Motor imagery retraining after stroke with virtual hands: An immersive sensorimotor rhythm-based brain-computer interface

A Thesis
SUBMITTED TO THE FACULTY OF
UNIVERSITY OF MINNESOTA
BY

Alexander James Doud

IN PARTIAL FULFILLMENT OF THE REQUIREMENTS
FOR THE DEGREE OF MASTER OF SCIENCE

Bin He

June 2013

Acknowledgements

I would like to thank Dr. Diane M. Chappuis for assistance in patient selection and recruitment, Karl Lafleur, Arman Shahriar, and Emal Alwis for assistance with data collection, and Eitan Rogin for useful discussions on the implementation of the stimulus presentation in Java. I would like to give special thanks to Kaitlin Cassady for in depth discussion, ideation, as well as assistance with data collection, data analysis and figure production. I give particular thanks to my advising committee members, Matt Johnson, my clinical mentor Dr. Andrew Grande, and Dr. Bin He, my academic mentor and role model in scientific thinking of seven years. I thank my senior colleagues Han Yuan, Chris Wilke, Zhongming Liu, my contemporary colleagues Keith Jamison, Nessa Johnson, Huishi Zhang, Abhrajeet Roy and my friends at the Santa Lucia Neurological Hospital, Fabio Aloise, Fabrizio deVico Fallani, Donatella Mattia, and Febo Cincotti. I thank my benefactor, Dr. Scott Augustine, whose generous contributions have laid a strong foundation for the combined MD/MS program through which this work was enabled. I would also thank the kindness and dedication of my superb patient cohort, from whom I learned much more than I can summarize in the findings of this study.

This work was supported in part by NSF DGE-1069104 and NSF CBET-0933067, and ONR N000141110690.

Dedication

I dedicate this work to my father, whose tireless dedication to the pursuit of excellence in his own life, has set the stage for me to realize excellence in my own, to my mother who taught me to push for the road less traveled by, to my wife Natalie, who has joined me on that non-traditional path in the pursuit of a better medicine, to my brother Sam who I hope may follow his dreams in his own way, and to my dear friend Elissa who has stood beside me in the transition from medical school to graduate school and back again.

Table of Contents

List of Tables

List of Figures

Introduction:

Stroke is a prolonged interruption of the supply of blood to the brain, which causes the neural tissue to become starved of oxygen, and ultimately leads to neuronal death. In the United States, stroke claims the lives of approximately 795,000 people each year, and leaves over 7 million individuals with lasting deficits that directly impact the patient's quality of life. In terms of the economic impact, health care costs and indirect factors that are related to lost productivity, as well as the cost incurred by the chronic management of patients by caretakers and loved ones, stroke cost the United States economy 73.7 billion dollars in 2010 (stroke.org).

Both Cortical and basal ganglia stroke can lead to upper-limb hemiparesis, where the loss of ability to control the extremities is a significant contributor to prolonged morbidity and decreased quality of life. Patients spend months in occupational therapy, where the goal of treatment is to increase patient autonomy by restoring some of the basic functions of daily living.

Current rehabilitative practices focus on emphasizing movement of the deficit limb, while inhibiting output from the non-affected side. Recent characterization of the neuroplastic changes that occurs during stroke recovery has shown that, in some cases, maladaptive change may arise through the unchaperoned healing of the patient's brain (Takeuchi 2012). In much the same way that a child with amblyopia wears a patch over the good eye to strengthen the weaker one, patients that undergo constraint induced movement therapy may benefit from physically inhibiting the unaffected limb through casting it in plaster. The patient practices movements with the deficit limb, or is instructed to imagine movement of the affected limb while a therapist moves the limb through a series of actions. The coordination of the patient's mental state, and the proprioceptive feedback that is associated with the active movement of the limb by the therapist has been shown to have benefits in promoting motor recovery (Schaechter 2004, Duncan 1997). The difficulty in this approach arises in ensuring the patient's compliance in properly imagining use of the affected limb. In the situation of patients with receptive or expressive aphasias, communication with the therapist may be difficult for even simple instructions. The abstract concept of imagining the use of a limb can be difficult to communicate in these instances, creating a bottleneck in the efficacy of these therapies.

The human mirror neuron system is unparalleled in nature in its capacity to allow us to emulate an observed action. The capacity of primates to imitate the actions of successful peers in tasks like tool making, hunting and social interaction has been postulated by some evolutionary researchers to be at the heart of the incredible success of the species (Greene 2012). Mirror neurons are populations of neurons that fire when an action is observed, especially a motor action by another living creature. It has been postulated that these neurons may have arisen evolutionarily due to the benefit imparted in predicting and understanding the actions of other species to facilitate hunting, but have likely extended in capacity to play a role in human social interactions (Heyes 2010). Being able to imagine the pain of an injured limb, or sense sadness in another person are all likely primate characteristics arising from the sophisticated development of the mirror neuron system.

In 1996, Vilayanur Ramachandran pioneered an innovative technique that leveraged this powerful evolutionary trait in the use of mirror box therapy. Patients suffering from phantom limb pain after amputation were able to reduce or eliminate these sensations through the observation of a simple illusion. The patient's intact limb was presented to him or her as a reverse image, seen in a mirror and presented such that it occupied the space that the missing limb once inhabited (Ramachandran 1996). Through the viewing of the mirror image, patients were able to down regulate the perception of the phantom pain (Greene 2012). It may be that the induction of the mirror neuron system and a neuroplastic modulation of the phantom pain pathways play a significant role in the efficacy of this therapy. What is clear, however, is simply presenting a video does not have the same efficacy in pain reduction. This points to an important role of volitionally controlled feedback in the therapeutic benefits of mirror box therapy. While this kind of approach has been identified as having potential applications in the rehabilitation of stroke (Mei Toh 2012, Nojima 2012), the intrinsic setups of these systems in that application suffers from some inherent flaws. In traditional mirror therapy, the patient is asked to move the healthy limb, potentially invoking a down regulation of the activity of the contralateral affected side. While an appropriate strategy for pain reduction, in the application to stroke, similar down regulation of the affected side would result in a reduction of function. Instead, a means of presenting the same kind of intention mediated feedback in the absence of contralesional cortical activation would present the ideal conditions for recovery of function.

Brain-computer interface technologies have been identified as powerful tools in replacement and rehabilitation therapies for stroke (Soekadar 2011, Mattia 2012). While until recently these systems primarily found novel application in healthy user populations (Doud 2011, Royer 2010, Yuan 2008), in a recently published, large clinical assessment of the efficacy of brain-computer interface, daily use of the technology was shown to promote improvement in the Fugler-Meyer motor function scores when compared to controls with randomly moved orthosis robotics (Ramos-Murguialday 2013). As was seen in mirror box therapy research, in this application ensuring that the user is actively participating in the generation of relevant motor imagery while undergoing movement of the affected limb by a therapist or orthotic robot is important for generating the effects. While such findings are a huge step forward in the use of brain-computer interface in the rehabilitation of stroke, the robotic systems that are proposed for use in the study may prove to be prohibitively expensive, need supervision for safe use, and require expert maintenance for optimal performance. Such limitations undoubtedly create a barrier to access for many lower-income patients. Considering these factors, a system that optimally leveraged the therapeutic benefits of both mirror-box therapy and brain-computer interface technology could be a powerful tool in motor rehabilitation following stroke. Efforts to provide such a solution at low cost to patients would mean that this approach could be accessible to patients with a wide range of socioeconomic backgrounds. Producing a prototype system that meets these specifications is the major motivation of this work.

Here we present a tabletop, immersive 3D environment for motor imagery training in stroke. While remaining perfectly still, the subjects could control three-dimensional photorealistic hands positioned to create the illusion that the subject's own hands were moving. Analogous to mirror box feedback in the illusory effect generated for the subject, this approach did not require the activation of the subject's muscles, but only that the subject focus on the thought of moving the arm or hand. While the patients did not receive the proprioceptive feedback present in an orthosis system, the strong visual illusion under direct control by the user's thoughts may prove to be an efficacious and cost effective solution for the future of motor rehabilitation in stroke. Using the system provided, the subject's own functional hand may be "mirrored" on the deficit side to create the illusion of two functional limbs under direct cortical control. The implications of this training are explored in 6 patients who had suffered cortical or basal ganglia stroke. Using the system described below, the subject's were able to achieve control accuracies as high as 87.4% (Cursor) or 81% (VR) and showed progression of skill in as little as three, two-hour experimental sessions.

Materials and Methods:

Experimental Design:

The study cohort consisted of 6 subjects with a medical history significant for cortical or basal ganglia stroke, and 4 subjects of similar age to serve as healthy controls. Subjects performed 3 experimental sessions of two hours duration during which approximately 10, 3-minute runs were performed. The exact number of runs and sessions varied depending on subject availability. At the beginning of each experimental session, subjects performed two clinical assessments of motor ability: the Action Research Arm Test (ARAT), and the Box and Block Test (BBT). The performance in these tests was used to establish a baseline of motor function in each subject, and to allow for monitoring in changes in motor function over the course of the study. Both tests were selected for their ability to objectively discriminate between different degrees of motor function. These assessments were performed while the subject was seated at a comfortable chair, in front of a table containing each test's materials.

After completing the two motor assessment tests for each session, subjects participated in up to 10 trials of three minutes duration during which time one of two motor control tasks were performed. In the first task, the subjects controlled a circular cursor that moved to the left and right side of a computer screen. For three minutes, targets on the left or right side were presented to the subject at random. The subject was instructed to use motor imagery of the hands to move the cursor to hit the presented target. Each trial, during which a subject was presented with a target, lasted no more than six seconds total, with the potential for a trial to end earlier should the target be hit before the six-second time limit. In addition to the visual presentation of the target, each subject received auditory instruction as to the position of the target.

In the second brain-computer interface task, the subject wore a pair of anaglyph 3D goggles and viewed a virtual 3D environment. The subjects sat in front of the stimulation presentation box, as shown in figure 1.

Figure 1: ***Experimental apparatus for the presentation of the 3D stimulus. The subjects were presented with either the standard 1D cursor task or the analogous movement of the 3D hands. Subjects wore anaglyph 3D goggles when presented with the VR task.***

The box was constructed such that its top is angled toward the subjects with a computer monitor built into the surface. In the forward-facing surface of the box are two holes to accommodate the subjects' arms. In this way, the subject could position the arms behind the screen. The task begins by showing the virtual interior of the box. Inside sit two virtual cups, one holding coffee and the other water.

Performing motor imagery caused a photorealistic arm to reach out, grasp, and lift the cup on the imagined side as shown in figure 2. During the 3-minute task, each trial consisted of the subject receiving auditory instruction to reach and grasp either the left or right cup. In each experimental session, the subjects performed up to five, three-minute experimental runs of each task with the order of tasks randomized via coin flip.

Study Cohort

The stroke cohort included 1 female and 5 male patients with relevant past history of cortical or basal ganglia stroke and ranged in age from 47 to 71. Subjects had experienced at least partial hemiparesis as a result of the episode of stroke, implicating motor pathway involvement in the pathogenesis of their condition. Patients were recruited from the practices of Dr. Andrew Grande (University of Minnesota Neurosurgery Clinic) and Dr. Diane Shipwice (Sister Kenny Rehabilitation Institute). After an initial screening with the physicians, all patients were familiarized by a member of the research team with the study protocol over the phone. The patient's had undergone physical rehabilitation therapy with some patients continuing participation in therapeutic sessions during the course of the study. Among the types of therapy patient's reported having participated were occupational therapy, constraint induced movement therapy, elastic band therapy, and in the case of one patient, botox therapy for spasticity relief. Subjects that served as healthy controls from the general population were approximately age matched to the study cohort. The control cohort included 2 female and 2 male subjects. Prior to conducting the study, a change in protocol request was submitted to the U of MN IRB to expand current BCI efforts to a stroke population.

Subject	Age	Gender	Time from Stroke (Months)	Lesion Hemisphere
1	54	F	7 mo, 29d	Right
2	66	M	5 mo, 21d	Right
3	60	M	3-4 mo	Left*
4	47	M	7 mo, 1d	Left*
5	71	M	1 yr, 29d	Right
6	71	M	7 mo, 5d	Right

Table 1: ***A summary the demographic and clinical information for each of the members of the experimental cohort is presented. Asterisk's denote patient's for whom the lesioned hemisphere was also the dominant hand.***

Data Acquisition:

Participants were seated in a comfortable, padded chair that was fitted with armrests, and with seat height adjusted to each participant's preference. An EEG cap with 64 sensing electrodes was fitted to the subject's head with electrodes positioned according to the 10-20 international system. Data were filtered from DC-200Hz and were acquired at a sampling rate of 1000Hz using a Neuroscan Synamps 2 amplifier. During the experimental recordings, subjects placed their hands into the forward facing holes, as shown in Figure 1. Data were then ported to the BCI2000 software platform with no spatial filtering. Subjects attended three experimental sessions, each consisting of ten, three-minute experimental trials. Trials were randomized via coin flip such that approximately 50% of recorded trials were performed using the virtual reality hands feedback and 50% of trials were performed using the traditional 1D cursor task, a task that is widely available as part of the BCI2000 distribution. In the traditional 1D cursor task, an autoregressive filter outputs the time-varying amplitude of a chosen frequency component of a given electrode's signal. The cursor's position is a weighted difference of the 12Hz component of the user's C4 and C3 electrodes. In the presented protocol, the initial system settings used the C4 and C3 electrodes weighted at +1 and -1 respectively. Using the offline analysis toolbox provided with the BCI2000 distribution, more complex subject specific electrodes and weightings could be chosen as training progressed. The virtual reality hands environment was implemented as a Java application that operated with the traditional cursor task active in the background. Data were sent from the BCI2000 cursor task to the virtual hands program every 30ms over the UDP data transmission protocol in order to update the position of the virtual hands, mapping the position of the hands to the position of the cursor in 1D space.

Virtual Reality Hands Task

The implementation of an online, immersive 3D feedback system that displays photorealistic human arms and hands that are positioned in alignment with the subject's actual arms and hands is an important, novel component of this study. Participants viewed the stimulus while seated in a comfortable chair, and were given a pair of 3D anaglyph goggles to use during the stimulus presentation. Although in reality only viewing an angled screen that was set into the top of the stimulus box, to the subjects it appeared as though they were peering "through" the top of the stimulus presentation box and viewing the inside. In addition, subjects were presented with a pair of hands that moved inside the box in coordination with their production of motor imaginations as shown in figure 2.

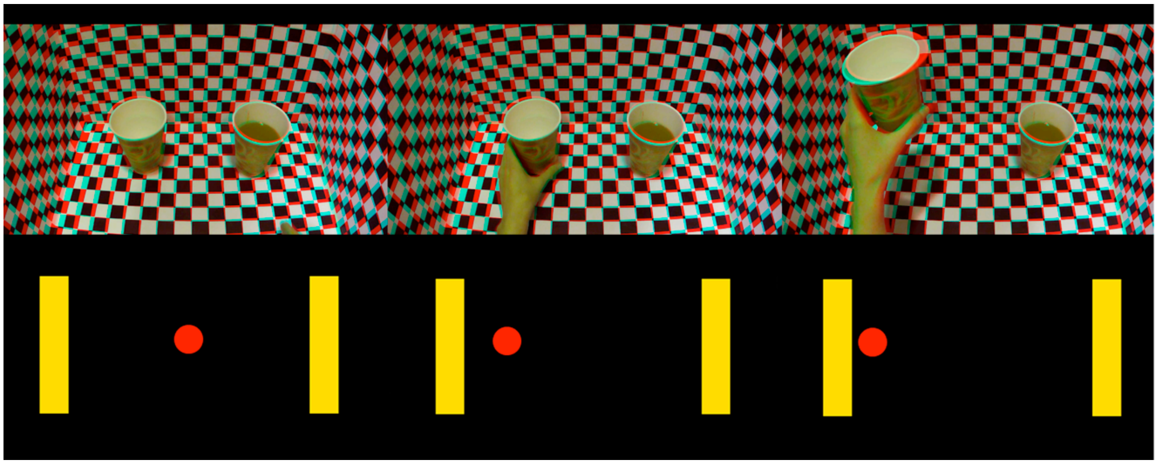


Figure 2: ***The 3D stimulus presented to the subjects simulated the movement of hands. The movement of the virtual hands coincided with the position of a traditional BCI cursor task. In this setup, the figure shows how cursor movement to the left of the screen coincides with a left hand reaching out to grasp and lift a cup.***

While previous studies and systems have offered 3D avatar hands as feedback for brain-computer interface control (Mattia 2012), the addition of photorealism and the positioning of the subject’s actual hands to align with the avatar hands introduces additional elements from the fundamentals of a mirror neuron system (MNS). Subjects reported that it was easy to imagine that the stimulus hands and arms were in fact their own, and reported an unusual, disconnected sensation when the virtual arms moved in the direction that was opposite of the imagination. The importance of embodiment in BCI avatar systems has been emphasized in past literature that is aimed at higher dimensional limb control using BCI (Velliste 2008). This virtual reality stimulus and instructions regarding its operation were more readily understood when explained to the older patients in the study, in comparison to the more abstract instructions related to the use of the traditional 1D cursor task.

Results

The Action Research Arm Test (ARAT), and the Box-Block test (BBT) were chosen to assess the degree of motor deficit in each patient that was enrolled in the study, and assess the stability of the deficit during the experimentation period. These evaluations were chosen because of their comparable objectivity and ease of implementation within the laboratory setting. The ARAT assesses subjects in four broad categories of motor action, and has varying levels of difficulty based on subject performance. The motor competencies that were tested include grasp, grip, pinch, and gross movement. The Box and Block exam is another clinical test of motor function chosen for its simplicity of application, high resolution of objective criteria, and familiarity to the patient population.

In the Box and Block exam, subject move as many colored cubes from the lid of one side of an open box, across an elevated barrier and over to the other side. No significant changes in ARAT. Modest improvement was seen with the BBT in one subject. However, the performance on such metrics informed the research team of the degree of deficit severity for each of the subjects. Subjects that participated in the study were assessed on the grounds of control accuracy, speed and fluidity when using the brain-computer interface. These behavioral outcomes are summarized in figure 3 for the three experimental sessions that each subject completed. The metrics have been presented for both the subject's deficit and non-deficit side and have been broken out by experimental task (virtual reality v.s. traditional cursor control). Table 2 summarizes the overall group performance in comparison to the control cohort.

Accuracy of control was calculated as the percent valid correct metric (PVC) as previously reported, and was computed as the number of correct target acquisitions divided by the number of attempts that ended in either a success or failure (Doud 2011). The PVC calculation is straightforward and is outlined in equation 1.

$$PVC = \frac{Correct\ Attempts}{Total\ Trials - Incomplete\ Trials}$$

In this metric, not making a decision in a given target presentation trial does not contribute to the overall score, but an incorrect decision is penalized. Under these criteria, subjects varied considerably in performance. Figure 3 shows the progression in the PVC accuracy metric over three experimental sessions. PVC can be directly calculated for both the virtual reality, and traditional cursor tasks since both tasks retain the same underlying timing and rules. As a group, only the VR task on the side of the affected hand showed improvement in PVC accuracy over the three experimental trials.

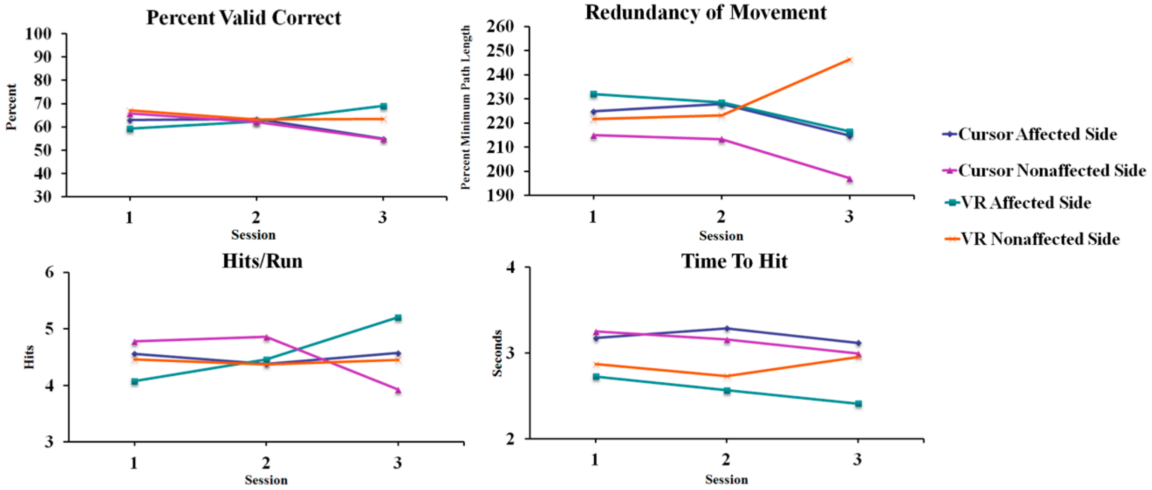


Figure 3: ***Behavioral outcomes data for cursor and virtual reality control on subject's deficit and non-deficit sides.***

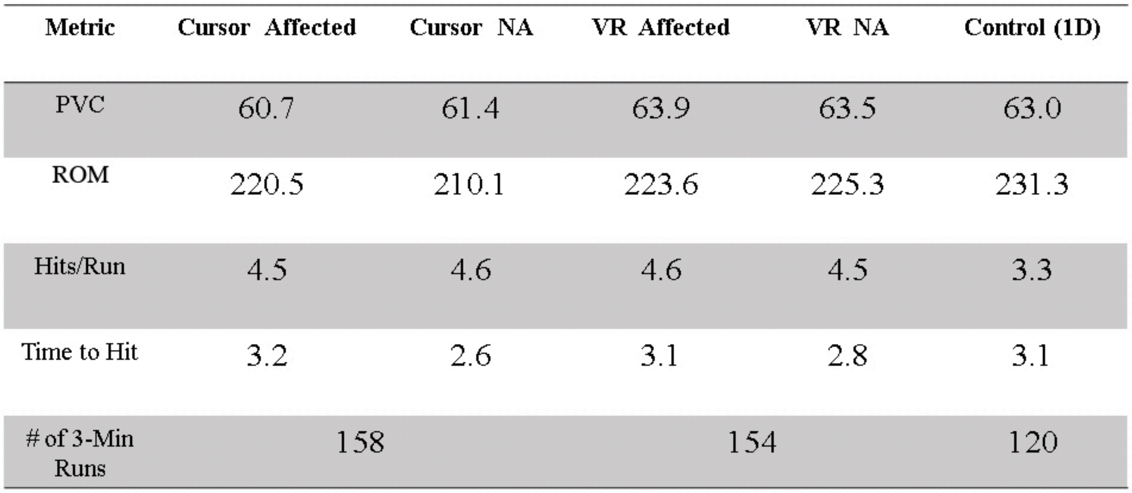
In performance of standardized clinical examinations of motor function such as the ARAT and box block test, the fluidity with which a motor action can be performed is a marker of the degree of disease severity. It is of interest whether the impairment of fluidity of movement that is seen in the context of stroke carries through to the control of a brain-computer interface. Fluidity of control was calculated as the distance traveled toward the desired target, divided by the minimum travel distance required to successfully reach the target as shown in equation 2. This quantity may be referred to as redundancy of movement (ROM) and is expressed as follows.

$$ROM = 100 * \frac{\sum_{i=0}^{n} di}{M}$$

In this equation, n is the number of programmatic steps during a given experimental trial. The numerator of this equation is the sum of all position changes that the cursor makes in the direction of the desired target. M is the minimum distance required to successfully hit the target, supposing a direct path is followed. In this way, ROM represents a percentage of the minimum necessary distance for target acquisition, and has a minimum value of 100 percent for a target acquisition where the cursor moved only towards the desired target with no redundant displacement.

Thus highly oscillatory paths to the target would report high ROM, while a direct path, even achieved over a longer time period would produce a low ROM score. Only modest differences were seen between the stroke population and the control group for the redundancy of movement metric. The largest difference was seen between the non-affected side in the virtual reality task and the non-affected side in the cursor task for the patient population. Subjects' non-affected hand acquired targets with an average ROM of 210.1% using standard cursor control, while achieving an ROM of 225.3% when using the modified virtual reality task. The method of stimulus presentation was the only factor that was altered between these two conditions.

Speed of control may be easily assessed in the presented paradigm through the use of a hits-per-minute metric. In this case, we report the number of successfully implemented hits and divide by the total trial time. Subjects in both the control and patient populations scored comparable hits-per-minute, with around 1 hit extra scored per minute by the patient population. Little to no difference was seen in speed of control whether the target was presented on the patient's affected or non-affected side (+- .1 hit per minute). Table 2 summarizes the experimental results in all behavioral metrics for the population and compares it to the control group in these metrics of interest.



Metric	Cursor Affected	Cursor NA	VR Affected	VR NA	Control (1D)
PVC	60.7	61.4	63.9	63.5	63.0
ROM	220.5	210.1	223.6	225.3	231.3
Hits/Run	4.5	4.6	4.6	4.5	3.3
Time to Hit	3.2	2.6	3.1	2.8	3.1
# of 3-Min Runs	158		154		120

Table 2: ***Summary of experimental results for the patient cohort as compared to the control group. NA is the patient's non-affected side and is presented for both the VR and the Cursor Task, together with the affected side.***

Time Frequency Analysis

The Morlet wavelet technique is a well-characterized method of investigating the frequency components of a signal while retaining temporal information (Büssow 2007). In contrast to the fast Fourier transform technique (FFT), the time course over which the signal propagates is retained in the Morlet treatment. Furthermore, the resulting output of multiple such time courses may be averaged to produce a time-dependent characteristic response for a signal or system of interest. While a comprehensive treatment of the Morlet algorithm and the nuances of this analysis are beyond the scope of this investigation, basic Morlet analysis is informative in assessing the function of the BCI when used by healthy users or those with neurological deficit. Differences between the cursor-based feedback, should they exist, may also be identified through this analysis technique. Before becoming immersed in a description of the TFR findings, let us review the expectations for motor imagery-mediated activation of a brain computer interface.

Using electrodes C3 and C4, a motor imagination of the left hand should cause desynchronization of the contralateral hemisphere, and will be reflected in a drop in amplitude in the C4 electrode. To accompany this, an increased synchronization of the C3 electrode will appear. This phenomena is known as ERD/ERS, the event related synchronization and event related desynchronization accompanying motor imagery. A right imagination could be expected to produce the opposite result. In a patient with stroke however, depending on the location and severity of the lesion a similar left imagination may have various outcomes. In the event that viable neural tissue is missing below the sensor, no meaningful SMR desynchronization or contralateral ERS will be expected. In the event that some viable tissue remains, desynchronization may occur, but due to lost connectivity from the lesion, the accompanying contralateral ERS may be diminished or fail to occur entirely. Table 3 summarizes the expected outcomes in healthy and stroke subject groups. It is possible that the contralateral ERS during motor imagery is partially effected via transmission through the basal ganglia corticospinal pathways before being relayed back to the contralateral cortex. For this reason, a subject with basal ganglia stroke could lose the capacity to affect ERS.

	Control Imagine Left	Stroke (Left) **Imagine Left**	Control **Imagine Right**	Stroke (Left) **Imagine Right**
C3	↑↑	↓ or no change	↓↓	↓ or no change
C4	↓↓	↑ or no change	↑↑	↑↑ or ↑

Table 3: ***Possible anticipated outcomes for ERD/ERS modulation for control and patient subjects.***

These expectations were tested against the averaged time-frequency reconstructions from two subjects training periods. One basal ganglia stroke patient and one age and gender matched control were used to perform a comparative analysis and identify the means by which each user become competent in the brain computer interface. Figure 4 shows the initial 25% and the final 25% of each subjects training. Each subplot is the average of 80 or more independent trials. At time 0 the target was presented to the subject and the motor imagery period begun. This period lasted a maximum of 6 seconds. Trials were selected on the grounds that they last at least 4 seconds. Raw data were detrended and a notch filter was implemented to remove a significant AC artifact prior to Morlet processing.

Figure 4 shows the neural signal during right and left imagination periods for the standard cursor task. The control subject shows very little modulation of the C3 electrode, which is compensated for by the control the subject was able to exert over the β band. Late in training, this subject's control signal was changed to include C4 18Hz weighted at +1. This proved to be an effective control strategy and reflects the importance of control signal optimization in achieving good control results.

Using the cursor task, the representative basal ganglia stroke (left deficit) subject shows no modulation of C3 or C4 during the Left imagination state. This was one of the possible expected outcomes presented in Table 3 for a patient with a left deficit. During the right imagination state, C4 does seem to exhibit ERS. This could be caused by the retained functionality of the engaged right side, which, at least in the first 25% training period, appeared to respond to suppression of mu in the C3 electrode.

In contrast to the cursor task, when the subject was using the VR task, modest C4 suppression is seen in figure 5 in the last 25% of left imagination training sessions. In both left and right imagination tasks, the stroke subject modulated signal in the high mu range, indicative of a particularly focal or specific motor action. This effect of inducing a more focal signal can be seen in the topographical spatial representation given in figure 6.

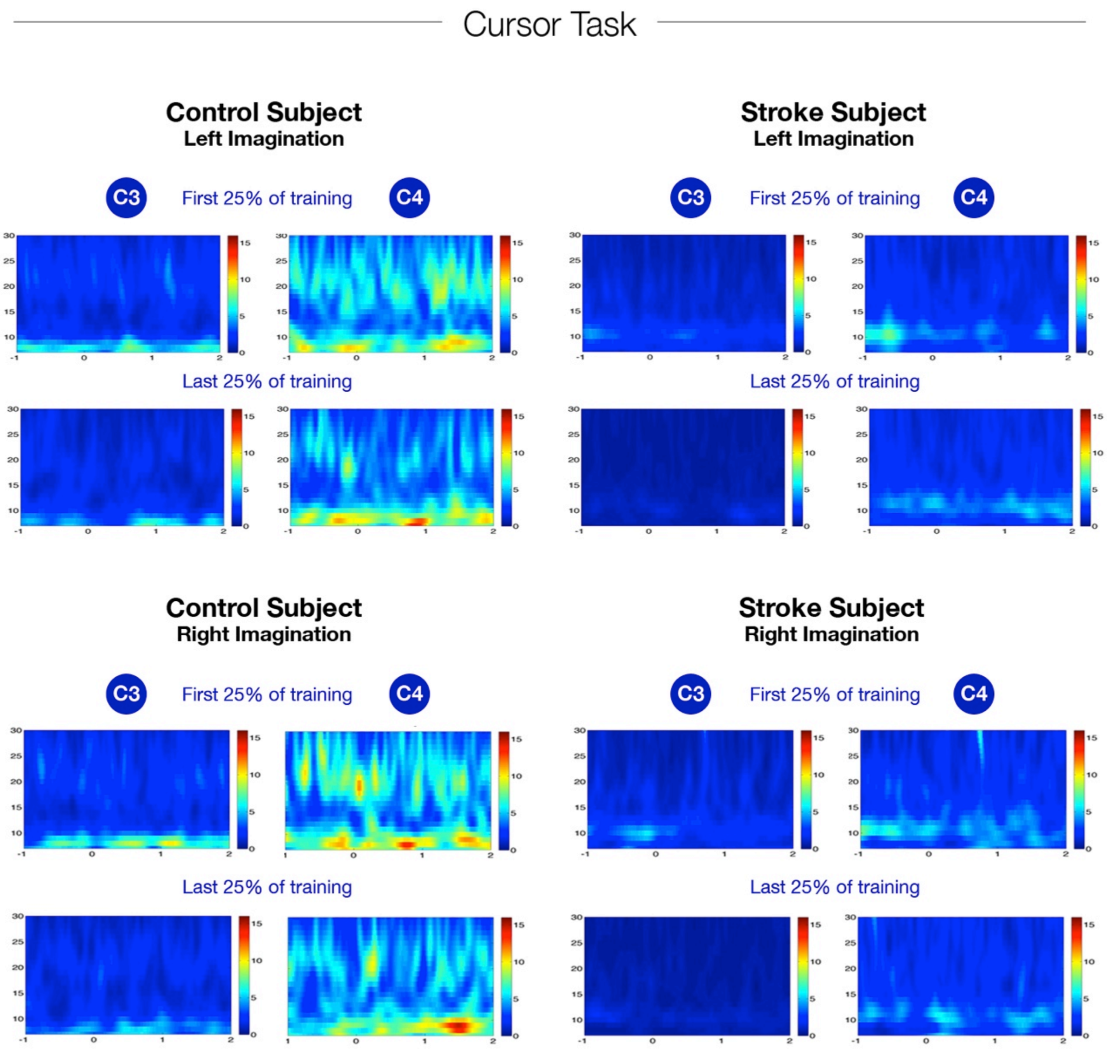


Figure 4: ***β modulation of the C4 electrode allows this control subject to successfully control the system. The stroke patient does not show much capacity to modulate activity during the left state, but can produce temporally relevant desynchronization when imagining right (non-lesion side).***

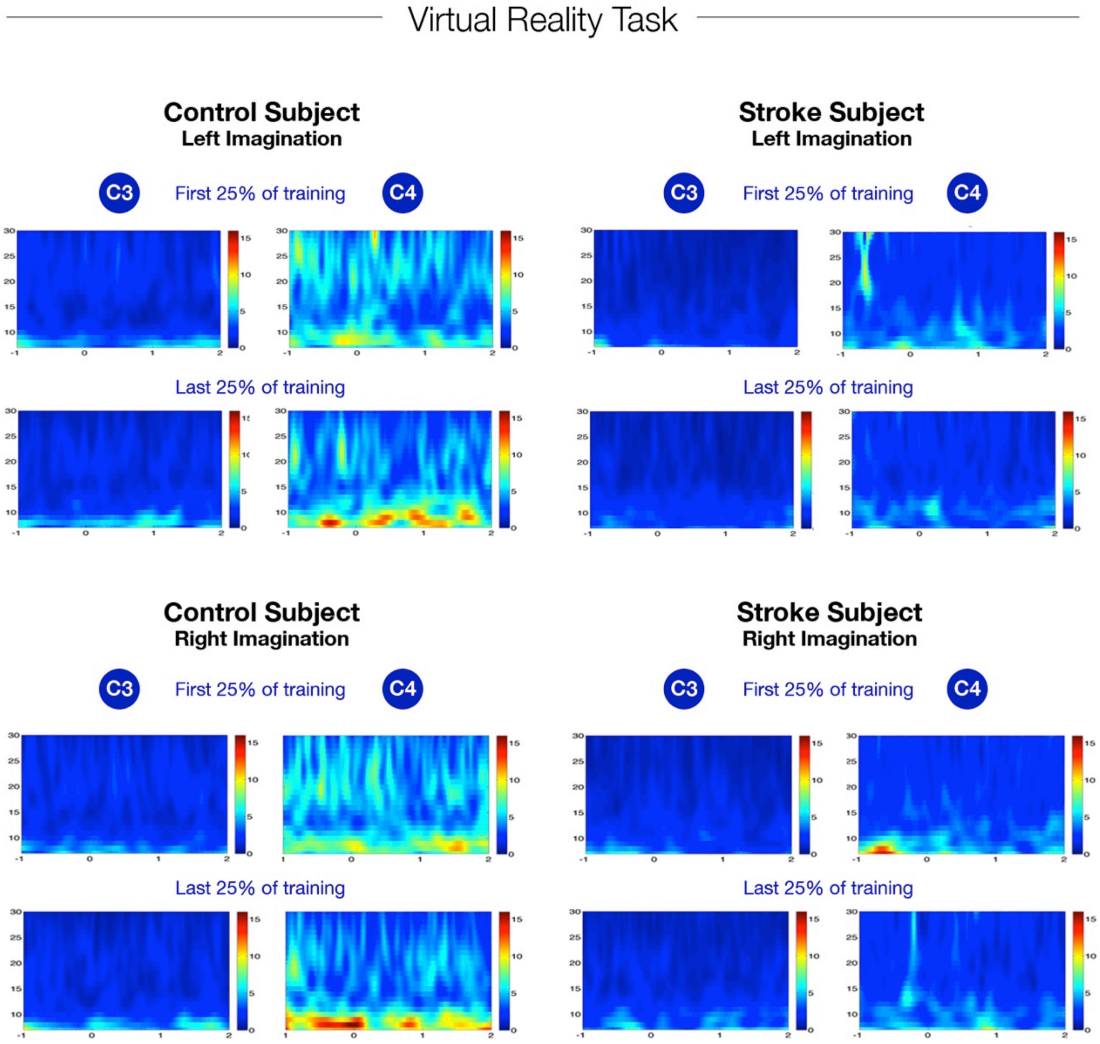


Figure 5: ***The virtual reality task showed similar activation patterns to those of the traditional cursor task. Of note is the expanded mu range activity for the basal ganglia stroke subject. As before, modulation of β allowed the control subject to successfully control the system with only the C4 electrode.***

When considering the differences arising in the signal from the stimulus, we would anticipate a more robust neural activation when presented with the virtual reality hands task. This expectation can be explained by the following considerations. In the standard cursor task, the motor imagery that is produced by the subject is entirely internally driven. The subject imagines a motor activity that exists only in his or her own mind. The motor imagery is then interpreted by the subject, such that it corresponds the task at hand, in many cases, the movement of a cursor or avatar in proportion to the magnitude of imagination. Even for a trained subject, fixating on a single imagination or motor task can be challenging, and the novelty of a given imagination may wear off. When we consider in contrast the activation elicited by viewing a virtual hand under neural control, a type of feedback reinforcement can be anticipated. In this scenario, the passive observation of the stimulus alone has been shown to elicit a cortical motor response in the mirror neuron literature. Coupling this effect with a sense of subject agency may well create a positive feedback system in which neural activation promotes further embodied movement, which in turn further activates the mirror neuron system. The expectation then, would be a more powerful neural response when viewing the virtual hands stimulus when compared to the keyboard task. Despite the wider expected bandwidth produced by this stimuli, cuing the subject to particular motor stimulus could be expected to produce a more focal control signal, as is reflected in the figure 6 scalp topography.

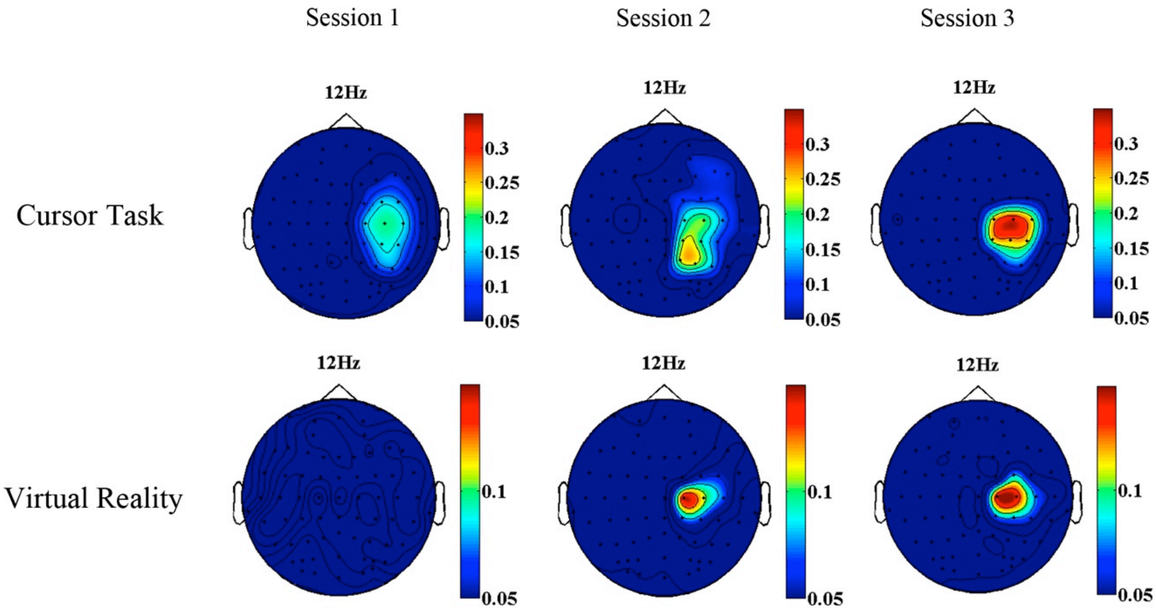


Figure 6: ***Topographic analysis for a representative subject. The activated control signal for an averaged series of trials shows progression towards a more focal signal. R squared values are presented as the degree of difference in the behavior of each component between the subject's left and right imagination states.***

This analysis showcases the progression from the untrained state with diffuse cortical activation, to a focal activation pattern most conducive to use with a brain-computer interface system. It is interesting to note the focal nature of the response elicited by use of the virtual reality feedback. While focal, the degree of separability of imaginative states (as reflected by the R squared value) was seen to be less in the virtual reality task when compared to the cursor control task.

To take a deeper look at the changes that are present when performing the brain-computer interface task with a virtual reality vs. standard cursor task, a more advanced spectral analysis was performed on a single subject's data. The subject chosen showed progressive improvement over three 2-hour sessions from 42 blocks transferred with the affected side in session 1 to 59 blocks transferred on the affected side on session three as measured by the box-blocks test. While a modest improvement, this functional change represents a change from 54.56% to 76.6% age matched healthy capacity (Mathiowetz, 1985). To eliminate some of the noise seen in previous analyses and get a better sense of the underlying signal, the patient's signal was band-pass filtered (7-40Hz) with a 60 Hz notch filtering (using Matlab's onboard filtering capabilities). In addition, a simplified "nearest neighbor" Laplacian spatial filter using the four electrodes surrounding C3 and C4 was implemented. The results of the described analysis are shown in figure 7. Upon inspection of the figure, it is clear that enhanced theta activation (4-7Hz) is present for imagery of the right hand when using the virtual reality stimulus. This differential theta activation is not seen when viewing similar conditions for the cursor task. Theta synchronization has been linked to the induction of the mirror neuron system and has been postulated as a necessary condition for effective neuroplastic (Hebbian) learning (Del Giudice, 2009).

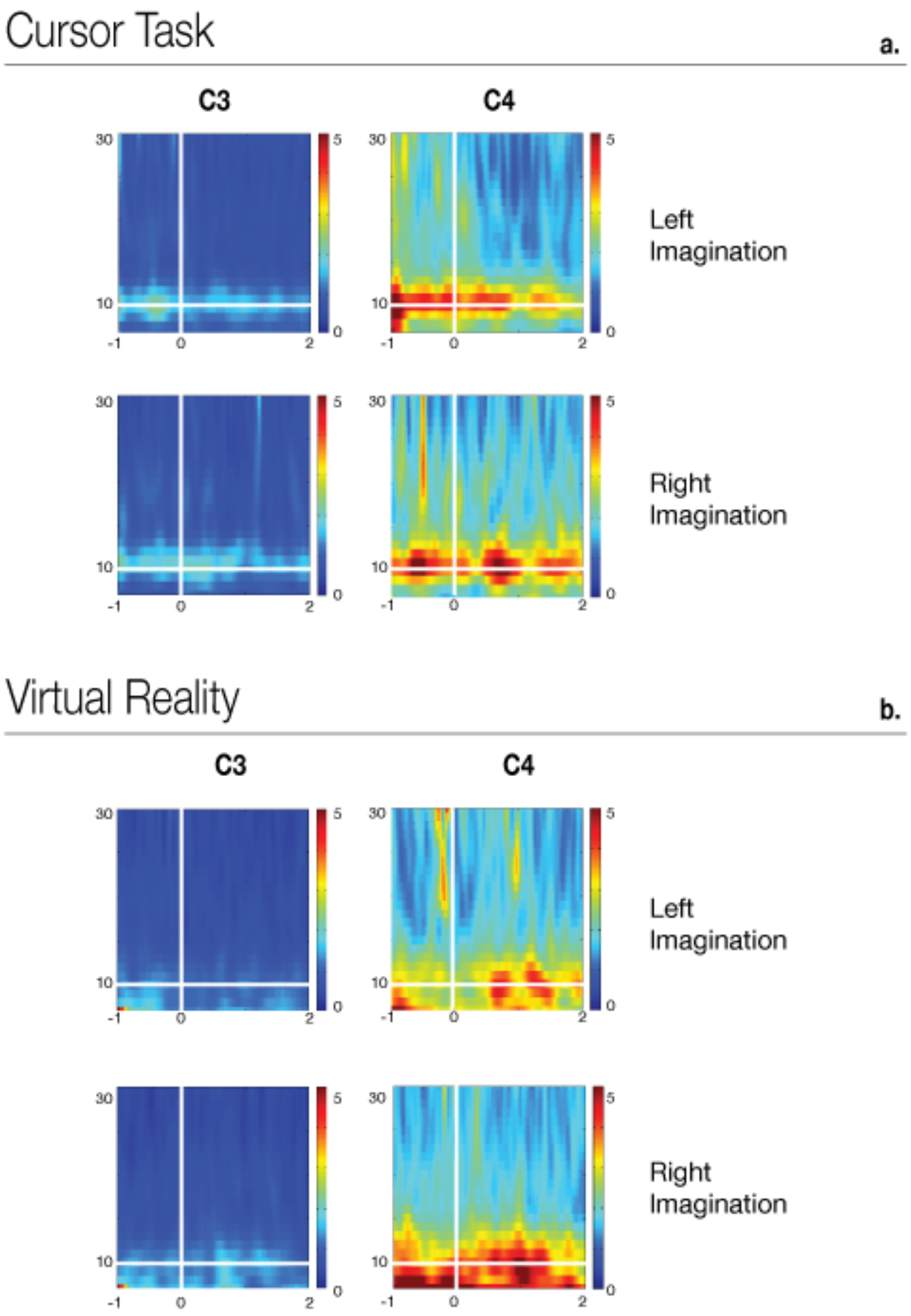


Figure 7. ***Averaged time-frequency reconstruction for a single subject's motor training during the three experimental sessions. Subsection a. shows cursor task averaged trials and subsection b. shows virtual reality averaged trials. Note the activation of theta activity (4-7 Hz) during right imagination with the virtual reality environment. Theta synchronization has been linked to induction of the mirror neuron system and to neuroplastic (Hebbian) learning.***

Discussion

The performance assessment for the virtual reality system presented for use with a stroke population may be thought about in two ways. In one sense, it may be seen as ideal for the system to outperform the standard cursor task in the presented metrics. This would be the ideal case for a replacement therapy. However, we may also consider the case in which performs equal or nearly equal to the standard system to be a favorable outcome. To borrow an analogy from weight training, two exercises may be performed at equal numbers of repetitions, to an equal degree of completion and at equal speed but may offer different capacities to impart benefit. The exercise that best isolates the desired muscle group, and which preferentially trains it is the preferred practice. Unlike a replacement technology, the proposed system should be thought of an exercise platform, where engagement with the control system is as important as the outcome of successful target acquisition. Metrics like ROM or the time to hit metric are informative in their ability to discriminate between the affected and non-affected side, but should not necessarily be crucial in system comparison. Since the standard BCI2000 cursor task algorithm is implementing the movement of the virtual reality hands, this should be self-evident.

If then the system may be thought to perform equally, or approximately equally in most regards to the traditional cursor task, one may ask what benefit the system imparts to the user? Supposing the system does not substantially subtract from the user's control capabilities, in the context of stroke rehabilitation, the ability to perform mental practice with task relevant feedback is an important therapeutic characteristic. Rather than interfacing with an abstract cursor, the subject can allow the feedback to inform the motor imagery. This becomes important with older, less technically savvy patients who may fail to grasp the abstraction of motor imagery controlling a cursor, but who may readily understand the concept of thinking about hand movement to move an image of hands. Performing a task that the user is hoping to pair with eventual regained functionality, i.e. “I imagine movement of my hand and see my hand move” is at the core of Hebbian plasticity, the concept that neurons that fire in temporal and spatial proximity to each other acquire dependent characteristics and promote each other’s functioning. By pairing a meaningful control task to the actuation of motor imagery, the fundamental principles of this type of plasticity may be leveraged towards a therapeutic goal. Motor imagery while using the virtual reality environment induced theta activation in the affected hemisphere of a basal ganglia stroke subject. This may be related to the induction of the mirror neuron system when presented with a realistic motor feedback stimulus as contrasted with the standard cursor task. Using the standard cursor task, similar theta activation was not induced. This subject for whom the theta activation was shown to be differentially active during the virtual reality task showed the greatest change in ability to perform the Box and Blocks test, progressing from 42 blocks transferred with the affected side in session 1 to 59 blocks transferred on the affected side on session three as measured by the Box and Blocks test, a change from 54.56% to 76.6% age matched healthy capacity (Mathiowetz, 1985).

Another truly powerful aspect of the system is the low cost involved in its implementation. Inexpensive 3D cameras widely available for use in extreme sports (in this case the 3D setup for the GoPro camera series available for approximately $800) were perfectly serviceable for use in creating a wide array of experimental stimuli. The importance of this factor in the system design is twofold.

Photorealistic hands may be created at low cost. In the implementation of a similar system by researchers at the Santa Lucia Neurological hospital in Rome Italy (Kaiser 2012), the avatar hands used for a randomized controlled trial were modeled with a computer graphics software package. While some attention was paid to creating a platform that could alter the appearance of the computer model to match a subject's hand size, color and gender, it was not trivial to alter the feedback of such a system, and heavy distortion is seen in videos of the projected feedback related to both the imperfection of the three-dimensional model and the surface upon which the stimulus was projected. In contrast, the proposed system employs a photorealistic 3D presentation system. Stimulus creation is performed in a shooting stage where either a caregiver or the patient may serve as the model for the video produced. This video is integrated into the system and provides feedback to the patient during training. For patients who retain the use of one arm, the healthy arm may be used for the video model and mirrored to create a stimulus with two functional arms that are perfectly matched to the patient. Patient goals may be identified and quickly integrated into the system. A diverse set of tasks such as turning a key, using a brush or opening a door handle are quick and easy to implement. The addition of patient centric goal based training is a crucial element to any rehabilitation strategy and is leveraged in this system in hopes of creating a strong motivation in the patient group to continue engagement with the device.

Spectral analysis supports an activation of a more focal control signal that engages the upper bounds of the mu band. This is intuitive to understand when we consider the nature of the stimulus presented. In contrast to an internally driven motor imagery event as would be used to drive a cursor, the subject was shown a photorealistic hand reaching with the intent to grasp an object. The characteristics of realism, goal-based action and synchrony to the users thoughts all may play a role in eliciting a strong motor neuron response in addition to the naturally evoked EEG changes seen in general purpose SMR brain-computer interfaces. The analysis supports the concept that the ability to modulate a single electrode, even when this is not the intended function of the system, can lead to users with a high degree of control and who possess a strong sense of agency. In the case of the stroke patient, a mechanism of retained functionality may be the induction of desynchronization in the lesioned cortex through the action of the healthy cortex. However, the degree to which the lesioned cortex may itself desynchronize and induce synchrony in the healthy cortex may be limited depending on the severity of the disease process.

Conclusions

Currently approved therapies for evidence-based treatment of hemiparetic stroke are mainly limited to lengthy rehabilitation sessions with a specialist, or some variant of constraint induced therapy. While patient rehabilitation is often diminished greatly after

6-months following the stroke, it is not until 2 years post event that improvements in motor function truly are recognized to plateau. In order to get the most rehabilitative benefit, patients must have a system of rehabilitation that is simple to use, affordable, and requires little technical expertise. Furthermore, those therapies which aim at functional recovery of the activities of daily living are more likely to have a lasting benefit on patients perceived quality of care and functional outcomes. It is these therapies that find the greatest capacity for subject engagement and retention through what is most certainly a frustrating recovery process.

Here we have presented a system that addresses the rehabilitation of stroke from all of these perspectives. The low-cost nature of the system, even in its prototype phase, promises an even more affordable solution should the design be mass-produced. The attention paid to the realism of the stimulus means that the patients interacting with the device would have some meaningful positive feedback early in training, and at the same time receive a stimulus that will pair what they are thinking with the desired mode of recovery. Furthermore, the attention paid to the realism of the provided feedback may be paid back in the system's capacity to powerfully induce the activation of the patient's mirror neuron system and play a role in enhanced neuroplastic learning.

Performance using this system was found to be comparable to that achieved when presenting the subjects with the traditional cursor training task for brain-computer interface. However, the subject engagement and perception of utility to recovery was far higher when using the virtual system. Furthermore, neurological activation patterns were found to be more spatially focal, and to elicit a broader range and higher power signal when conducting time frequency and topographic analysis. Further explorations will focus on the patient customization of the system through both the use of novel control signals, and the refinement of the stimulus to match with patient specific goals. These factors form the human side of brain-computer interface and represent a discipline of study in the field that has yet to undergo full expansion. Through the unity of novel training techniques, user interface refinement and customization, algorithm development and human-factors research, all geared at delivering what patients are most interested in from the system, we may begin to initiate a translational period of brain-computer interface research. It will be in this phase that these systems may begin to move from concept to implementation in a clinically meaningful way.

Bibliography:

Ang et. al. A Large Clinical Study on the Ability of Stroke Patients to Use an EEG-Based Motor Imagery. Clin EEG Neurosci 2011 42: 253.

Brunner P, et. al..Rapid Communication with a "P300" Matrix Speller Using Electrocorticographic Signals (ECoG). Front Neurosci; Volume: 5, Date: 2011,

Bundy et. al. Using ipsilateral motor signals in the unaffected cerebral hemisphere as a signal platform for brain–computer interfaces in hemiplegic stroke survivors. 2012 J. Neural Eng. 9

Büssow R. An algorithm for the continuous Morlet wavelet transform. Mechanical Systems and Signal Processing. Volume 21, Issue 8. Pg 2970-2979. 2007 Elsevier.

Daly JJ, Cheng R, Rogers J, Litinas K, Hrovat K, Dohring M. Feasibility of a new application of noninvasive Brain Computer Interface (BCI): a case study of training for recovery of volitional motor control after stroke. J Neurol Phys Ther 2009; 33(4): 203-211.

Daly JJ, Wolpaw JR. Brain-computer interfaces in neurological rehabilitation. Lancet Neurol. 2008;7:1032–1043.

Del Giudice M, et. al. Programmed to learn? The ontogeny of mirror neurons, *Developmental Science*, vol. 12, no. 2, pp. 350–363, 2009.

Doud A, Lucas JP, Pisansky MT, He B. Continuous Three-Dimensional Control of a Virtual Helicopter Using a Motor Imagery Based Brain-Computer Interface. PLoS ONE 2011 6(10): e26322. doi:10.1371/journal.pone.0026322

Fok et. al. An EEG-based Brain Computer Interface for Rehabilitation and Restoration of Hand Control following Stroke Using Ipsilateral Cortical Physiology. 33rd Annual International Conference of the IEEE EMBS Boston, Massachusetts USA, August 30 - September 3, 2011.

Greene R, Mastery. 2012. Penguin Group. 375 Hudson Street, New York, New York 10014.

Heyes C. Where do mirror neurons come from?, *Neuroscience & Biobehavioral Reviews*, vol. 34, no. 4, pp. 575–583, Mar. 2010.

He B, Gao S, Yuan H, Wolpaw J. Brain-Computer Interface, Neural Engineering, 2nd Ed, Ed: He B, Springer, 87-151, 2013.

Hochberg et. al. Reach and grasp by people with tetraplegia using a neurally controlled robotic arm. Nature Vol 485 17 May 2012.

Hsieh, Yu-Wei Wu, Ching-Yi; Lin, Keh-Chung; Yao, Grace; Wu, Kuen-Yuh; Chang, Ya-Ju. Dose-Response Relationship of Robot-Assisted Stroke Motor Rehabilitation: The Impact of Initial Motor Status.Stroke; Date: 2012 Aug 14.

Jing Fang, MD, Kate M. Shaw, MS, Mary G. George, MD. Prevalence of Stroke — United States, 2006–2010. Morbidity and Mortality Weekly Report. May 25, 2012. Vol. 61 No. 20.

Kaiser, Vera. Daly, Ian. Pichiorri, Floriana. Mattia, Donatella. Müller-Putz, Gernot R. and Neuper, Christa. Relationship Between Electrical Brain Responses to Motor Imagery and Motor Impairment in Stroke. Stroke. published online August 14, 2012.

Kamousi B, Amini AN, He B: "Classification of Motor Imagery by Means of Cortical Current Density Estimation and Von Neumann Entropy for Brain-Computer Interface Applications," *Journal of Neural Engineering*, 4:17-25, 2007

King, Christine E.. Wang, Po T. Mizuta, Masato. Reinkensmeyer, David J. Do, An H. Moromugi, Shunji. and Nenadic, Zoran. Noninvasive Brain-Computer Interface Driven Hand Orthosis. 33rd Annual International Conference of the IEEE EMBS Boston, Massachusetts USA, August 30 - September 3, 2011

Mathiowetz V, G. Volland, N. Kashman, and K. Weber, “Adult norms for the Box and Block Test of manual dexterity,” *Am J Occup Ther*, vol. 39, no. 6, pp. 386–391, Jun. 1985.

Mattia D, Pichiorri F, Molinari M, Rupp R. Brain computer interface for hand motor function restoration and rehabilitation. In: Allison B, Dunne S, Leeb R, Milla´n JDR, Nijholt A, eds. Towards practical brain computer interfaces. Berlin Heidelberg: Springer-Verlag GmbH, Biological and Medical Physics, Biomedical Engineering; 2012.

McFarland, D. J., Sarnacki, W. A., & Wolpaw, J. R. (2010). Electroencephalographic (EEG) control of three-dimensional movement. Journal of neural engineering, 7(3).

Nojima I, et. al. , Human motor plasticity induced by mirror visual feedback, *J. Neurosci.*, vol. 32, no. 4, pp. 1293–1300, Jan. 2012.

Mei Toh S. F., and Fong K. N. K., “Systematic Review on the Effectiveness of Mirror Therapy in Training Upper Limb Hemiparesis after Stroke,” *Hong Kong Journal of Occupational Therapy*, vol. 22, no. 2, pp. 84–95, Dec. 2012.

Park C,et. al.. Longitudinal Changes of Resting-State Functional Connectivity During Motor Recovery After Stroke. Stroke. 2011;42:1357-1362

Pfurtscheller et. al. The hybrid BCI. Front Neurosci; Volume: 4, Date: 2010 , Pages: 30.

Prasad et al. Applying a brain-computer interface to support motor imagery practice in people with stroke for upper limb recovery: a feasibility study Journal of NeuroEngineering and Rehabilitation 2010, 7:60 http://www.jneuroengrehab.com/content/7/1/60.

Ramachandran VS and Rogers-Ramachandran D, Synaesthesia in Phantom Limbs Induced with Mirrors, *Proc. R. Soc. Lond. B*, vol. 263, no. 1369, pp. 377–386, Apr. 1996.

Ramos-Murguialday A et. al. Brain-machine-interface in chronic stroke rehabilitation: A controlled study, *Annals of Neurology*, p. n/a–n/a, 2013.

Roger et. al. Heart Disease and Stroke Statistics−−2012 Update : A Report From the American Heart Association. Circulation. 2012;125:e2-e220; December 15, 2011.

Royer AS, Doud AJ, Rose ML, He B 2010 EEG Control of a Virtual Helicopter in 3-Dimensional Space Using Intelligent Control Strategies. *Neural Systems and Rehabilitation Engineering, IEEE Transactions on* 18: 581-589.

Royer A, Rose M, He B: "Goal Selection vs. Process Control while Learning to Use a Brain-Computer Interface," Journal of Neural Engineering, 8(3):036012, 2011.

Schaechter J. D., Motor rehabilitation and brain plasticity after hemiparetic stroke, *Progress in Neurobiology*, vol. 73, no. 1, pp. 61–72, May 2004.

Shih J, Krusienski D,. and Wolpaw J R. Brain-Computer Interfaces in Medicine. MayoClinProc.2012;87(3):268-279

Silvoni et. al. Brain-Computer Interface in Stroke: A Review of Progress. Clin EEG Neurosci 2011 42: 245

Soekadar S. R., Birbaumer N., and Cohen L. G., Brain–Computer Interfaces in the Rehabilitation of Stroke and Neurotrauma, in *Systems Neuroscience and Rehabilitation*, K. Kansaku and L. G. Cohen, Eds. Springer Japan, 2011, pp. 3–18.

Takeuchi N, and Izumi S. Maladaptive Plasticity for Motor Recovery after Stroke: Mechanisms and Approaches. Volume 2012, Article ID 359728, 9 pages doi:10.1155/2012/359728

Vallabhaneni A and He B: “Motor imagery task classification for brain computer interface applications using spatio-temporal principle component analysis,” Neurological Research, 26(3): 282-287, 2004.

Velliste et. al. Cortical control of a prosthetic arm for self-feeding. Nature Letters. Vol 453| 19 June 2008.

Wilson, J Adam. Schalk, Gerwin; Walton, Léo M; Williams, Justin C. Using an EEG-based brain-computer interface for virtual cursor movement with BCI2000. J Vis Exp; Issue: 29, Date: 2009.

Wolpaw JR, Birbaumer N, McFarland DJ, Pfurtscheller G, Vaughan TM.Brain-computer interfaces for communication and control. Clin Neurophysiol. 2002;113:767–791.

Yuan H, Doud A, Gururajan A, He B. Cortical imaging of event-related (de)synchronization during online control of brain-computer interface using minimum-norm estimates in frequency domain. IEEE Trans Neural Syst Rehabil Eng. 2008 Oct;16(5):425-31.

Yuan H, Liu T, Szarkowski R, Savage M, Ashe J, He B: “An EEG and fMRI Study of Motor Imagery: Negative Correlation of BOLD and EEG Activity in Primary Motor Cortex,” NeuroImage, 49: 2596-2606, 2010.

Yuan H, Perdoni C, Yang L, He B: “Differential Electrophysiological Coupling for Positive and Negative BOLD Responses during Unilateral Hand Movements. ,” Journal of Neuroscience 2011 Jun 29;31(26):9585-93.