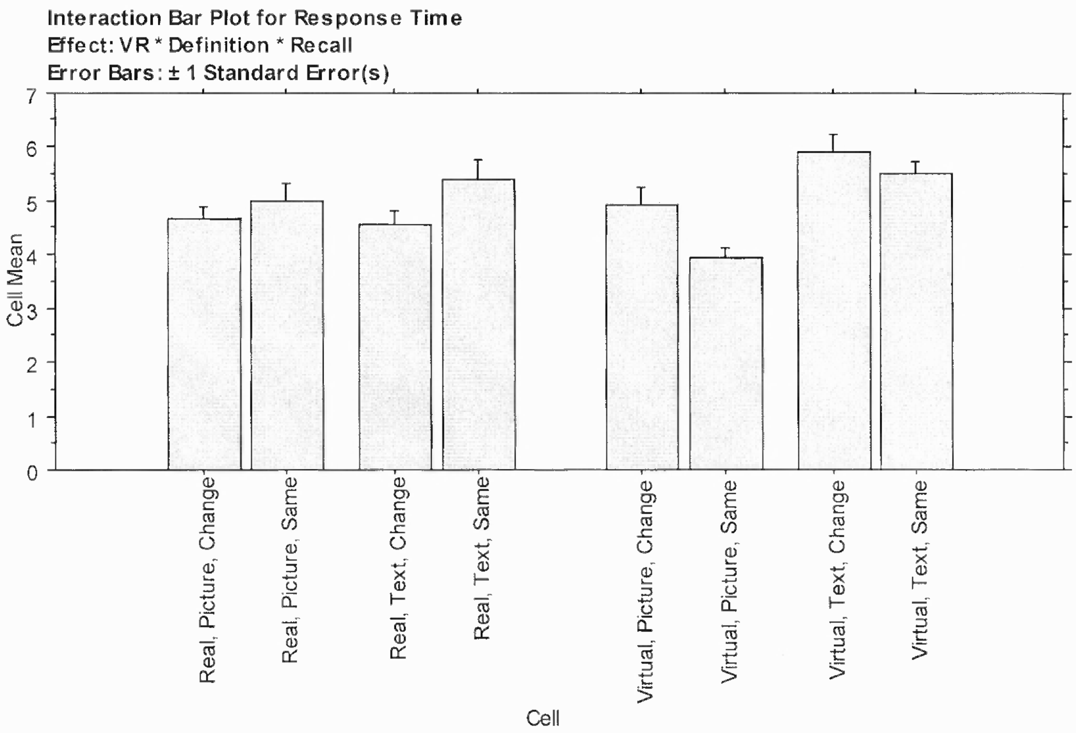


Figure C.4 RT Effect: Visual Feedback * Definition * Recall, VR * Definition * Recall.

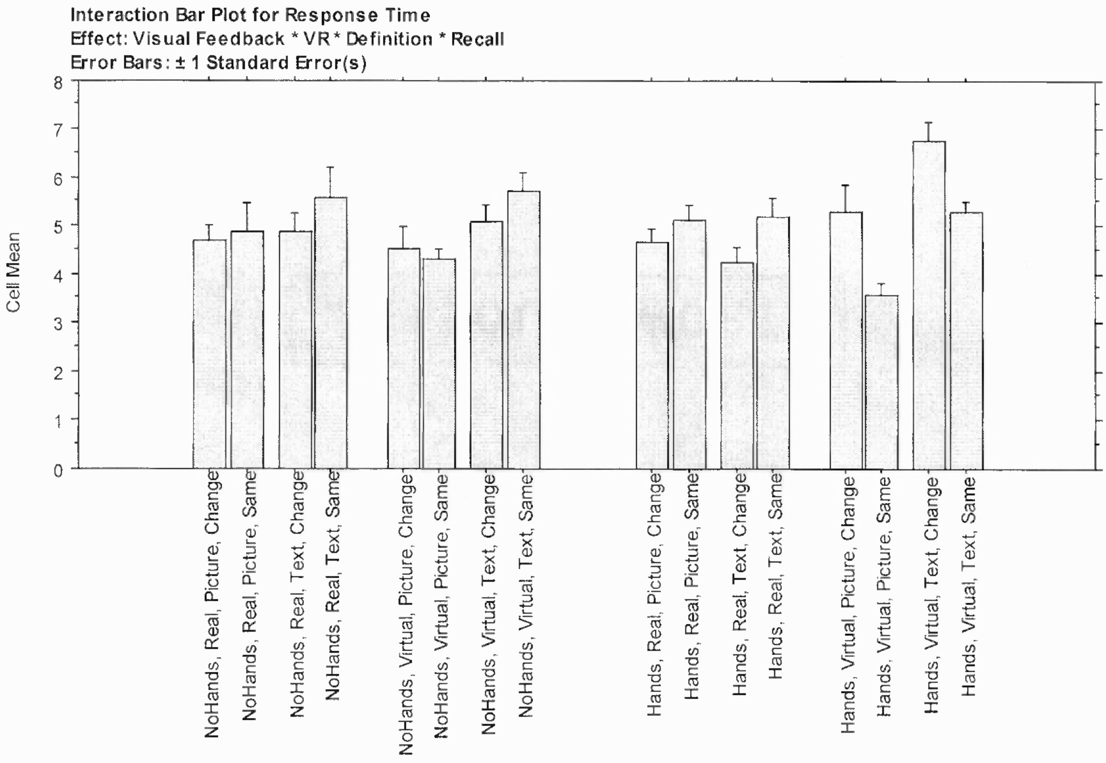


Figure C.5 RT Effect: Visual Feedback * Definition * Recall, VR * Definition * Recall.

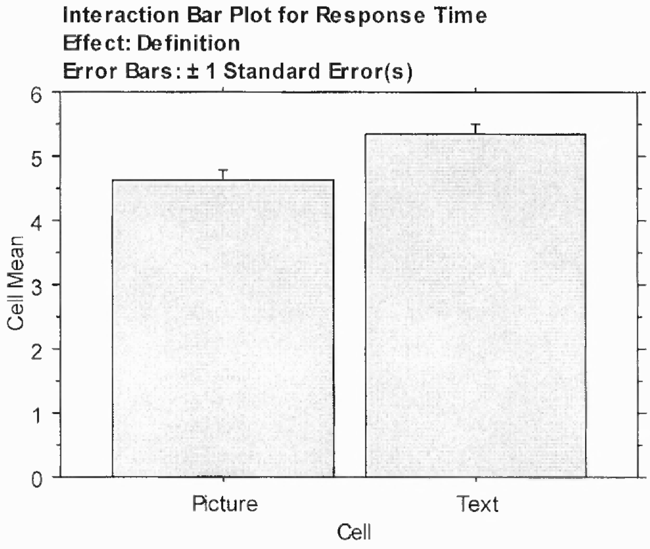


Figure C.6 RT Interaction Effect: Definition.

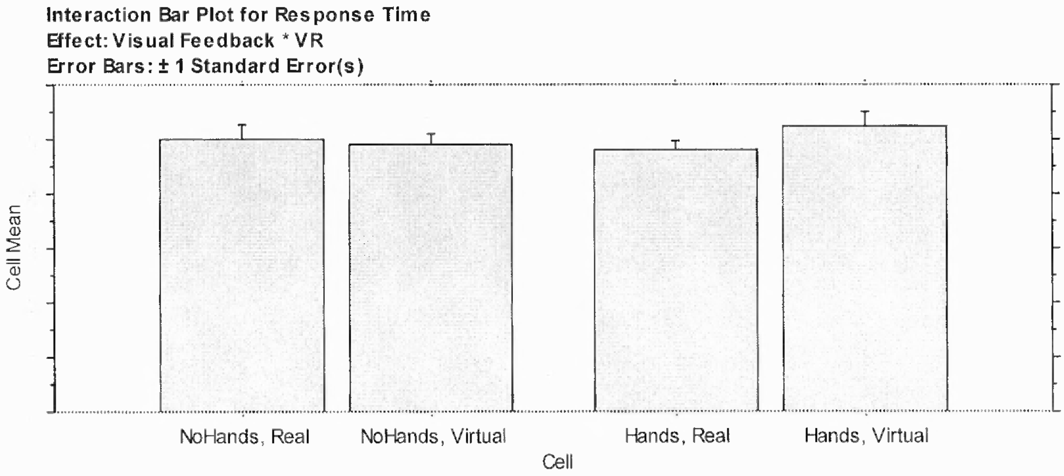


Figure C.7 RT Interaction Effect: Visual Feedback * VR.

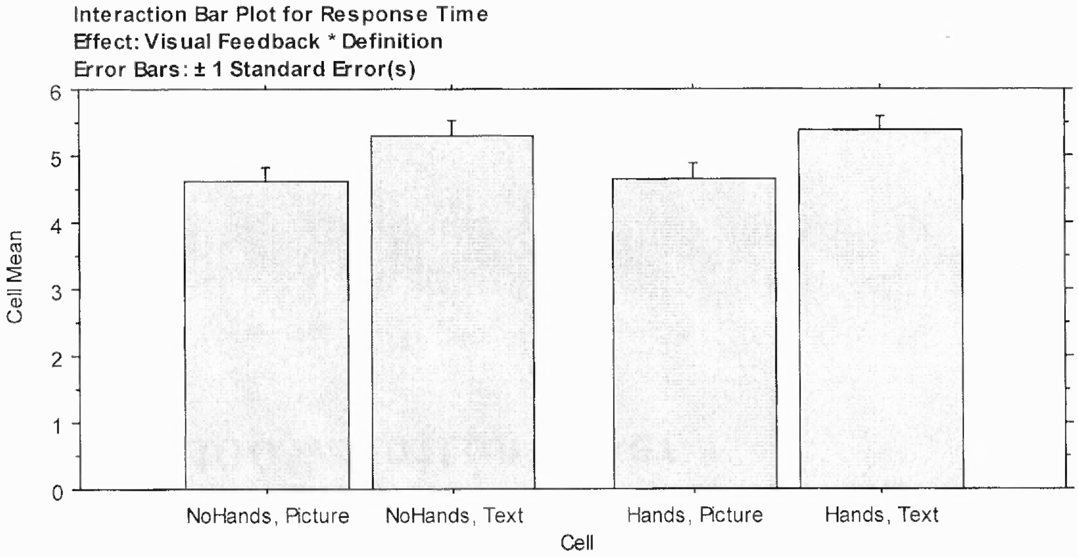


Figure C.8 RT Interaction Effect: Visual Feedback * Definition.

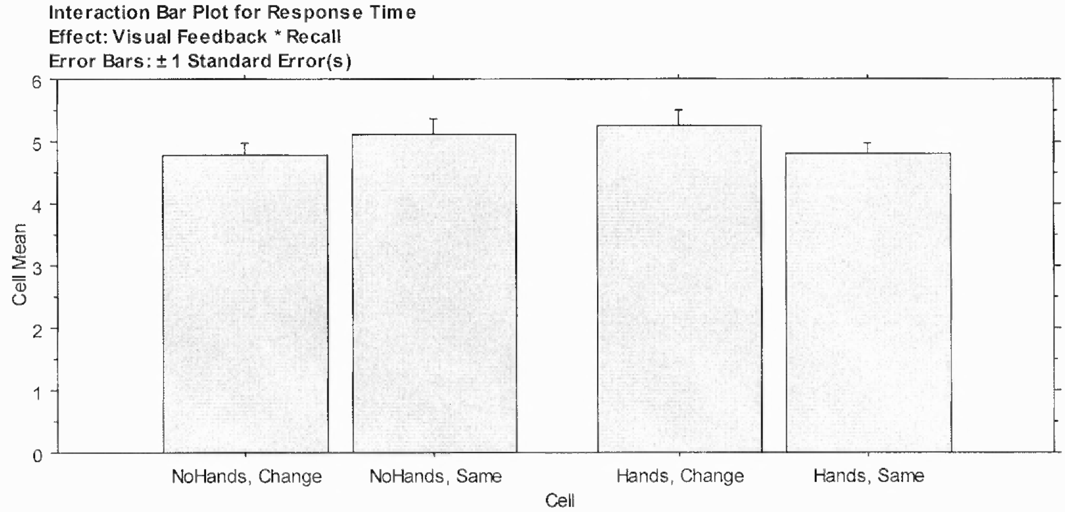


Figure C.9 RT Interaction Effect: Visual Feedback * Recall.

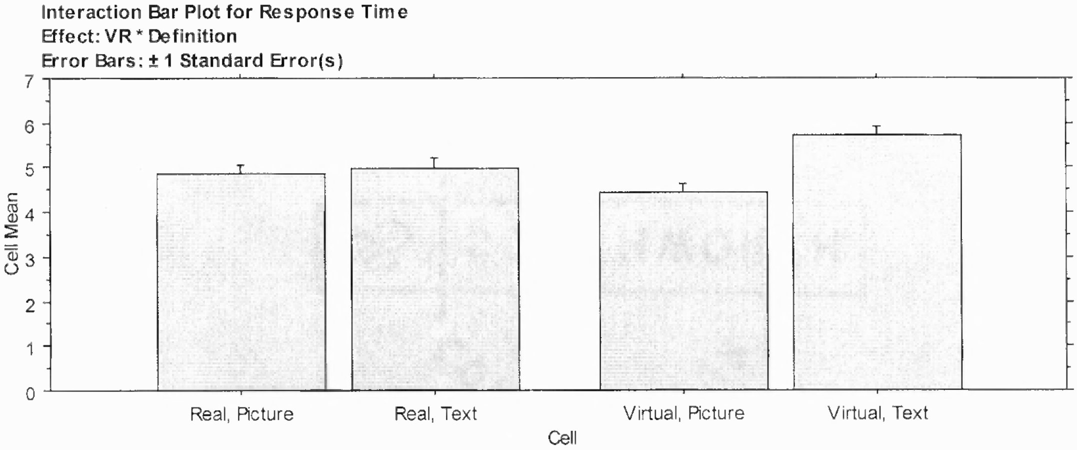


Figure C.10 RT Interaction Effect: VR * Definition.

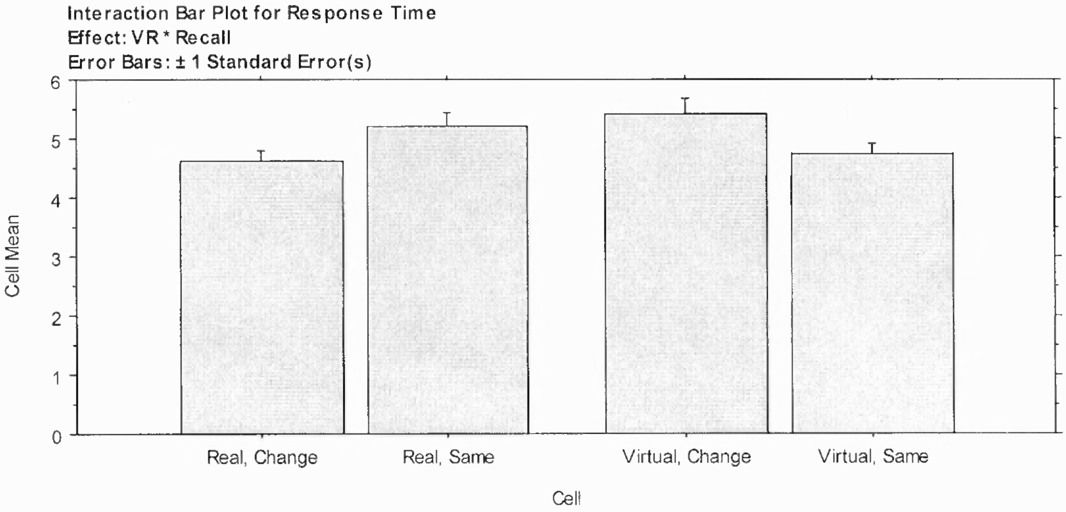


Figure C.11 RT Effect: VR * Recall.

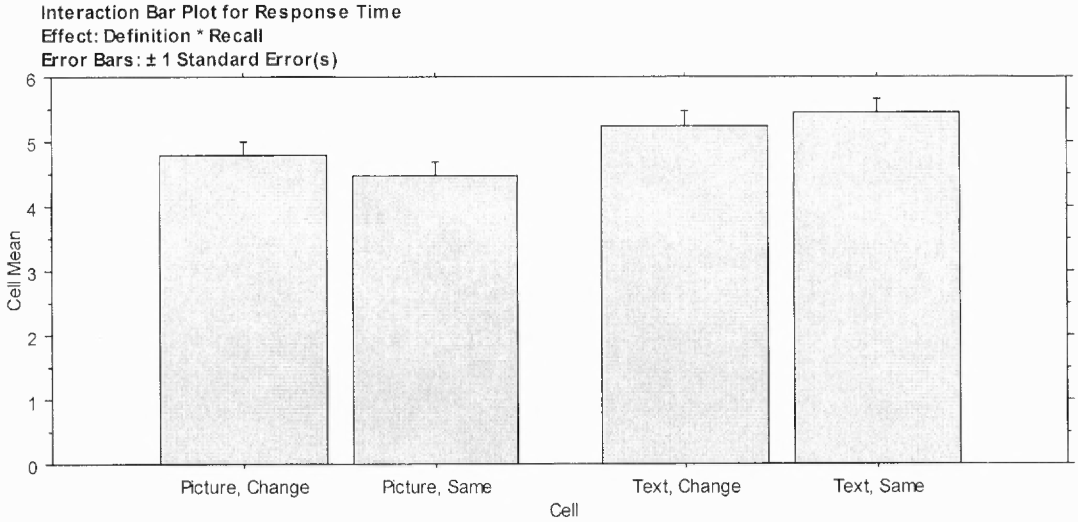


Figure C.12 RT Effect: Definition * Recall.

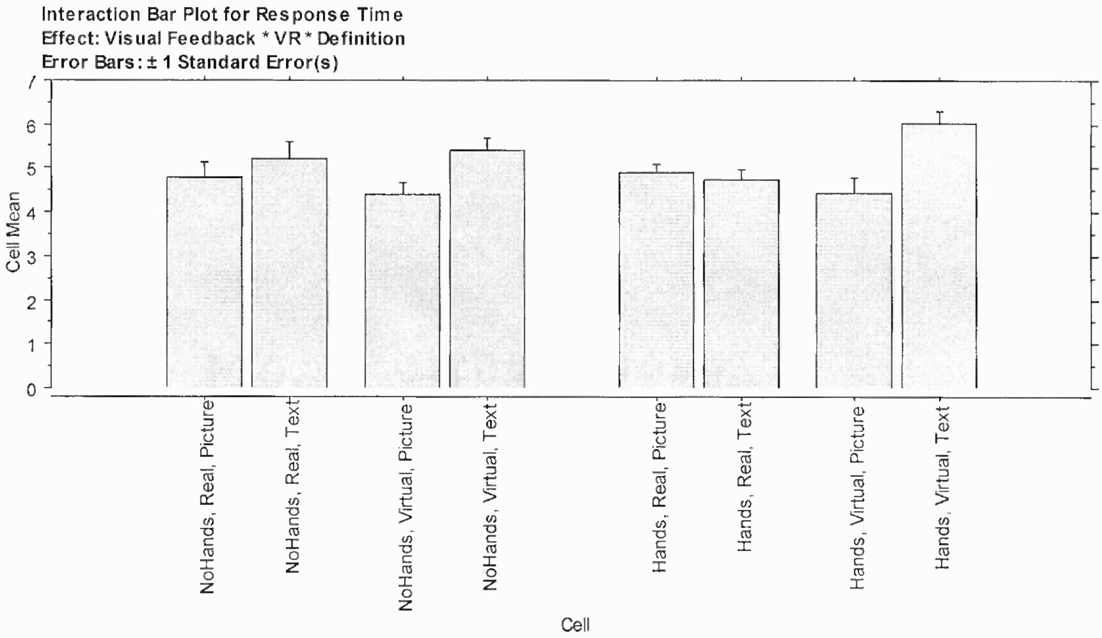


Figure C.13 RT Effect: Visual Feedback * VR * Definition.

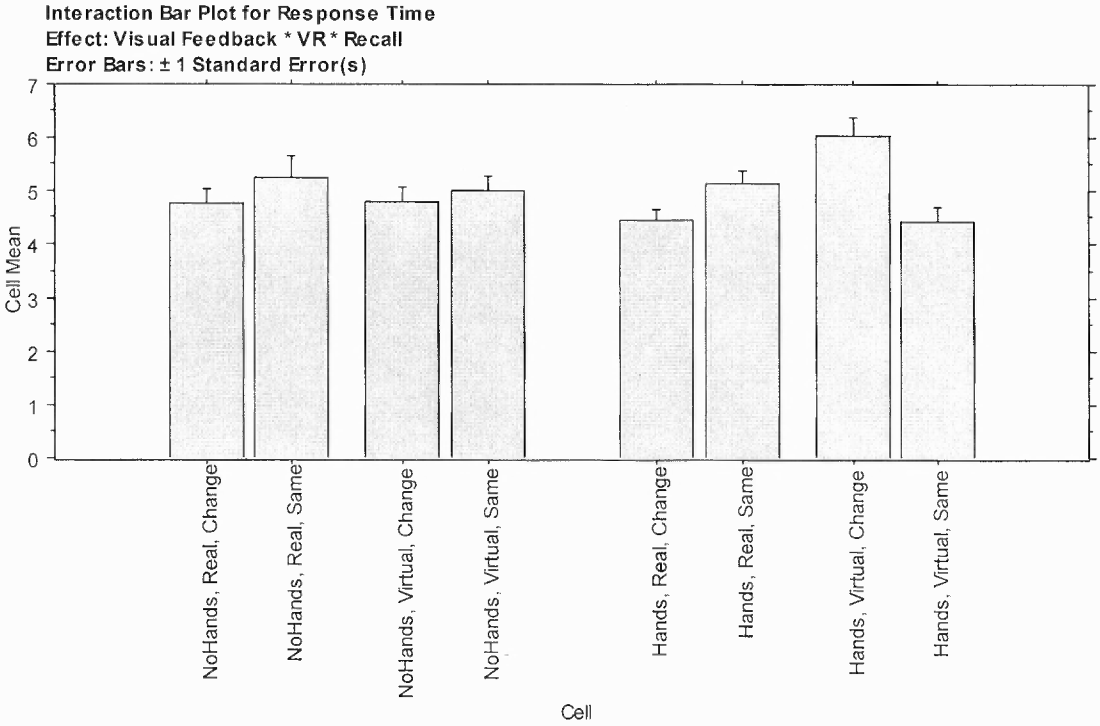


Figure C.14 RT Effect: Visual Feedback * VR * Recall.

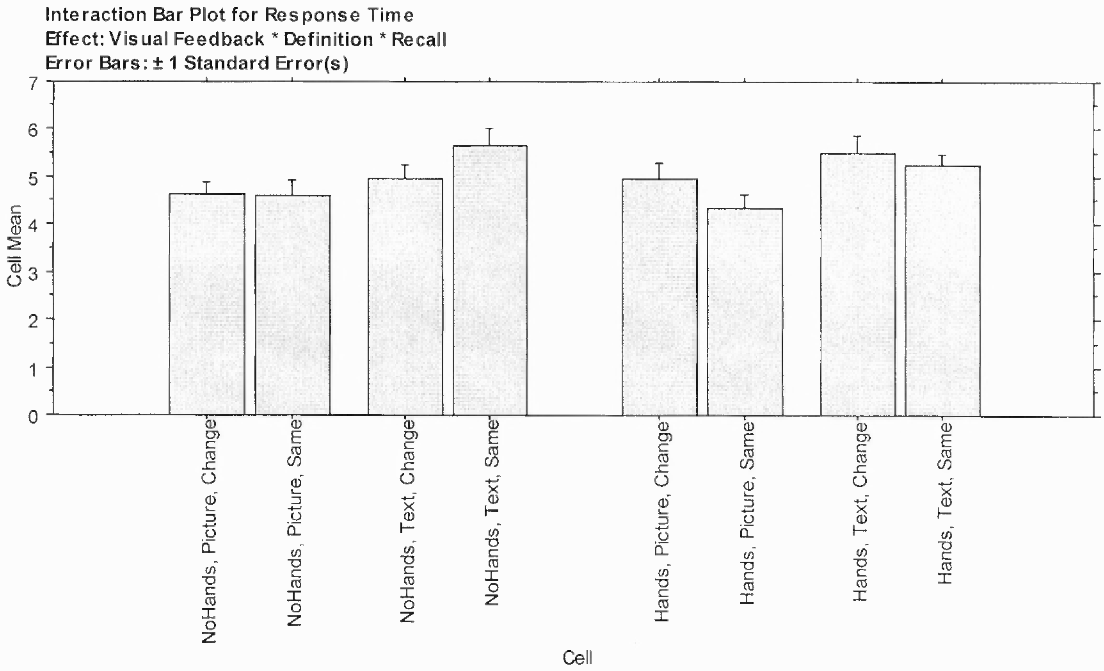


Figure C.15 RT Effect: Visual Feedback * Definition * Recall.

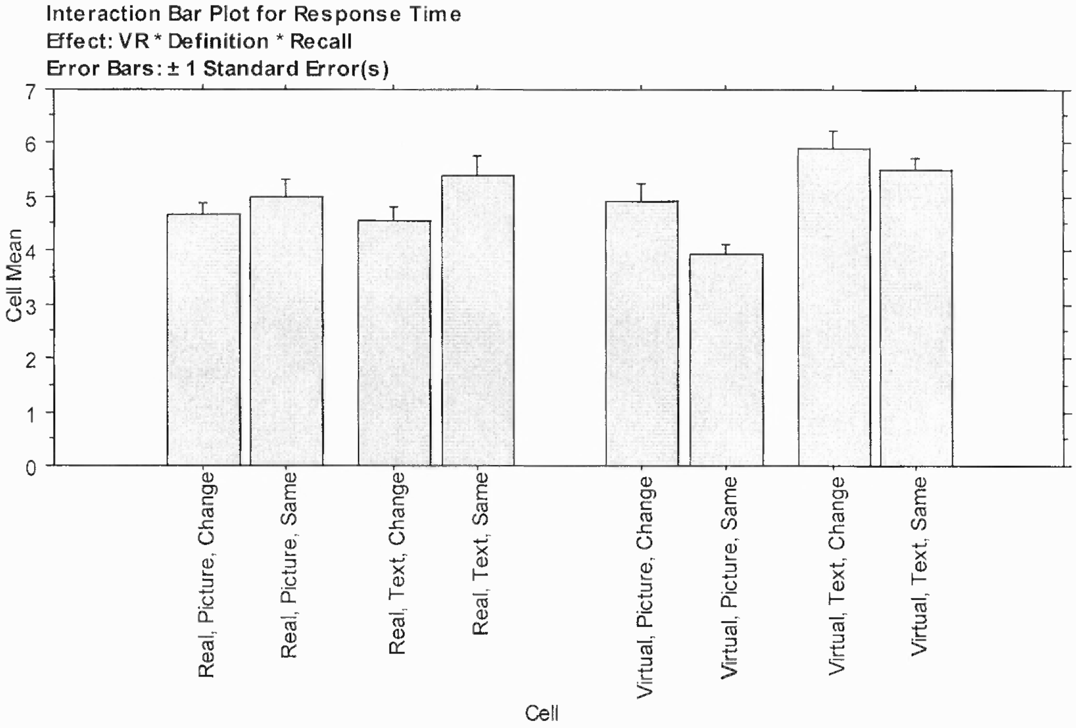


Figure C.16 RT Effect: VR * Definition * Recall.

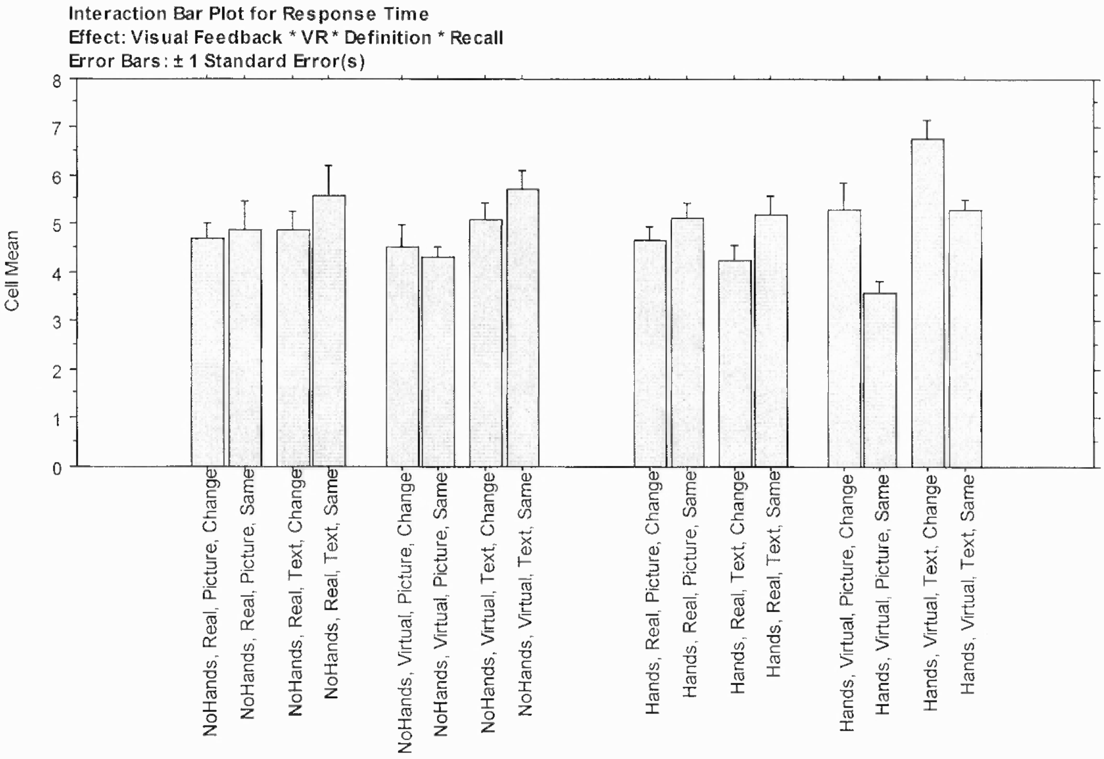


Figure C.17 RT Effect: Visual Feedback * VR * Definition * Recall.

APPENDIX D

HUMAN SUBJECT RESEARCH REVIEW FORM

PLEASE PRINT OR TYPE

Date:__17 April 2007 __________

HUMAN SUBJECT RESEARCH REVIEW FORM
NEW JERSEY INSTITUTE OF TECHNOLOGY
INSTITUTIONAL REVIEW BOARD APPLICATION
Revised January 16, 2007

Name of Principal Investigator(s): Sergei Adamovich, (Katherine August – corresponding team member)
Faculty members and/or staff must be principal investigators. Students can serve as co-principal investigators under faculty/staff supervision for expedited projects.

NJIT Address: __Fenster Hall, Room 616 ________________________

Department: __Biomedical Engineering ________________________

E-mail Address: _ adamovic@njit.edu , ka38@njit.edu (kitty123@optonline.net) __________

NJIT Affiliation of Principal Investigators (Check all that apply):

☐X Faculty ☐X Student ☐ Other (Describe: ____________________________)

*Note students and doctoral candidates applying for IRB approval must submit written documentation from their faculty advisors (via e-mail) stating that research is being conducted under their supervision.

Project Title: Use of Virtual Reality in Studying Sensory Influences on Motor Learning

This project will be conducted:

☐X On Campus ☐ Off Campus (Location:________________________) ☐ Both

Is this research funded by outside source(s)? ☐ X Yes ☐ No

If yes, indicate name(s) and type of funding source(s):

Name of Funding Source(s): National Institute of Disability and Rehabilitation Research_

Type: ☐X Government (County, State or Federal) ☐ Foundation ☐ Corporation
☐ Other (Describe: ____________________________)

Anticipated Starting Date of Project:__ May 2007____________________

Anticipated Closing Date of Project:__ 2010____________________

Number of Subjects:__ 30 ____________________________

NOTE: All principal investigators, faculty, and students who will be interfacing with human subjects in this study must complete an online training course in the protection of human subjects. This course can be accessed by going to the US Department of Health and Human Services' Office for Human Research Protection website (http://www.hhs.gov/ohrp/) and clicking on "Education." At the bottom of this page, you will see the tutorial for the training module for assurances. All certificates indicating course completion must be submitted with this application.

To Principal Investigator: In addition to the questions below, please furnish copies of any questionnaires interview formats, testing instruments or other documents necessary to carry out the research. Any advertising materials used to recruit subjects must also be submitted.

The completed forms should be sent to:

Dawn Hall Apgar, PhD
dawn.apgar@njit.edu
Chair, IRB
DD Planning Institute – CABSR
Campbell 330
New Jersey Institute of Technology
University Heights
Newark, NJ 07102-1982

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1. Project Title: Use of Virtual Reality in Studying Sensorimotor Influences on Motor Learning

2. List the names and status (faculty, student, etc.) of the persons conducting the research:

    a. Principal Investigator(s): Sergei Adamovich, Assistant Professor

    b. Other Members of Research Team: Katherine August, Ph.D. Candidate

    c. NJIT Faculty Advisor(s) if Student Project: Sergei Adamovich, Assistant Professor

3. Describe the objectives, methods and procedures of the research project. This summary will used to describe your project to the IRB. Use up to 2 pages, if necessary. You may also attach a copy of an abstract or full research proposal describing this work.

Background

In this study, we plan to investigate the role of visual feedback on sensorimotor learning. In particular, we will study whether viewing one's own hands (Poizner, 1987) will facilitate learning sign language hand gestures (Hamzei, 2002) or grasping or moving objects. Also in this study, we will conduct virtual environment experiments in the lab where the subject will watch a virtual agent (computer-generated human) in either first person perspective or third person perspective (Jackson, 2006). The agent will demonstrate American Sign Language gestures (Corina, 2006) accompanied with either text or picture descriptions (Kahn, 2004; Davachi, 2006) or grasping or moving objects. In addition, the effects of viewing one's own hands during the learning process will be compared with the effects of viewing computer-generated hand models actuated by one's own hands or learning while hands are concealed.

Although it has been shown that goal-oriented, intensive, prolonged, and rewarded practice is necessary to promote brain plasticity and reorganization according to the biological model, and that skill development (acquisition or adaptation) is a necessary component of the process, the specifics of the sensory stimulation have not been identified. Virtual environments, enabled through an ever increasing abundance of practical equipment presenting realistic yet synthetic experiences, allow for systematic manipulation of sensory stimuli and feedback that is not achievable through conventional means (Merians, 2006). There is little information on the relationship between various virtual sensory stimulations and neural processing. Moreover, little is known about the effect of these stimuli and the perception of self and other (agent or teacher) on motor learning (Decety, 2006). There is little information about how to exploit modalities available in virtual environments to access target neural networks for learning facilitation. Virtual environments enable observation of novel hand tasks for imitation and also enable the subject to observe his or her own hands producing the hand gestures or object grasp or movement in the lab, for fMRI, and TMS studies, while sensory stimulus and feedback may be modified to explore a variety of learning protocols. To further clarify the biological model of motor learning and to understand the role of virtual sensory stimulation and feedback which includes seeing one's own hand movement, it is important to study the underlying science, to develop functional brain mapping of motor learning in the virtual environment and correlate to the behavioral/phenomenological measurements and outcomes. In this way, one can predict the success of application and interface design for virtual environments that can accomplish desired learning conditions for specific goals and with target audiences. As an initial portion of this body of research, we have developed the Virtual Environment Sign Language Instruction (VESLI) System that can utilize biometric information to provide rehabilitation for hand skills and to provide a means of measuring behavioral aspects of learning. Visual and auditory sensory feedback, virtual agent, assistance, instruction, and measurement are controlled in a virtual reality environment. Visual and auditory language learning activates targeted neural networks (Newman-Norlund, 2006). Since we are concerned with American Sign Language and instruction with text or pictures, our subjects will be screened for their understanding of English. Our selected signs (gestures, grasps, or movements) will be described in Pictures and in Text and therefore, most signs will be nouns, verbs, adjectives, or adverbs. We will integrate a variety of hand-shapes from among the 17 used in American Sign Language (Costello, 2002) and grasping or moving typical objects.

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Experimental Design

Subjects will be informed about the nature and goals of the experiment. They will be instructed in their role and activities associated with their participation. They will be asked to provide informed consent in order to participate. The subjects will be able to withdraw from the experiment at any time.

Methods and Analysis may be found in Chapter 5 of this document.

4. List name and institutional affiliation of any research assistants, workers student that will be working on this project.

   Ms. August holds an MS in Computer Science and is currently a Ph.D. candidate in the Department of Biomedical Engineering, at New Jersey Institute of Technology.

5. If research assistants, workers, students will be working on the project describe their qualifications, special training and how they will be supervised.

Ms. August holds an MS in Computer Science, she is a former Member of the Technical Staff of Bell Laboratories, and is currently a Ph.D. candidate in the Department of Biomedical Engineering, at New Jersey Institute of Technology. She holds thirteen US Patents. She will be closely supervised by Dr. Adamovich. Ms. August and Dr. Adamovich have designed the study, and assembled the materials. Current team members have been trained in the study design and purpose of the study, and in the use of human subjects and safety. Dr. Adamovich has supervised the training of all members of the team. Any new members to join the team will be supervised by Dr. Adamovich who will assure that they have been trained in Human Subject Safety, that they have reviewed the experimental procedure and analysis methods, and that they are aware of the lab procedures, study equipment, materials, and procedures of the lab, and that they can find important contact information for other team members and safety personnel. Any new members of the team will be required to observe an experienced experimenter as a subject experiment is conducted. The new team member will be required to operate the study instruments while Dr. Adamovich observes. The new team member will learn to turn on all the lab equipment used in this experiment, will learn how to operate the equipment, and will learn how to turn the equipment off. The new team members will learn how to administer the experimental materials including the VESLI Learning Sessions and the VESLI Memory Sessions. New team members will be trained by Dr. Adamovich to ensure that they are aware of safety procedures in the lab.

6. What is the age of the subjects and how will they be recruited?

Subjects will be 18 and up. The experiment will be conducted with healthy controls. Healthy control subjects will be recruited through fliers on the campus at NJIT. (Please see Attached Recruitment Posters.) Subjects must be fluent in English, and may not be experienced with American Sign Language, BSL, Tic-Tac, or other formalized hand sign gesture systems. Subjects will be asked to identify the dominant hand. Subjects who are recruited to be healthy controls must be free of neurological diagnoses. If a subject is eliminated for some reason relating to the requirements of the experiment, the records will remain confidential.

7. Attendant risks: Indicate any physical, psychological, social or privacy risk or pain, which may be incurred by human subjects, or any drugs medical procedures that will be used. (This includes any request for the subjects to reveal any embarrassing, sensitive, or confidential information about themselves or others.) Also, indicate if any deception will be used, and if so, describe it in detail. Include your plans for debriefing.

The risks to the subjects are minimal. To reduce the potential for fatigue, each task will be broken into two portions with a break in the middle. After the subject participates in the study, he or she will be asked for input about how to improve the study experiment experience for the participant, and for general feedback about the study experience.

8. Evaluate the risks presented in 7.

a. Is it more that would normally be encountered in daily life?

The subject will be asked to sit in a chair, watch a virtual agent projected onto the two-way mirror, will be asked to move his or her hands to imitate the virtual agent demonstrating hand gestures from the American Sign Language dictionary. These hand gestures will be accompanied with text or picture definitions. The subjects will be wearing gloves containing bend sensors. The subject may experience occasional fatigue in their hand or arm. This will be addressed through frequent rest periods. These movements are not extraordinary. These hand gestures do not require movements that are different from those encountered in any everyday hand tasks or gestures.

b. Do your procedures follow established and accepted methods in your field?

The equipment that will be used in these experiments (cameras, electromagnetic motion trackers, sensor instrumented gloves, a two-way mirror, a virtual reality projector) is commercially designed for use in experiments with human subjects. They are electrically shielded and grounded, and subjects are at no risk of electrical shock. All equipment may only be connected to UL, TUV, CSA, or CE approved equipment.

Materials

Hardware includes: The CyberGlove ® and instrumentation unit (CGIU) including 22 sensor CyberGlove ® (CG2202) with 10' cable and 44 pin, high-density D-sub male connector, a CyberGlove ® Interface Unit (CGIU2402) including: a) CyberGlove 44 pin female high-density connector, b) on/off indicating LED on the front panel, c) DE-9 male serial port connector (RS232C), d) DE-9 female analog/sync port connector, e) 5 pin female DIN power plug, f) 8 position DIP switch, g) on/off switch and h) momentary reset switch on the back panel. In-line power supply with 5 pin male DIN connector and standard 3-prong AC plug. 10' serial cable to connect the CyberGlove to the host computer. Velcro ™ pad and nylon screws to mount a position sensor to the CyberGlove wristband. The CyberGlove is installed so that the power outlet into which it is plugged is near the equipment and is easily accessible. Instructions for donning the CyberGlove are available for experimenter and test participant to use before during and following the study experiment. The Flock of Birds position and orientation measurement system from Ascension Technology Corporation will be used with sensors attached one each to the wrist straps of the CyberGloves mentioned above, and configured as prescribed by the manufacturer in the user manual. The Flock of Birds (FOB) is a six degree-of freedom measuring device that can be configured to simultaneously track the position and orientation of up to thirty receivers by a transmitter. Each receiver is capable of making from 10 to 144 measurements per second of its position and orientation when the receiver is located within +/- 4 feet of its transmitter. An extended range transmitter increases this operating range to +/- 8 feet. The FOB determines position and orientation by transmitting a pulsed DC magnetic field that is simultaneously measured by all receivers in the flock. From the measured magnetic field characteristics, each receiver independently computes its position and orientation and makes this information available to the host computer. In this manner, the subject's hands and wrist orientation will be tracked and along with the finger positions captured by the CyberGlove, these bio-metrics will be captured to provide information about the subject responses, wrist position, and movements and will be used to drive the virtual reality animations. A work lamp with UL certification will be used. The lamp will be used to illuminate the subject's hands while he or she is practicing the hand gestures demonstrated by the virtual agent, which they may view on the special reflective mirror. This work lamp is connected to a UL approved serge-protection device. The virtual agent will be projected by a Texas Instruments DLP Cinema projector, connected to one of the lab's DELL computers, onto a special reflective virtual reality multi-media screen, then through a rear projection screen, and onto a special two-way mirror arranged in a custom-made presentation frame which is adjustable to accommodate varying protocol designs. The CyberGlove, Flock of Birds, DLP projector, and work lamp are only connected to UL, TUV, CSA, or CE approved equipment. The two-way mirror or mirrored glass is a technique that exploits the use of a darkened space and an enclosed well-lighted work-area separated by a pane of highly reflective glass that will serve in this experiment as the practice space where the subject will rehearse the hand gestures. This special glass is coated with a very thin layer of metal to enhance its reflective properties. When the hands of the subject are brightly lighted using the work lamp, they may be viewed easily through the special glass. Simultaneously, the animated virtual agent and other images may be projected onto the glass and may be easily viewed by the subject. When the hands of the subject are in darkness, they may not easily be viewed through this special glass, yet the animated virtual agent and other images may still be projected onto and viewed on the surface of the special glass. The images projected onto the glass serve to increase the illusion and the subject's hand will be much more difficult to view during the Hidden condition. Hand gestures are inspired by illustrations and descriptions available in the Random House Webster's Concise American Sign Language Dictionary with Elaine Costello, Ph.D., founder of the Gallaudet University Press and author of Signing. Virtual Reality animations are produced using Jack and a suite of authoring tools developed by NJIT's Dr. Richard Foulds and his students. Jack is a software package developed at the Center for Human Modeling and Simulation and is available from UGS. Jack provides a 3D interactive environment for controlling articulated figures. It features a detailed human model and includes realistic behavioral controls, anthropometric scaling, task animation and evaluation systems, view analysis, automatic reach and grasp, collision detection and avoidance, and many other useful tools for a wide range of applications. Inverse Kinematics using Analytical Methods (IKAN) is a complete set of inverse kinematics algorithms suitable for an anthropomorphic arm or leg. IKAN uses a combination of analytic and numerical methods to solve generalized inverse kinematics problems including position, orientation, and aiming constraints. The combination of analytic and numerical methods results in faster and more reliable algorithms than conventional inverse Jacobian and optimization based techniques. IKAN allows the user to interactively explore all possible solutions using an intuitive set of parameters that define the redundancy of the system. Protocol procedures follow standard learning-memory protocols resembling those found in current literature. Our procedures follow established and accepted methods in the field of sensorimotor rehabilitation. For a background or relevant details, please see the following:

9. How will the risk be kept at a minimum? (E.g. describe how the procedures reflect respect for privacy, feeling, and dignity of subject and avoid unwarranted invasion of privacy or disregard anonymity in any way.) Also, if subjects will be asked to reveal any embarrassing, sensitive, or confidential information, how will confidentiality of the data be insured? Also include your pans for debriefing. If subjects will be placed under any physical risk, describe the appropriate medical support procedures.

Confidentiality will be insured by keeping the data in a locked file cabinet in the laboratory, Room 655 in Fenster Hall. Data should be kept in a locked file cabinet. Since NJIT is not certified under HIPPA, subject data will not be transmitted electronically from NJIT to any individual or institution. Furthermore, subject confidentiality will be strictly maintained. Research data maintained at NJIT on subjects will not contain any personal identifiers such as name, age, gender, social security number, address, zip code. Subject names will never be used in reports; rather subjects will be assigned initials or numbers as identifiers.

Only healthy subjects will be recruited for this study.

If there is any need of immediate medical assistance, for any reason, the experimenter will call 911 and ask for emergency transportation to get to the local hospital emergency room **(St. Michael's Medical Center ER:** 973-877-5525**)**. Every student in the lab will be informed of this procedure. Special attention will be given to international students who might not be familiar with the emergency phone service. A message detailing this procedure will be posted on the wall of the experimental room. All experimenters will be trained on this study protocol, on all the equipment involved in the study, and on safety of human subjects before becoming involved with this study.

10. Describe the benefits to be derived from this research, both by the subject and by the scientific community (this is especially important if research involves children).

In this case, the subjects may benefit from learning some gestures associated with the American Sign Language. For the scientific community: better understanding of the effect of viewing one's hand (visuo-sensory stimulus) during practice on learning hand gestures, better understanding of the effect of viewing a virtual hand actuated by one's own hand during practice (visual-feedback mechanisms) on learning hand gestures, and better understanding of the effect of viewing first-person and third-person virtual agents (observation with intent to imitate) on learning hand gestures. If a person with a paretic (partial motor paralysis) hand cannot see his or her own hand move during practice, virtual reality may provide that sensory input during practice. We wish to understand if a subject with a paretic hand can learn a hand gesture better when watching a hand positioned as if it is his or her own hand while he or she practices the gesture, thereby gaining the value of visual sensory input provided by the virtual reality system. We also endeavor to understand if the position of the "teacher", which is presented herein as first-person or third-person perspective for observation and imitation, influences the success of learning the hand gesture, perhaps from the underlying mechanisms of action observation and execution networks including "mirror neurons". Since the subject and also real-world stroke subjects may not be able to voluntarily produce the sign, we will ask our subjects to identify the meaning from two choices. We believe the process of making such a selection necessarily actuates the neural network engaging Broca's Area, an area common to premotor regions, and is a likely brain region target, and as such may therefore be beneficial to plasticity-based rehabilitation for paretic persons. We believe the scientific community will benefit from findings of this study. It has been determined that stroke patients who are successful in moving have recruitment of secondary motor regions including premotor regions during movement output. Outcomes of this study represent significant new understanding of sensory stimulation on hand gesture learning in the healthy subject, and correlate performance assessment using rehabilitation tasks that target specific neural networks demonstrated in functional imaging studies, therefore performance using this paradigm may be observed and measured in a simulated rehabilitation environment. The potential benefits are large and include development of new methods for rehabilitating individuals after stroke or other forms of brain injury when they may not be capable of voluntary movement, and may increase our understanding of motor and cognitive rehabilitation and the relationship between cognitive and motor tasks. Thus, the risk/benefit ration is extremely low.

11. Describe the means through which human subjects will be informed of their right to participate, not to participate, or withdraw at any time. Indicate whether subjects will be adequately informed about the procedures of the experiment so that they can make an informed decision on whether or not to participate.

    All procedures of the experiment will be documented and discussed with the subjects so that they may make an informed decision about whether or not to participate. The subjects will be provided with a summary description of the study design. The consent form will be reviewed with each subject. The subject will be reminded that at any time, he or she may choose not to participate and may also withdraw at any time.

12. Complete the attached copy of the Consent Form and the Institutional Review Board will make a determination if your subjects will be at risk. This Consent Form must include the following five pieces of information: (1) The purpose of the research, (2) the procedures involved in the work, (3) the potential risk of participating, (4) the benefits of the research, (5) that the subjects are free to withdraw from the research at any time with no adverse consequences.

13. Furnish copies of questionnaires, interview formats, testing instruments or other documents to carry out the research. If questionnaires are not complete pleas submit an outline of the questions to be used. You will have to submit the completed questionnaire to the Committee before the research can begin.

14. If the subjects will be minor children, complete Consent Form as prescribed in paragraph 12 for signature by parent or guardian. If the project is approved (regardless of the Board's determination concerning risk), it will be necessary that a Consent Form be secured for every minor child.

15. Attach copy of permission of facility to conduct the proposed research (if other that NJIT).

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