McNair Scholars Research Journal

Volume 2 Article 6

2009

Demonstrating Ipsilateral Cortical Connectivity with Lower-Limb Spinal Motor Neurons

Janan Daniel
Eastern Michigan University, jdaniel6@emich.edu

Demonstrating Ipsilateral Cortical Connectivity With Lower-Limb Spinal Motor Neurons

Janan Daniel
James Stinear, DC PhD and
Sangeetha Madhavan, PT PhD, Mentors

AUSPICES OF RESEARCH

This research was done for the Summer Internship in Neural Engineering (SINE) during a three month period, June 2008 until the end of August 2008. The SINE program is affiliated with the Sensory Motor Performance Program (SMPP) at the Rehabilitation Institute of Chicago (RIC) and the Biomedical Engineering program at Northwestern University. I worked in the Neuralplasticity Laboratory, which is a part of the SMPP located at the RIC. I worked under Dr. Stinear and Dr. Madhavan to test protocols developed by my advisors as candidate techniques for demonstrating ipsilateral connectivity between the lower limb motor cortex and spinal motor neurons. The goal of the research was to develop a candidate stimulation protocol to demonstrate ipsilateral connectivity in stroke patients between the lower limb motor cortex and spinal motor neurons.

INTRODUCTION

Biomedical Science

Knowledge gained from biology and medicine has been used to improve human life in the past and will be used to improve and preserve human life in the future. Biology, intertwined with medicine, has created a broad field of disciplines that all have the aim of understanding the complicated wonder of the human body and to improve upon this system through research and technological advancement. In general the six main areas of biomedical science include: bioelectrics, biomaterials, biomechanics, biomedical imaging, biotechnology, and ergonomics/rehabilitation. The six main themes of biomedical science each have different strategies that are utilized to reach one universal goal of restoring structure and/or function in human tissues when deficits occur due to in-

jury or natural causes (BME Justification, 2008). Signal processing, the designing of circuit systems and devices that mimic effects of the human body, is an integral part of the bioelectric field. The electrical component of implantable medical devices is the focus. Biomaterials involves using materials that are alive and active and materials that are non-living in order to restore function. These materials can be manipulated and used to make an array of prostheses: orthopedic, dental, cardiovascular, and neurosensory. In addition, artificial organs can also be made from biomaterials. The field of biomechanics aims to design tissue/devices and manipulate people's everyday environments to better work with the mechanics of the human body. This involves designing equipment that will allow the least physical stress on the human skeleton to studying how cells and tissues in the body respond to mechanical stimuli. Magnetic resonance imaging, functional magnetic resonance imaging, radiography, nuclear medicine, optics, and ultrasound are all components of biomedical imaging. Each component is primarily used as a diagnostic aid to help practitioners and researchers identify where deficits, defects, and activity are occurring in the human body. Biotechnology is at the root of the cellular and chemical levels applied to human biological systems. Tissue engineering, the designing of new therapeutic drugs, and the designing of prosthetics/implants are at the core of the biotech field. Ergonomics and rehabilitation is an area that focuses on allowing people to function at their optimal levels in daily living activities, leisure, and work. Observation of living environments such as the work place and the home are a critical aspect of the rehabilitation area. The designing and implementation of assistive technologies and equipment that is safe and ergonomically friendly for the user are also important foci of the rehabilitation field. The rehabilitation area of biomedical science combines the use of biomaterials, biomechanics, human skills, and biotechnology in order to restore or allow function with safe environments and equipment. The person and their environment is the main focus of the rehabilitation and ergonomic area of biomedical science spectrum.

Rehabilitation Science

Disability within the human condition occurs because of environmental factors. The person experiencing the disability usually has an impairment of some type, such as a stroke or cerebral palsy. Due to the fact that the environment is not specifically tailored to a person's functional limitations disablement occurs. The person may not be able to play their favorite sport or use equipment in their household due to their

impairment. The overarching goal of rehabilitation science is to restore function to an individual that has an impairment. Enabling the person involves modifying and adapting the environment or changing the impairment within the person. Therefore the fundamental components of rehabilitation science that drive the disabling to enabling process are the person and the environment (Brandt & Pope, 1997). Analytical skill is necessary when modifying/adapting the environment or changing the impairment in the person. Rehabilitation science emphasizes the different contextual factors of the environment and the interactions that the person has with these factors, including the barriers and supports within the different environment factors. The environment is composed of physical, biological and social factors. These factors affect the lifestyle of the person that has the impairment. Rehabilitation science aims to change the environment or/and the person in-order to give the person the opportunity to function at their optimal performance level. Usually the person's environment may be changed through utilizing universal design, or equipment design that is tailored specifically to the individual. In addition the person may require surgery or therapy that will allow him or her to have restored functional capacity (Brandt & Pope, 1997). Physical and occupational therapy can be used, or other therapeutic modalities such as different stimulation techniques, specifically trans-cranial magnetic stimulation. The translational nature of the health sciences, engineering, and social sciences create the dynamic that is rehabilitation science.

Rehabilitation Neuroscience

In order to change the environment or the person, knowledge of the impairments must be garnered through research within the biological sciences. Research at the molecular, cellular, tissue, organ, and systems level is a precursor to the rehabilitation process. Neuroscience is a part of the biological sciences that is used to study the structure and function of an impairment, which in turn plays a part in the disablement of the individual. Within neuroscience the brain is investigated and neurological research is geared towards understanding how the neurological component of the human dynamic affects a person's function after impairment. In addition, research is used to invent or expand upon methods to change the output of the nervous system, and to manipulate the neuronal material that is already there. The Rehabilitation Institute of Chicago's Sensory Motor Performance program is at the forefront of rehabilitation neuroscience. The computational, muscle properties and neuromechanics laboratories all use feedback and feedforward in terms of neuronal

input and output to improve and restore function to people that have neurological injuries. However the Neuralplasticity Laboratory specifically focuses on upper and lower limb cortical motor impairment caused by stroke. The impairment of stroke is a specialty of the Neuralplasticity Laboratory due to the fact that stroke is a widespread condition in the United States. Currently stroke is the third leading cause of death in the United States, and is responsible for one out of fourteen deaths (Atchinson & Dirette, 2007). Within the US alone there are over five million stroke survivors.

Understanding the inner working of cortical control in terms of how it affects human movement is also at the core of the Laboratory's research. Currently movement- and stimulation-induced techniques are being developed to promote neuroplasticity within stroke survivors. The upper limb stimulation techniques for stroke survivors has been researched and studied extensively within the rehabilitation science community. The Neuralplasictity Laboratory has had a hand in upper limb stroke research. Currently high frequency repetitive transcranial magnetic stimulation (rTMS) at 5 Hz is being researched to see if it can be used as a tool to enhance hand function during physical therapy sessions. The affected hemisphere of the brain is being stimulated with rTMS to get an increase in excitability beyond the period of stimulation. After the period of stimulation physical therapy is done with the patient in order to capitalize on the increased excitability and the higher cortical signals that are being relayed to the affected hand. The lower limb is also a focus with in the Neuralplasticity Laboratory. However, due to the cortical map of the human motor cortex, the lower limb has not been studied as extensively as the upper limb. Stimulation techniques applied to the lower limb motor cortex are very difficult to attempt and achieve successfully. The two cortices that control the lower limbs are very close together. Therefore, it is often difficult to decipher which hemisphere one is stimulating or if both hemispheres are being stimulated at the same time. Usually the latter is the case. Although stimulating the lower limb motor cortex is seen as a daunting task, researchers within the Neuralplasticity Laboratory have taken on this challenge. Researchers decided to examine lower limb cortical stimulation techniques in response to recent fMRI data that suggested that the non-lesioned hemisphere within stroke patients helps to control the paretic lower limb after a stroke (Enziger et al., 2008). The output signals that spinal motor neurons receive while a person is walking are affected following stroke. The lesioned area of the motor cortex as a result of stroke negatively interferes with the output signals. These fractured output signals result in uneven gait. In order to improve

the quality of walking researchers aim to stimulate the hemisphere that is controlling the paretic limb. Logically to do this, researchers must first find out which hemisphere is controlling the paretic limb and if the controlling is done through contralateral or ipsilateral connectivity. Ipsilateral connectivity has been a subject of argument within the scientific community. However, fMRI imaging has shown that following stroke the ipsilateral hemisphere may pick up some of the lower limb control. Although ipsilateral connectivity is debatable, it should not be ruled out as random activity that cannot be capitalized upon through therapeutic modalities. Depending on where the lesion is located in the brain, ipsilateral connections may strengthen after a stroke. If the hemisphere that is controlling the paretic limb happens to be the ipsilateral hemisphere then this hemisphere should be stimulated through a standard protocol.

The overarching goal of the study conducted during the summer is to develop a candidate stimulation protocol to demonstrate ipsilateral connectivity in stroke patients between the lower limb motor cortex and spinal motor neurons. The end goal is to utilize this protocol through therapeutic stimulation of the specific hemisphere controlling the cortical output sent from the lower limb motor cortex to the spinal motor neurons. Transcranial magnetic stimulation and transcranial direct current stimulation were used as measuring and stimulation tools respectively to demonstrate ipsilateral connectivity.

METHODS

Several different protocols were tested on eight healthy participants. The final protocol used is a candidate technique for demonstrating ipsilateral connectivity between the lower limb motor cortex and spinal motoneurons.

Candidate Protocol

- Two EMG electrodes were placed on the belly of the tibialis anterior and vastus lateralis of each leg.
- Maximum voluntary isometric contractions (MVIC) were conducted for each muscle. Participants were asked to contract 5–10% of their MVIC while the amplitude of motor evoked potentials (MEPs) were being measured in EMG recordings from the TA and VL. MEP amplitude was also determined when participants were at rest.
- TMS (Magstim 200) was used to measure connectivity between the motor cortex and the four muscles.
- Single pulse TMS was delivered via a double cone coil.
- The double cone coil was placed 2 cm to one side of ver-

tex to measure contralateral connectivity to muscles on the opposite side of the body, and ipsilateral connectivity to muscles on the same side.

- The coil was also placed 2 cm to the other side of vertex to measure contralateral connectivity and ipsilateral connectivity to the other muscles.
- Transcranial direct current stimulation was given at 0.5 mA for 10 minutes to one hemisphere in the first session, and to the other hemisphere in the second session to increase the excitability of the target hemisphere.
- As a pre-stimulation measure, MEP amplitude was measured in EMG from the VL and TA using the single pulse TMS and the lateral-to-vertex stimulation points. Transcranial direct current stimulation was given, and as a post-stimulation measure, MEP amplitude was measured again, to display ipsilateral connectivity.
- Rectified integrated MEP area and MEP amplitude were then analyzed using Spike 2 and Matlab software.

RESULTS

Contralateral Rest MEPs of the Tibialis Anterior: Right TA

This graph (Figure 1) is a reflection of what occurred contralaterally after anodal tDCS was given to the left hemisphere. The PRE bar shows the rest MEP amplitude of the right TA before tDCS was given to the left hemisphere. The POST bar shows the rest MEP area after tDCS was given to the left hemisphere. In neurologically intact people the right leg is controlled by the contralateral hemisphere, which is the left hemisphere. The increased level of MEP amplitude in the TA indicates that the left hemisphere was facilitated (increase in excitability) after the tDCS.

Contralateral Rest MEPs of the Tibialis Anterior: Left TA

It is important to realize that whenever one hemisphere is facilitated or increased in excitability, the other hemisphere will be inhibited due to the transcallosal inhibitory connections between the two hemispheres. The graph above (Figure2) is showing just that. After the left hemisphere was facilitated the rest MEPs area for the left TA decreased showing inhibition of the right hemisphere.

Left M1 Anodal tDCS: Vastus Lateralis

The value of the bars are group average POST MEP area values

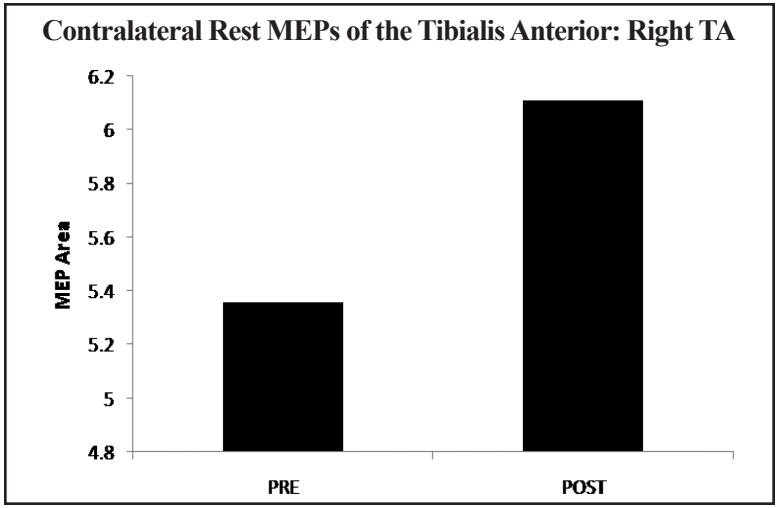

Figure 1: Contralateral Rest MEPs of the Tibialis Anterior: Right TA

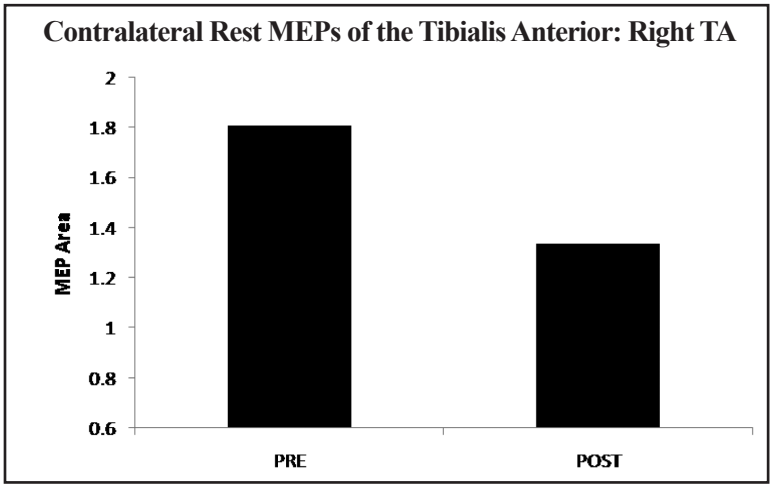

Figure 2. Contralateral Rest MEPs of the Tibialis Anterior: Left TA

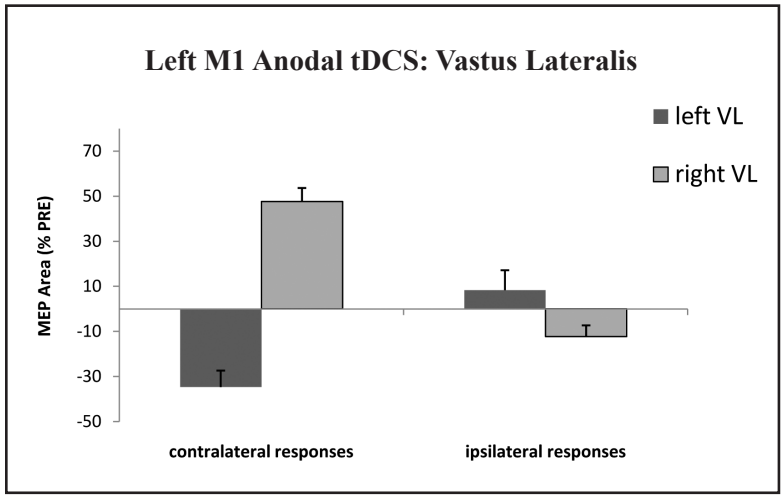

Figure 3. Left M1 Anodal tDCS: Vastus Lateralis

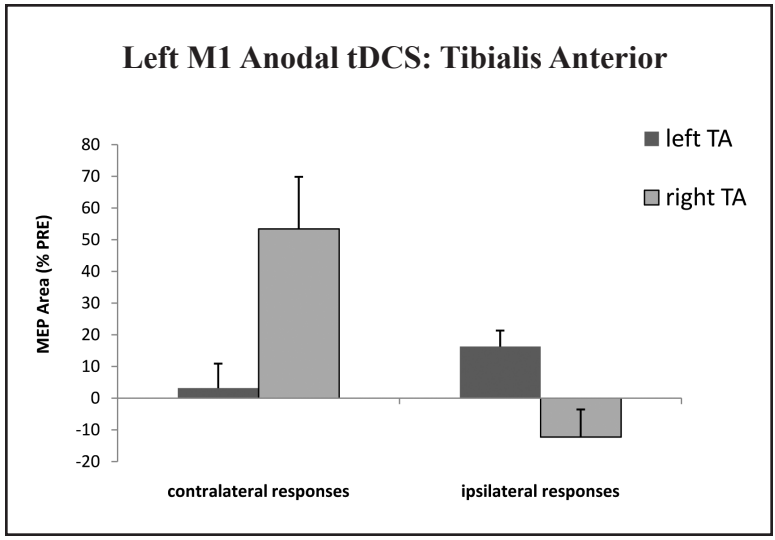

Figure 4. Left M1 Anodal tDCS: Tibialis Anterior

calculated as a percentage of PRE for each subject and muscle.

Contralateral responses. (Figure 3).

Left VL: dark bar. After the tDCS was applied to the left hemisphere the contralateral response of the right hemisphere was inhibition. This is why the MEP area of the left VL decreased.

Right VL: light bar. tDCS increased the excitability of the left hemisphere. Contralaterally the right VL is controlled by the left hemisphere. Therefore the increase in MEP area of the right VL is a direct result of the increased excitation of the contralateral left hemisphere.

Ipsilateral responses.

Left VL: dark bar. The ipsilateral hemisphere of the left VL is the left hemisphere. The tDCS applied to the left hemisphere caused the left hemisphere to have an increase in excitability. The increased MEP area of the left VL is due to the increased excitability of the left hemisphere post tDCS. Therefore ipsilateral connectivity is demonstrated between the left VL and the left hemisphere.

Right VL: light bar. The ipsilateral hemisphere of the right VL is the right hemisphere. The increased excitability of the left hemisphere caused the excitability of the right hemisphere to decrease due to the transcallosal connections. The inhibition of the right hemisphere is reflected in the decrease in MEP area of the right VL.

Left M1 Anodal tDCS: Tibialis Anterior

Contralateral responses. (Figure 4).

Left TA: dark bar. The MEP area increased in the left TA. This was not expected because the right hemisphere should have been inhibited due to the facilitation of the left hemisphere with the tDCS. However, the increase in MEP area is extremely minimal, and could be due to direct current leaking into right hemisphere.

Right TA: light bar. The increase in MEP area was expected for the right TA, because the left hemisphere was stimulated with tDCS.

Ipsilateral responses.

Left TA: dark bar. The left hemisphere was facilitated and the left TA increased in MEP area. The ipsilateral response of the left TA to the left hemisphere is positive. This bar is displaying ipsilateral connectivity between the left hemisphere and the lower limb spinal motoneurons.

Right TA: light bar. The left hemisphere was facilitated with tDCS which caused the right hemisphere to become inhibited. The inhibition of the right hemisphere is reflected in the decreased MEP area of the right TA, which also helps to show ipsilateral connectivity.

DISCUSSION

The increase and decrease of contralateral and ipsilateral MEPs when the coil was over the left hemisphere or right hemisphere demonstrates that the ipsilateral response was not due to contralateral connections. When looking at the contralateral and ipsilateral bars one can see that the ipsilateral bars were smaller than the contralateral bars. The four subjects' data analyzed were all neurologically intact individuals. Neurologically intact people may have weaker ipsilateral connections as a result of the lower limbs dominantly being controlled by the contralateral hemispheres. When a person has a stroke, the contralateral connectivity can be re-organized and changed to the point where the paretic lower limb is being controlled by the ipsilateral hemisphere depending on where the lesion is located within the cortex. In addition, when viewing the contralateral and ipsilateral bars, the tibialis anterior contralateral and ipsilateral MEP area responses are larger than the vastus lateralis contralateral and ipsilateral MEP responses. The vastus lateralis is a muscle that is mainly used for postural control, weight bearing, and gross motor activity. The tibialis anterior is a smaller muscle that is more distal and is involved in finer control of muscle movement and responses and is therefore more responsive to TMS. It is also important to note that connectivity strength varied across subjects. Several protocols were done before the final candidate protocol was chosen. This protocol chosen and illustrated in the methods section is a candidate technique for demonstrating ipsilateral connectivity between the lower limb motor cortex and spinal motoneurons. The potential of this protocol is one of tremendous significance. This is the first time a protocol of this nature has ever been attempted. The candidate protocol will potentially allow

researchers to identify which hemisphere controls the paretic limb. This knowledge will allow researchers to know which hemisphere to stimulate in a therapeutic setting in terms of up-regulation or down-regulation. This protocol also will allow researchers to see if reorganization of the brain has happened after stroke in relation to paretic lower limb control. Knowing which hemisphere to stimulate and enhance in order to have positive therapeutic outcomes is critical.

The study will continue to be conducted and in the future fMRI will be incorporated. Some subjects will have fMRI to determine if there is an association between our demonstration of ipsilateral connectivity and ipsilateral cortical activation during lower limb muscle contraction.

REFERENCES

Atchinson, B.J., & Dirette, D.K. (Eds.). (2007). *Conditions in occupational therapy: effect on occupational performance.* Baltimore, MD: Lippincott Williams & Wilkins.

Brandt, E.N., & Pope, A.M. (Eds.). (1997). *Enabling America: assessing the role of rehabilitation science and engineering.* Washington, DC: National Academy Press.

Enzinger et al., (2008) Functional MRI correlates of lower limb function in stroke victims with gait impairment [Electronic version]. *Stroke.*

University of Michigan justification for biomedical engineering concentrations. Retrieved August 19, 2008 from http:// www.eecs.umich.edu/~odonnel/bme295/bme_curriculum_conc.pdf