A Pilot Study to Investigate the Effects of Imperceptible Wrist Vibration on the Corticospinal Motor Excitability of Healthy Adults

by

Tibor Ferenc Raminelli Nagy

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	Andrew Bellemer, Ph.D, Thesis Director
	Mark Zrull, Ph.D, Second Reader
Ted Zerucha, I	Ph.D., Interim Director, The Honors College

ABSTRACT

The study investigated changes in corticomotor excitability of healthy adults with imperceptible white-noise vibration applied to the wrist. Previous studies have shown that the application of unperceivable white-noise vibration to the wrist induced improvements in sensory and motor function of the hand, not only in stroke survivors but also in healthy adults (Seo et al., 2014; Hur et al., 2014; Enders et al., 2013; Lakshminarayanan et al., 2015). Despite the potential that this vibration protocol me be adopted for therapy and in daily living activities to result in clinical benefits of stroke survivors and others with sensorimotor issues, knowledge about the way this vibration affects the neurophysiology, specifically the sensorimotor excitability, is not well understood. The purpose of this study was to investigate the neurophysiological effects of the imperceptible white-noise vibration on corticospinal motor excitability of the hand. Motor excitability was assessed using Transcranial Magnetic Stimulation (TMS), and by measuring the cortical silent period, intracortical inhibition and facilitation, and slope of the recruitment curve of the primary motor cortex for a hand muscle. These measures were compared between the vibration on and off conditions which were tested in a random order. Twelve healthy adults were tested. The results showed that the vibration resulted in marginally less intracortical inhibition when compared to the off condition (p < 0.04). Other corticomotor excitability measures were not affected by the vibration (p >0.29). Taken together with previous studies, imperceptible white-noise vibration may improve hand function by enhancing sensation and not directly the motor excitability of the hand, although more Subjects need to be tested for intracortical inhibition. This study contributes to elucidating neural mechanisms of the vibration-based sensory stimulation approach.

INTRODUCTION

According to the 2015 report of the American Heart Association every 40 seconds someone in the United States has a stroke, and approximately 795,000 people in the United States continue to experience a new or recurrent stroke each year (Mozaffarian et al., 2015). Strokes are the leading cause of serious long-term disability in the United States, landing stroke among the top eighteen diseases contributing to years lived with a disability (Mozaffarian et al., 2015). After a stroke, some of the most common complications patients suffer from include visual impairments, speech impediments, weakness on one side of the body, joint pain, muscle stiffness, coordination loss, and upper/lower body loss of sensation (Mozaffarian et al., 2015). It is estimated that there are about 7 million stroke survivors in the United States who experience sensation and coordination losses, especially in the hands (Enders et al., 2013). Hand impairment can impose an obstacle in the lives of stroke survivors since their self-care ability decreases, meaning that day-to-day simple activities become difficult (Hartmann-Maier et al., 2007). Hand impairment is attributed to muscle atrophy, defective supraspinal input, but also somatosensory deficits that are crucial to maintaining motor control of the hands (Pearson, 2000; Seo et al., 2014).

The Human Brain

The brain, the most energy-consuming organ in the human body, composes around 2% of the weight of an adult, and it consumes 20% of the energy produced by the body (Kolb & Whishaw, 2001; Purves et al., 2001). It contains a staggering one hundred billion neurons and it produces every thought, action, memory, feeling, experience, and muscle movement of the body (Kolb & Whishaw, 2001). Therefore, the brain requires a constant and nutrient rich supply of blood to maintain its executive function active throughout an individual's entire

life-span. The brain and the spinal cord make up the central nervous system (CNS), and all the nerve fibers projecting from the brain and the spinal cord form the peripheral nervous system (PNS) (Kolb & Whishaw, 2001). The human brain is divided into several different parts and regions such as the frontal lobes, occipital lobes, temporal lobes, parietal lobes, brainstem and the cerebellum. Each different region and part regulate a certain aspect of the human body (Kolb & Whishaw, 2001). Several diseases, illnesses and different types of trauma may affect the brain and prevent it from carrying its normal functions. A stroke occurs if the flow of oxygen-rich blood to a portion of the brain is stopped, and it requires immediate medical attention. Without oxygen, brain cells start to die after less than five minutes due to the fact that brain cells require a vast amount of oxygen and nutrients to carry out numerous metabolic functions (Mozaffarian et al., 2015; "What Is a Stroke?" NHLBI, 2015; Kolb & Whishaw, 2001). As a result, brain hypoxia can cause severe brain damage rapidly or death of the patient (Mozaffarian et al., 2015; "What Is a Stroke?" NHLBI, 2015). If brain cells die or are damaged because of a stroke, symptoms occur in the parts of the body that these brain cells control or affect ("What Is a Stroke?" NHLBI, 2015).

Stroke Types, Symptoms and Diagnostic Techniques

The two main types of stroke are ischemic and hemorrhagic, with ischemic strokes being the more common type of stroke seen by physicians ("What Is a Stroke?" NHLBI, 2015; Johnston, 2002). An ischemic stroke occurs if an artery that supplies oxygen-rich blood to the brain becomes blocked ("What Is a Stroke?" NHLBI, 2015). Blood clots, caused by atherosclerosis, are often the origin of the blockages that lead to an ischemic stroke ("What Is a Stroke?" NHLBI, 2015). Atherosclerosis is a disease in which a fatty substance called plaque accumulates on the inner walls of the arteries, and after time, the plaque

hardens and constricts the arteries limiting the flow of blood to the brain ("What Is a Stroke?" NHLBI, 2015). Eventually, the plaque in an artery may rupture and blood platelets will stick to the site of the plaque injury and clump together to form blood clots. On the other hand, hemorrhagic strokes occurs when an artery in the brain leaks blood or ruptures and the pressure from the leaked blood damages brain cells and cause other parts of the brain not immediately affected by the ruptured artery to lose the oxygen and nutrient supply (Mozaffarian et al., 2015; "What Is a Stroke?" NHLBI, 2015). High blood pressure and aneurysms, balloon-like bulges in an artery that can stretch and burst, are examples of conditions that can cause hemorrhagic strokes ("What Is a Stroke?" NHLBI, 2015; Johnston, 2002). Another condition that is comparable to a stroke is a transient ischemic attack (TIA), also commonly referred to as a "mini-stroke" ("What Is a Stroke?" NHLBI, 2015; Johnston, 2002). A TIA occurs if blood flow to a portion of the brain is blocked only for a short time. Thus, damage to the brain cells is not permanent or long-lasting (Johnston, 2002). Similarly to an ischemic stroke, TIAs often are caused by blood clots (Mozaffarian et al., 2015; "What Is a Stroke?" NHLBI, 2015; Johnston, 2002). Although TIAs are not complete strokes, they significantly increase the risk of having a stroke.

Certain traits, conditions, and habits, referred to as risk factors, can raise the risk of an individual having a stroke or TIA. Some risk factors can be treated or controlled, such as high blood pressure and smoking. However certain risk factors, such as age, gender, ethnicity/race, and genetic predisposition, cannot be controlled. The list of risk factors that can be controlled at some level include high blood pressure, diabetes type I and II, certain heart diseases, cardiomyopathy, atrial fibrillation, smoking, alcohol consumption, obesity, stress, and lack of physical activity (Mozaffarian et al., 2015; "What Is a Stroke?" NHLBI,

2015). As a precautionary measure, physicians recommend following a healthy lifestyle, which can lower the risk of strokes. Some individuals rely on medication to lower their risks, but sometimes strokes can occur in people who do not have any previous known risk factors ("What Is a Stroke?" NHLBI, 2015).

The symptoms depend on the type of stroke and the area of the brain that is affected (Mozaffarian et al., 2015; "What Is a Stroke?" NHLBI, 2015). How long symptoms last and how severe they are vary among different people. Signs and symptoms of a stroke may include but are not limited to sudden weakness, paralysis or numbness of the face, arms, or legs, confusion, trouble speaking or understanding speech, trouble seeing in one or both eyes, breathing difficulty, dizziness, trouble walking, loss of balance or coordination, unexplained falls, loss of consciousness, and severe headaches (Mozaffarian et al., 2015; "What Is a Stroke?" NHLBI, 2015). A TIA has the same signs and symptoms as a stroke but TIA symptoms usually last less than 1 to 2 hours; although some individuals have reported symptoms that lasted more than 24 hours ("What Is a Stroke?" NHLBI, 2015; Johnston, 2002).

Physicians will diagnose a stroke based on signs and symptoms, medical history, physical exams, and test results. These results will indicate to the doctor what type of stroke the patient experienced, the cause, and the part of the brain that was affected ("What Is a Stroke?" NHLBI, 2015). Common diagnostic tests and procedures to analyze the brain itself include Brain Computed Tomography (CT scan), Magnetic Resonance Imaging (MRI), Computed Tomography Arteriogram (CTA) and Magnetic Resonance Arteriogram (MRA), and Carotid Ultrasound and Angiography. A brain CT scan, is an instrument that uses x-rays to take detailed pictures of the affected brain and is often done right after a stroke is

suspected by the attending physician (Koenig et al., 1998). The brain CT scan will show bleeding in the brain or damage to the brain cells from a stroke (Koenig et al., 1998). An MRI uses magnets and radio waves to create pictures of the brain, and this test can detect changes in brain tissue and damage to brain cells from a stroke (Schellinger et al., 1999). A CTA and/or MRA can show the large blood vessels in the brain, and these tests provide the doctors with more information about the site of a blood clot and the flow of blood through the affected brain (Kouskouras et al., 2004). Carotid ultrasound is a test that uses sound waves to create pictures of the insides of carotid arteries and show whether a plaque has narrowed or blocked the carotid arteries (Nederkoorn et al., 2003). Carotid angiography is a test that uses dye and special x-rays to show the inside of the carotid arteries. For this particular test, a small tube called a catheter is put into an artery and the tube is then moved up into one of the carotid arteries, followed by the injection of a contrast dye into the artery. The dye will then assist on making the artery visible on x-ray pictures (Nederkoorn et al., 2003).

Many types of treatment for a stroke exist depending on whether it was ischemic or hemorrhagic. Treatment for a TIA depends on its cause, how much time has passed since symptoms began, and whether any other medical conditions exist. Treatment for an ischemic stroke or TIA may include medicines and medical procedures such as clot-dissolving medication called tissue plasminogen activator (tPA), or a carotid endarterectomy or carotid artery angioplasty, respectively (McPherson et al., 2001). Both procedures open blocked carotid arteries. Conversely, the first steps in treating a hemorrhagic stroke is to find the cause of bleeding in the brain and then control it ("What Is a Stroke?" NHLBI, 2015). Most importantly, health care providers encourage preventive steps to avoid a stroke.

Life After Stroke Complications

Life after surviving a stroke can be challenging and full of obstacles. The time it takes to recover from a stroke varies by clinical case and it can take weeks, months, or even years. Some patients recover fully, while others have long-term or lifelong disabilities. Ongoing care, emotional support and rehabilitation are all strategies employed to attempt to restore that patient's mental and emotional heath. The National Stroke Association (NSA) reports that 10% of people who have had a stroke make a full recovery, 25% have only minor impediments, and 40% end up needing special care for moderate to severe post-stroke complications. Statistically, it has been estimated by the NSA that 10% of survivors require long-term care in a nursing home or other permanent health care facility. Several physical sequelae can emerge after surviving a stroke which include but not limited to language, speech, swallowing and eating problems, no bladder and bowel cognitive control, and muscle and nerve problems ("What Is a Stroke?" NHLBI, 2015).

Depending on the region affected by the stroke, especially Wernicke's area and Broca's area, the survivor may have trouble understanding language or producing speech, respectively (Brust et al., 1976). Speech and language therapists assist the patient to learn ways to communicate again and improve memory. A constant feeling of fear, anxiety, and depression are also commonly reported (Robinson et al., 1984). Since a stroke can affect the muscles and nerves that control the bladder, bowels, and swallowing, therapeutic treatment is recommended to help patients gain control of certain voluntary muscles and functions ("What Is a Stroke?" NHLBI, 2015). Dietary changes are recommended since patients can easily choke on certain food types due swallowing problems, called dysphagia ("What Is a Stroke?" NHLBI, 2015).

Due to the death and destruction of neurons and neural pathways in the brain after a stroke, the voluntary control of the muscles of the body is easily affected. These are physical sequelae that sometime require intensive rehabilitation and constant therapy. Destruction of neurons and neural pathways can cause paralysis, muscle weakness, foot drop, and hemiparesis. Therefore, the patient is at risk for falling and it also removes their ability to live independently. While there are lots of different symptoms of pain, they are generally categorized into two types: local and central post-stroke pain (CPSP) (Klit et al., 2009). Local, also referred to mechanical pain, is usually reported and felt in the joints by the patients, and shoulder pain is especially common among stroke survivors due to a combination of neural damage and long periods of time staying in bed (Klit et al., 2009; McVeigh, 2014). CPSP is described as constant, moderate, or severe pain caused by damage to the brain (Klit et al., 2009; McVeigh, 2014). This means that after a stroke, the human brain does not correctly filter and process afferent stimuli sent from the body in response to touch, warmth/cold, and pressure. Instead, the brain may register even slight sensations from the skin as uncomfortable and painful (McVeigh, 2014).

Physical paralysis is a serious and detrimental post-stroke sequela that affect as many as 90% of stroke survivors immediately after the stroke (Muscle Weakness After Stroke: Hemiparesis, 2014). Paralysis is the inability of a muscle or group of muscles to move voluntarily. Since the muscles are controlled by the brain, after a stroke the sensorimotor executive motor pathway can be completely or partially destroyed, and action potentials will not travel down to the target muscle. Paralysis is usually on the side of the body opposite the side of the brain damaged by stroke, and may affect any part of the body (Muscle Weakness After Stroke: Hemiparesis, 2014). One-sided paralysis is known as hemiplegia, and one-sided

weakness, known as hemiparesis. Locked-in syndrome is an example of severe paralysis, or hemiplegia, that leaves the stroke survivor unable to move any muscles except those that control the eyes and completely dependent of constant assistance and care (Smith & Delargy, 2005). Locked-in syndrome is caused by an infarct, hemorrhage, or trauma to the ventral pons (Smith & Delargy, 2005). The ventral pons are located in a region of the brain called the brainstem, which is consisted of the medulla oblongata, pons, and midbrain, and continuing downward to form the spinal cord (Kolb & Whishaw, 2001; Purves et al., 2001).

Hemiparesis

About 80% of people who have had a stroke experience weakness on one side of their bodies (Muscle Weakness After Stroke: Hemiparesis, 2014). Right-sided hemiparesis is a result from injury, or in this case a stroke, to the left side of the brain (Muscle Weakness After Stroke: Hemiparesis, 2014). In specific, hemiparesis affect each survival differently, but many common problems that are seen include trouble moving arms and legs, difficulty walking, and loss of balance (Smith & Delargy, 2005). As a result of this condition, performing mundane tasks such as grasping objects, dressing, eating, and using the bathroom can be difficult for a stroke survivor.

Despite the fact that lower body hemiparesis is a major problem survivors face after stroke, upper body hemiparesis can significantly reduce a person's ability to complete both simple and complex daily living activities (Enders & Seo, 2015). Stroke survivors frequently experience long-lasting motor deficits, especially in the hands, resulting in diminished capacity to manipulate objects with the hand affected by the stroke (Seo et al., 2009). Hand motor impairment is common and contributes enormously to the ensuing long-term disability (Raghavan, 2007). Nevertheless, the connection between hand motor impairment and hand

function is uncertain as much of the improvement in function occurs due to compensation rather than true recovery of impairment from the damage caused from the stroke (Raghavan, 2007). Hand motor impairment in the production of finger movements and fingertip forces after stroke may be explained from two approaches in the literature. The first one relates hand motor impairment as a deficit in motor execution, resulting from weakness, spasticity, and abnormal coactivation of muscle groups during isolated movements (Raghavan, 2007). The second approach sees a deficit in higher-order processes, such as motor planning and motor learning, which leads to poorly formed sensorimotor associations or internal representations that lead to impaired motor control of the phalanges and hand as a whole (Raghavan, 2007). Both of these views can be seen as independent or a combination of the two in order to explain the phenomenon of hand impairment post-stroke.

The weakness or paresis of the hands are the most noticeable sign of a stroke that resulted in damage to the descending motor pathways of the brain (Raghavan, 2007). The beginning of hand impairment, or any upper limb part affected by the stroke, is characterized by the limb appearing flaccid and then developing excessive tone in a characteristic flexor synergy pattern (Raghavan, 2007; Neckel et al., 2006; Jinsook et al., 2013). Flexion synergy patterns are anatomically described as scapular retraction, shoulder abduction and external rotation, elbow flexion, forearm supination, and wrist and finger flexion in the upper extremity (Neckel et al., 2006; Jinsook et al., 2013). The Fugl-Meyer Motor Assessment Scale, which assesses the presence of synergistic versus isolated patterns of movement, is the predominant measure of hand motor impairment used after a stroke (Gladstone et al., 2002; Raghavan, 2007; Fugl-Meyer et al., 1974). However, some critics of the Fugl-Meyer Motor Assessment Scale note that the results obtained from the assessment do not show significant

details of hand motor impairment such as whether a patient is unable to grasp and lift an object because of difficulty posturing the fingers to the dimensions of the object, or due to difficulty producing appropriate fingertip forces (Raghavan, 2007).

Somatosensory Signals Importance in Hand Function

The mechanism behind hand movements heavily depend on proprioceptive and somatosensory signals (Pearson, 2000; Seo et al., 2014). Proprioceptive signals inform the brain about the movements and positions of the limbs, and along with proprioceptive signals, somatosensory signals send to the primary motor cortex of the brain information about skin pressure, stretch, and vibration (Sainburg et al., 1995; Seo et al., 2014). Since these two types of signals are important to grip objects with the hands, impaired tactile and proprioceptive sensations of the fingers and hands cause post-stroke patients to lose the ability to properly and effectively handle objects. This is due to the fact that the brain lacks the information about the mechanical contact with the object inhibiting proper operation of the muscle (Riemann & Lephart, 2002; Johansson & Flanagan, 2009). Therefore, a need exists to address this deficiency by restoring somatosensory and proprioceptive sensations to the brain so that stroke survivors are able to restore hand function.

The somatosensory system has its afferent neurons beginnings with receptors located in the skin, joints, ligaments, muscles, and face (Purves et al., 2001). Neural receptors detect either environmental stimuli through receptors located in the dermis or changes within the body through proprioceptive receptors (Purves et al., 2001; Bhatnagar, 2008). The signals are transmitted via the peripheral nerves to the dorsal root ganglion, which houses the first-order neurons for the somatosensory system (Purves et al., 2001). The dorsal root ganglion comprises the cell bodies of the afferent fibers from the peripheral nervous system (Purves et

al., 2001). The pseudounipolar neurons located in the dorsal root ganglion and their central processes travel to and enter the spinal cord via bundles (Purves et al., 2001). At this point in the nervous system, the fibers split into two functional groups called anterolateral system and the dorsal column-medial lemniscal system (Bhatnagar, 2008). The anterolateral system transmits using mainly unmyelinated fibers that carry pain and temperature sensations, whereas the dorsal column-medial lemniscal system carries mainly myelinated fibers that convey proprioceptive impulses (Purves et al., 2001; Bhatnagar, 2008).

The anterolateral system, also known as the lateral group, enters the spinal cord, then ascend or descend approximately two spinal cord segments in the tract of Lissauer to terminate on the substantia gelatinosa and the nucleus proprius, where the second-order neuron are present (Purves et al., 2001; Bhatnagar, 2008). These particular neurons have projections that cross over to the contralateral side through a tract called the anterior white commissure (Purves et al., 2001; Bhatnagar, 2008). These neural fibers then ascend passing through the brainstem to the thalamus in the spinothalamic tracts (Purves et al., 2001; Bhatnagar, 2008). Two primary spinothalamic tracts are found in the human body called the lateral spinothalamic tract that carries pain and temperature information, and the anterior spinothalamic tract, which also conveys pain, and touch sensation (Purves et al., 2001; Bhatnagar, 2008). The lateral spinothalamic tract is coated with sacral fibers lying most laterally and cervical fibers (Bhatnagar, 2008). The anterior spinothalamic tract subserves diffused touch sensation (Purves et al., 2001; Bhatnagar, 2008).

The dorsal column-medial lemniscal system, also called the medial group, sends fibers into the posterior spinal cord, and when it reaches the spinal cord, most fibers ascend to the dorsal column nuclei in the medulla and synapse there (Purves et al., 2001; Bhatnagar,

2008). The fiber tracts that ascend are called the posterior funiculus which is composed of separate elements known as the gracile tract and the cuneate tract (Purves et al., 2001; Bhatnagar, 2008). These medial group synapse on a second-order neuron as well in the nucleus gracilis and cuneatus that are located in the medulla (Purves et al., 2001; Bhatnagar, 2008). Their axons then cross-over by means of internal arcuate fibers and form a bundle known as the medial lemniscus (Purves et al., 2001; Bhatnagar, 2008). Fibers of the posterior columns and medial lemniscus carry information about position sense and fine discriminative touches (Purves et al., 2001; Bhatnagar, 2008).

Once both the signals from the medial and lateral groups reach a second-order neuron, the action potential is relayed to third-order neurons, which are neurons that carry messages from the thalamus to the somatosensory cortex (Purves et al., 2001; Bhatnagar, 2008). The third-order neurons then carry the signal through the posterior limb of the internal capsule to the primary somatosensory cortex; located in the postcentral gyrus of the parietal lobe (Purves et al., 2001; Bhatnagar, 2008). The primary somatosensory cortex mediates general and proprioceptive sensations and serves to integrate sensory information (Sainburg et al., 1995; Seo et al., 2014). It also receives connections from the motor cortex, somatosensory association cortex, and the contralateral primary somatosensory cortex (Sainburg et al., 1995; Bhatnagar, 2008; Seo et al., 2014). The somatosensory cortex is organized in a sensory homunculus similar to the motor homunculus, where the hands, and other areas like the face and lips, are given a larger representation than other parts of the body (Purves et al., 2001; Bhatnagar, 2008).

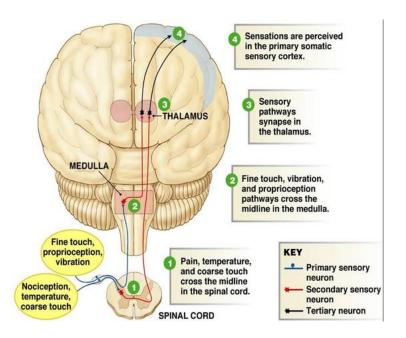


Figure 1. Somatosensory Tract Pathway from PNS to CNS in the Human Brain. Figure obtained from: Austin Community College (www.austincc.edu)

Since hand movements heavily depend on proprioceptive and somatosensory signals, any damage to the corticospinal or brain will impede the patient from properly using their hands. In specific, both the ascending and descending tracts can be affected by a stroke, diminishing hand coordination and hand function (Seo et al., 2014). Studies have shown that somatosensory impairment was common after stroke and that 7% to 53% of the survivors had impaired tactile sensations, 31% to 89% showed impaired stereognosis, and 34% to 64% demonstrated impaired proprioception (Connel et al., 2008). Hand function requires simultaneous control of multiple digits to grasp objects and a relative independent control of individual digits to perform specific and complex movements (Raghavan, 2007). The ability to produce independent digit movements remains quite impaired, creating a need for intervention by a rehabilitation specialist to restore some of the functions back (Raghavan, 2007).

Motor System and its Importance in Hand Function

Grip strength has been most commonly used to describe the impairment in grasp after stroke (Enders & Seo, 2015). Although recover of grip strength is indicative of restored corticospinal excitability, it is not related to dexterity (Thickbroom et al., 2002). Dexterity requires control of hand and finger movements and fingertip forces during hand-object interactions (Raghavan, 2007). A recent study that examined the control of finger movements to differently shaped objects during reach-to-grasp found that stroke survivors show impaired ability to form discriminatory finger positions to differently shaped objects despite being able to recognize the different shapes and grasp and lift the objects (Raghavan, 2007). Several recent studies have examined the control of two-digit grasp after stroke and showed two impairments in grasp execution (Raghavan et al., 2006; Seo et al., 2010). Patients generate excessive grip force in both the affected and unaffected hands even in the absence of tactile deficits (Raghavan et al., 2006; Seo et al., 2010), and other studies have indicated that patients have prolonged grip-lift duration, which is the time taken to stabilize an object in one's grip prior to lifting it (Seo et al., 2009). These studies about grip suggested that the temporal coordination between grip force applied by the fingers on the object and load force exerted by proximal arm muscles is disrupted after a stroke (Raghavan et al., 2006).

In order to elicit a movement, the motor system portion of the nervous system is responsible for such commands. Motor neurons travel by different tracts within the spinal cord when compared to the somatosensory system (Kolb & Whishaw, 2001; Purves et al., 2001). Similarly, ascending tracts send information to the brain and descending tracts are motor potentials that deliver the information to the periphery and elicit movements of the limbs, including the hand (Kolb & Whishaw, 2001; Purves et al., 2001). Common

terminology of the descending tracts of the motor system end with the word "spinal", like corticospinal (Kolb & Whishaw, 2001; Purves et al., 2001). The CNS conveys motor information in response to sensory information received in the somatosensory cortex. Motor commands are delivered by the somatic nervous system (SNS), which consciously controls skeletal muscles, and the autonomic nervous system (ANS) that directs the activity of glands, smooth muscles, and cardiac muscle in the human body (Kolb & Whishaw, 2001; Purves et al., 2001). There are two major descending tracts called the corticospinal tract and the subconscious tract. The subconscious tract regulates balance, muscle tone, eye, hand, and upper limb position, whereas the corticospinal allows for the conscious control of skeletal muscles (Kolb & Whishaw, 2001; Purves et al., 2001).

The primary motor cortex, or M1, the principal brain area involved in motor function (Kolb & Whishaw, 2001; Purves et al., 2001). The M1 is located in the frontal lobe of the brain, in a region called the precentral gyrus (Kolb & Whishaw, 2001; Purves et al., 2001). Signals from M1 cross the human body's midline to control skeletal muscles on the opposite side of the body. Every part of the body is represented in the primary motor cortex, and these representations are arranged similarly to the somatosensory cortex (Kolb & Whishaw, 2001; Purves et al., 2001). A vast amount of the cortical space is required to control the complex movements of the hand and fingers, and these body parts have larger representations in M1 than the trunk or legs, whose muscle patterns are relatively simple (Kolb & Whishaw, 2001; Purves et al., 2001). This disproportionate map of the body in the motor cortex is called the motor homunculus.

Other regions of the cortex involved in motor function are called the secondary motor cortices (Kolb & Whishaw, 2001; Purves et al., 2001). These regions include the posterior

parietal cortex, the premotor cortex, and the supplementary motor area (SMA) (Kolb & Whishaw, 2001; Purves et al., 2001). Neurons in M1, SMA and premotor cortex send axons that make the corticospinal tract (Kolb & Whishaw, 2001; Purves et al., 2001). The corticospinal tract is the uninterrupted pathway from the cortex to the spine and is composed of millions of fibers (Kolb & Whishaw, 2001; Purves et al., 2001). These fibers make their descent through the brainstem, where the majority of them cross over to the opposite side of the body (Kolb & Whishaw, 2001; Purves et al., 2001). After the cross, the fibers continue to descend through the spine, ending at the appropriate spinal levels for the particular limbs (Kolb & Whishaw, 2001; Purves et al., 2001). There are other motor pathways which originate from subcortical groups of motor neurons and they control posture and balance, coarse movements of the proximal muscles, and coordinate head, neck and eye movements in response to visual targets (Kolb & Whishaw, 2001; Purves et al., 2001).

Each motor neuron in the spine is part of a functional unit called the motor unit (Kolb & Whishaw, 2001; Purves et al., 2001). Motor units are composed of the motor neurons, axons, and the muscle fibers that are affected by the neurons (Kolb & Whishaw, 2001; Purves et al., 2001). Smaller motor neurons characteristically innervate smaller muscle fibers in the body, like those of that hands and phalanges (Kolb & Whishaw, 2001; Purves et al., 2001). Motor neurons can innervate any number of muscle fibers, however, each fiber is only innervated by one motor neuron from the corticospinal tract (Kolb & Whishaw, 2001; Purves et al., 2001). When the motor neuron sends an action potential, all of its muscle fibers contract in response (Kolb & Whishaw, 2001; Purves et al., 2001). In relation, there are two types of motor neurons in the spine called the alpha and gamma motor neurons (Kolb & Whishaw, 2001; Purves et al., 2001).

Current Somatosensory Rehabilitation Methods

Several different rehabilitation methods are used by occupational therapists and physical therapists to rebuild some control of the patient's hand. Numerous studies have shown that the increase in motor function after a stroke is greatly attributed to improvements within cerebellar, and sensorimotor network efficiency to distribute signal to the brain (Westlake et al., 2012; Laney et al., 2015). Some post-stroke rehabilitation methods used in the United States to restore hand sensory function include sensory discrimination training, passive sensory stimulation, temporary deafferentation, and sensory noise (Seo et al., 2014).

During sensory discrimination training, different techniques are used to train stroke survivors to discern between different textures, size, and weight of objects (Carey & Matyas, 2005). The purpose behind this technique is to create new neural pathways in the brain of the stroke survivor to discern between objects to correct for any error that transpires when trying to use the hands (Seo et al., 2014). Touch discrimination by the patients is measured via the Tactile Discrimination Test (TDT) and the Fabric Matching Test (FMT). The TDT employs a finely graded plastic surfaces marked by ridges at set spatial intervals (Carey & Matyas, 2005). The texture grids are presented in sets of three to the patient, with two surfaces identical and one different. FMT includes two identical sets of ten cotton-based fabrics. ranked from smooth to rough by unimpaired Subjects (Carey & Matyas, 2005). These measures have high retest reliability, good discriminative validity, and normative standards aiding on the rehabilitation through sensory discrimination (Carey & Matyas, 2005). For the proprioception domain, the Wrist Position Sense Test (WPST) is a box-like apparatus that includes two protractor scales that indicate a target. The response positions quantifies the patient's ability to indicate wrist position after an imposed movement (Carey & Matyas,

2005).

Stimulus-specific training (SST) and stimulus-generalization training (SGT) are common therapeutic techniques used in sensory discrimination training (Carey & Matyas, 2005). The SST program was designed to maximize improvement of the specific sensory discriminations trained by principles of training that include a repeated presentation of targeted discrimination tasks (Carey & Matyas, 2005). In addition, the SGT program is designed to facilitate transfer of training effects to untrained and new stimuli (Carey & Matyas, 2005). A variety of training surfaces like paper, glass, leather, and rubber can be employed in the SGT program because these objects have a range of distinctive features of roughness that include contour, surface pattern, and grid to aid in the discrimination training (Carey & Matyas, 2005). Although this particular technique has been shown to improve hand coordination and movement through what is thought to be somatosensory improvements, it does not objectively evaluate cognitive function or validate the location of the lesion (Byl et al., 2003). Additional research was suggested since there is a need to determine variations in effectiveness based on different models of sensory discrimination, particularly those based on the principles of neural adaptation (Byl et al., 2003).

Passive sensory stimulation is an alternative to regular schedules of training since they require discipline and physical fitness (Kalisch et al., 2008). Certain approaches use this technique to enhance tactile and fine motor performance based on sensory stimulation by means of tactile coactivation (Kalisch et al., 2008). Passive sensory stimulation involves application of electrical, magnetic, or tactile stimulation to the nerves (Seo et al., 2014). The particular approach made is based on patterned, synchronous tactile stimulation applied to the fingertips for three hours (Kalisch et al., 2008). However, passive sensory stimulation

was demonstrated to only improve motor performance tasks for 96 hours (Kalisch et al., 2008). This technique aims to activate the nerve fibers that transmit somatosensory input originating from peripheral receptors to possibly produce cortical reorganization in the somatosensory cortex as well as in the primary motor cortex (Wu et al., 2006; Seo et al., 2014).

Temporary deafferentiation is done through anesthesia of the affected forearm or the contralateral hand (Sens et al., 2013; Seo et al., 2014). Results have indicated that sensory and motor performance was increased temporarily by a possible decrease in inhibitory drive of the action potentials to the affected hands of the stroke survivor's sensorimotor areas (Sens et al., 2013; Seo et al., 2014). Temporary deafferentation can be a painful procedure that leaves patients without motor control of the hand and nerve blocks are invasive and often not tolerated by the patients, especially when applied on a daily basis as a rehabilitation technique (Sens et al., 2012). In contrast, temporary deafferentation with an anesthetic cream could be used and it has shown to improve sensory relearning in nerve-injured patients six weeks after a daily treatment over a period of two weeks (Sens et al., 2012). Hand motor practice during a single induced anesthesia resulted in improved motor function in stroke patients two weeks after treatment, but this invasive technique can make patients feel uncomfortable and possible side effects from the drugs used can cause major problems (Muellbacher et al., 2002; Sens et al., 2012).

Vibrotactile Noise

Of the therapeutic procedures described above, vibrotactile or sensory noise have been shown to maximize the recognition and conduction of weak signals in healthy individuals at subthreshold levels (Collins et al., 1997; Wells et al., 2005). The sensory noise

method involves application of a small level of mechanical vibration to the skin to result in immediate improvement in sensorimotor function (Collins et al., 1996; Collins et al., 2003). Due to the increase of the research on this new technology, certain wearable devices have been developed to apply the vibrotactile noise in the fingertips of the post-stroke survivors (Enders et al., 2013; Kurita et al., 2013). The placement of the device on the fingertips may hinder the ability to comfortably handling objects, therefore the application of the noise to the wrists induced improvements in hand motor function, possibly mediated by cortical connections from the somatosensory region of the wrist to the fingertips (Seo et al., 2014).

The concept of stochastic resonance has been proposed as a method of improving hand coordination in stroke survivors by affecting the somatosensory system (Seo et al., 2014). The addition of noise to the skin improves signal detection and feedback-controlled system performance, and it has been demonstrated theoretically in varieties of mammals, especially human beings (Duan et al., 2013; Seo et al., 2014). In addition, subthreshold vibrotactile noise when applied to the foot has been shown to improve foot tactile sensation in stroke survivors, healthy young adults and old adults (Liu et al., 2002; Wells et al., 2005). Due to the vibrotactile noise applied to the feet, a reduction in postural sway was observed not only in stroke survivors, but also diabetic patients, and healthy adults (Liu et al., 2002; Wells et al., 2005). In specific to hand function, subthreshold vibrotactile noise when directly applied to the index fingertip has been shown to immediately improve finger tip tactile sensation in stroke survivors and healthy adults, but it also reduced the amount of excess grip force for lifting objects (Liu et al., 2002; Kurita et al., 2013).

Stochastic Resonance (SR) is broadly applied to describe neurophysiological phenomenon where the presence of this noise in a nonlinear system strengthens the output

signal quality than if the noise was absent (Gammaitoni et al., 1998; McDonnell & Abbott, 2009). The term SR was first used by Roberto Benzi as a name for the mechanism suggested to be behind the periodic behavior of Earth's ice age (McDonnell & Abbott, 2009). As explained by McDonnell & Abbott, 2009, the term nonlinear refers to the fact that noise, in this case subthreshold vibrotactile noise, is only beneficial in a non-linear system because only the more complex interactions between nonlinearities and randomness that can lead to SR (McDonnell & Abbott, 2009). This effect requires three components which are described as an energetic activation barrier, or threshold in the case of the somatosensory pathway, a weak coherent input, such as a periodic signal like the subthreshold vibrotactile noise, and finally a source of noise that is inherent in the system, such as an action potential fired by the neurons (Gammaitoni et al., 1998). After these stipulations are met, the response of the system undergoes resonance-like behavior as a function of the noise level, giving it the name stochastic resonance (Gammaitoni et al., 1998; McDonnell & Abbott, 2009).

Although vibrotactile noise has been shown to affect tactile sensory perception and dexterous hand function, the neurophysiologic basis behind the vibration intervention is unclear (Sainburg et al., 1995; Seo et al., 2014). Hand function requires synchronized control of multiple digits to grasp the objects and a relative independent control of individual digits to perform various fine and meticulous motor tasks (Raghavan et al., 2006; Raghavan, 2007). Although many patients recover the ability to produce a gross grasp after damage to the corticospinal tract, the ability to produce independent digit movements remains quite impaired (Lang & Schieber, 2003; Raghavan, 2007).

Neurotransmitters

The entire nervous system depends on chemical messengers that are used to transmit

messages from the brain all the way to the neuromuscular junctions (Long, 2006; Kolb & Whishaw, 2001; Purves et al., 2001). The connection of the somatic nervous system and the skeletal muscle system happens in a region called the neuromuscular junction (Samigullin et. al., 2015). The action potential generated by the central nervous system travels down along myelinated fibers into axons that end at the neuromuscular junctions. Within this junction, the axon terminal divides into branches that are called boutons (Sherwood, 2007). This region of the axon ending are called motor end plates and that is where the triggering chemical changes occur and allow for the sliding filament mechanism. The all-or-nothing excitation response of muscle fibers is regulated by the neurotransmitter called acetylcholine which is released by the terminal axons in the neuromuscular junctions in response to an action potential (Sherwood, 2007). Acetylcholine diffuses across the synaptic cleft and binds to specific receptors in the sarcolemma of the muscle fiber in the opposite side of the axon terminal in the neuromuscular junction (Nohmi and Kuba, 1984). This chemical message triggers the opening of sodium channels, which depolarizes and causes an action potential in the sarcolemma (Sherwood, 2007). This causes calcium channels to open and release it into the sarcoplasm (Brehm et. al., 1984). The calcium then initiates the formation of bridges between the actin and myosin by binding to troponin (Samigullin et. al., 2015). This reaction causes a conformational change that alters the position of tropomyosin, exposing the actin (Sherwood, 2007). The myosin then uses adenosine triphosphate (ATP) to bind to the actin (Bigland-Ritchie et. al., 1979). This is called the contraction or excitation of the skeletal muscle fiber since the chemical binding allows for the motion of the actin inward toward the M line causing the physical shortening of the sarcomere (Sherwood, 2007). The opposite process, called the relaxation of the muscle, happens when the adenosine diphosphate (ADP)

left on the myosin head is phosphorylated back into ATP allowing for sarcomeres to return to their original shape (Bigland-Ritchie et. al., 1979; Sherwood, 2007).

Gamma-aminobutyric acid, or GABA, is an inhibitory neurotransmitter that is very widely distributed in the neurons of the cortex and the corticospinal tract (Kolb & Whishaw, 2001; Purves et al., 2001). In the humans' CNS, GABA is the most widely distributed inhibitory neurotransmitter. The concept of GABA_A and GABA_B type receptors was introduced in 1981 by Hill and Bowery (Bormann, 2000). These two particular receptors differ in their pharmacological, electrophysiological and biochemical properties according to studies conducted (Olsen & DeLorey, 1999). Studies of the GABA_A-receptor complex indicate that it facilitates an increase in membrane conductance of ions with an equilibrium potential at around -70 mV, the common voltage observed in any resting cell (Olsen & DeLorey, 1999). The conductance increase is frequently followed by a membrane hyperpolarization, resulting in an increase in the firing threshold of the neuron (Olsen & DeLorey, 1999). This decrease in membrane resistance is accomplished by the GABAdependent facilitation of Cl⁻ ions influx through receptor-associated channels on the membrane (Olsen & DeLorey, 1999; Bormann, 2000). Conversely, improved Cl⁻ ion permeability will depolarize the target cell under some conditions of high intracellular Cl (Olsen & DeLorey, 1999; Bormann, 2000). This in turn theoretically excites the cell to fire or to activate Ca²⁺ ion entry through voltage-gated channels (Olsen & DeLorey, 1999; Bormann, 2000). Therefore, a decrease in the possibility of an action potential initiation is observed, causing neuronal inhibition of the action potential (Olsen & DeLorey, 1999).

Less is known about the GABA_B receptor in the literature because of the limited number of pharmacological molecules selective for this site (Olsen & DeLorey, 1999;

Bormann, 2000). GABA_B receptors are always inhibitory and are coupled to G proteins, contrary to GABA_A-receptors that can act as an inhibitor or facilitator of action potentials (Olsen & DeLorey, 1999; Bormann, 2000). GABA_B receptors are coupled indirectly to K⁺ channels and when activated, these receptors can decrease Ca²⁺ conductance and impede cAMP production through intracellular mechanisms mediated by G proteins (Olsen & DeLorey, 1999). GABA_B receptors are able to mediate both postsynaptic and presynaptic inhibition of neurons (Olsen & DeLorey, 1999). Presynaptic inhibition occurs as an effect of the GABA_B receptors on nerve terminals, which decrease in the influx of Ca²⁺ reducing the release of neurotransmitters (Olsen & DeLorey, 1999; Bormann, 2000). As a result, the neuromuscular junctions are not excited to elicit a muscle movement.

A gap in the research exists and it is unclear if the vibrotactile noise affects only the sensory threshold or both sensory and motor cortices. Several studies have demonstrated that sensory and motor connection overlap in mammals such as rats, monkeys, and humans through S1 and M1 pathways in order to calibrate and update the movement necessary to conduct the task (Donoghue & Wise, 1982; Matyas et al., 2010; Riemann & Lephart, 2002; Bard et al., 1995). By inhibiting somatosensory input, studies have established that somatosensory input is essential to the control of movement, coordination, and handling of objects and it updates closed-loop control motor planning and execution in the motor cortex through neural/functional connections between the sensory and motor cortices (Carey, 1995; Augurelle et al., 2003; Blennerhassett et al., 2006; Blennerhassett et al., 2007). Given this intimate functional connection between the sensory and motor areas of the brain, it may be possible that vibrotactile noise directly affects the cortical motor state such as corticospinal motor excitability.

The overall objective of this study is to measure the impact of the vibrotactile sensory stimulation, applied to the wrist, in increasing corticospinal excitability. This particular study focuses on the application of the model system in healthy adults. The hypothesis of this experiment states that corticospinal motor excitability of healthy adults will increase with the wrist subthreshold vibrotactile stimulation on when compared to when the vibrotactile noise is off. To test this hypothesis, corticospinal motor excitability was quantified using TMS as intracortical inhibition/facilitation, cortical silent period, and recruitment curve with the vibrotactile noise on and off.

METHODS

Subjects

Twelve healthy volunteers between the ages of 21 and 35 were used in this study, where 6 were males and 6 were females, and 8 of the Subjects were right hand dominant. To be considered a healthy Subject, the participant had no history of upper limb injury, musculoskeletal, or neurologic disorders. Healthy Subjects were not paid for their participation and a TMS safety screening was performed to ensure each Subject did not have an elevated health risk while being exposed to the TMS stimulations. All Subjects signed written informed consent forms prior to participating in the study (MUSC IRB #: Pro00042759; PI: Dr. Na Jin Seo).

Table 1. Summary table of race/ethnicity, gender and age of all healthy study Subjects. A total of 6 males and 6 females participated with an average age of 24 years. The range of age was from 21-35 year old.

Subject	Race/Ethnicity	Gender	Age
1	Asian	F	35
2	Latino	M	21
3	Asian	M	21
4	African-American	M	21
5	Caucasian	F	22
6	Caucasian	F	24
7	Caucasian	F	22
8	Caucasian	F	23
9	Caucasian	F	23
10	Caucasian	M	25
11	Caucasian	M	28
12	Caucasian	M	22
AVG	-	-	24

Procedure

Subthreshold Vibrotactile Noise

Vibrotactile noise was applied using a C-3 Tactor (Engineering Acoustics, Inc.,

Casselberry, FL, USA) attached to the volar wrist of the left arm, between the second and third wrist creases and medial-lateral direction using tape. The sensory threshold was determined by successively increasing and decreasing the intensity of the vibrotactile noise coming from a computer using the method of limits (Ehrenstein & Ehrenstein, 1999). The intensity, controlled by the volume of the noise, was increased in one unit steps until the noise was felt by the participant (ascending series), and the noise was decreased (descending series) by one unit from a clearly established feeling of the noise until the participant could not feel it anymore. The two types of series were alternated and the results of a total of 8 series were averaged to determine sensory threshold. Subthreshold vibrotactile noise at 60% of the sensory threshold was used during the TMS experiment.

TMS

Corticospinal motor excitability was examined while the vibrotactile noise was on or off. The variation between the two conditions were randomized. Participants were comfortably seated in the TMS chair and arms were rested on pillows. Surface EMG was recorded from the abductor pollicis brevis (APB) muscle (CED1902-11/4 Electrode, Cambridge Electronic Design Ltd., Cambridge, England). The recording lead was placed on the muscle belly of the APB, the reference lead was put on the tendon insertion, and the ground electrode was placed on dorsum of the left hand. The right hemisphere of the brain was stimulated using TMS to induce a motor evoked potential (MEP) of the left APB.

Brainsight software (Rogue Research Inc. Montreal, Quebec, Canada), along with an average brain MRI (Rogue Research Inc. Montreal, Quebec, Canada), was used to localize the motor dorsal lateral pre-frontal, the "motor hotspot", in order to stimulate the APB. A figure-of-eight TMS coil was positioned on the "motor hotspot" on the head of the Subject where the

largest MEP amplitude of the APB was consistently found by the EMG. Once the "motor hotspot" was determined the TMS coil was secured in position and Brainsight software was used to actively track any movements of the TMS coil from the "motor hotspot".

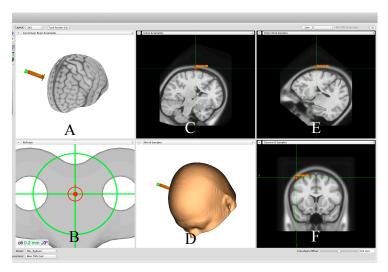


Figure 2. TMS coil software for finding of "motor hotspot". TMS coil was secured in position and Brainsight software was used to actively track any movements of the TMS coil from the "motor hotspot" to ensure precision of MEP. Six different images are present labeled A-F. Images A, C,D,E, and F represent the position of the coil in relation to the "motor hotspot" from different points of view of the human head. Image B represents the target "motor hotspot" target position in relation to the TMS figure-8-coil.

Resting Motor Threshold (rMT)

The rMT protocol was determined as the TMS stimulation output needed to elicit a 0.05 mV peak-to-peak amplitude for 50% of the trials using Parameter Estimation by Sequential Testing, or PEST (Ehrenstein & Ehrenstein, 1999).

Intracortical Inhibition and Facilitation

Short-interval intracortical inhibition (SICI) and long-interval intracortical facilitation (LICF) were assessed using paired pulse protocols. SICI is a method used to study cortical inhibition measured by combining a subthreshold conditioning stimulus followed by a suprathreshold test stimulus (Roshan et al., 2003). The test responses are inhibited with the conditioning stimulus preceded by a short interstimulus intervals (ISI) at 3 ms (conditioned

response). The percent reduction of the peak-to-peak MEP amplitude with the conditioning stimulus compared to without determined SICI. Testing stimulus intensity was determined by increasing the stimulator output until 1mV peak to peak MEP response at rest was reached consistently for three trials. Conditioning stimulation intensity was determined by taking 80% of the rMT. LICF can be produced following the same protocol as SICI but at a longer ISI from 6 ms to 30 ms (Rossini et al., 2015). In this study, ISI of 15 ms delay was used for facilitation. The percent increase of the peak-to-peak MEP amplitude with the conditioning stimulus compared to without determined LICF. The unconditioned response was obtained 10 times and the conditioned response for inhibition and facilitation were take 8 times each, from which an average for the unconditioned and conditioned responses were taken.

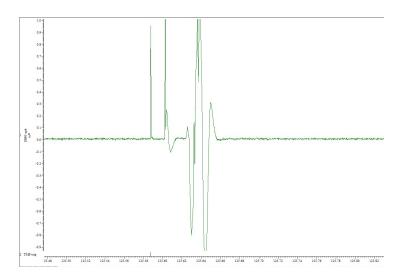


Figure 3. Intracortical Facilitation Example of MEP. The two first peaks represent the separation of the MEP in a 15 ms interval from each other. The waves following it represent the MEP seen through the EMG.

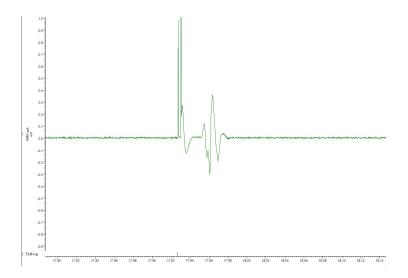


Figure 4. Intracortical Inhibition Example of MEP. The two first peeks represent the separation of the MEP in a 3 ms interval from each other (ISI). The waves following it represent the MEP seen through the EMG.

Cortical Silent Period

The Subject was asked to pinch a force gauge using all the strength they could generate. Once that was determined, the participant was asked to sustain a pinch at a 20% of the maximum determined force while the single-pulse stimulation was administered by the TMS instrument. The stimulation intensity used was 120% of the rMT. The silent period was determined as the duration from the TMS trigger until the EMG signal returned. An average of eight repetitions were taken when the vibrotactile noise was on and when it was off.

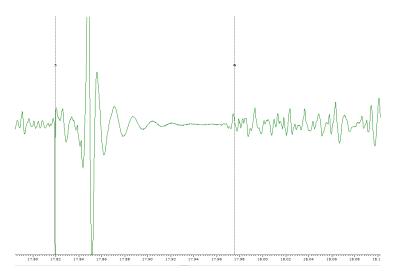


Figure 5. Cortical Silent Period Example Graph. A pinch at a 20% of the maximum determined force while the single-pulse stimulation was administered by the TMS instrument is seen by the small peaks. The silent period was determined as the duration from the TMS trigger until the EMG signal returned as seen by the two vertical continuous lines.

Recruitment Curve

The recruitment curve is a sigmoidal curve that indicates a relationship between the intensity of the stimulus (%Maximum Stimulator Output or %MSO) and peak-to-peak MEP amplitude (mV) (Rossini et al., 2015). A recruitment curve was acquired by plotting the mean peak-to-peak MEP amplitudes (mV) for a range of TMS intensity from 80% rMT to approximately two times the rMT in steps of five %MSOs. Approximately 40 to 50 stimulations were used per condition per person. The maximum slope of the recruitment curve was the outcome measurement (steepest slope).

Data Analysis

Spike 2 software was used to analyze the raw data collected from the TMS. A sample script ran the protocol to produce the motor evoked potential (MEPs). The average for each condition testing the baseline, inhibition and facilitation, were used to compare peak to peak MEPs. A percent change was compared to a non-conditioned response value. A paired two sample t-test was used to compare on vs off conditions. A paired two sample t-test was used

to compare the vibrotactile noise on versus noise off conditions for each of the response variables (rMT, intracortical inhibition, intracortical facilitation, CSP, and recruitment curve's steepest slope).

RESULTS

Cortical Inhibition

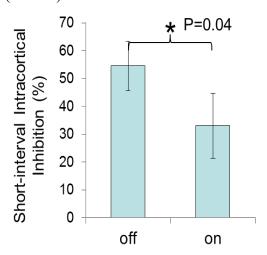
The percent reduction of the peak-to-peak MEP amplitude with the conditioning stimulus compared to without the determined 3ms short interval for each Subject is shown in Table 2. This raw data provides a closer look to how the vibrotactile noise affected the inhibition of the MEP caused from the TMS. Negative numbers on the table show that the peak was shorter when compared to the peak without the introduction of the SICI. The largest reduction was observed in Subject 4 with a -87.937% reduction from the baseline peak. The smallest peak reduction observed was for Subject 2 where only a -3.283% reduction from the baseline was observed while the vibrotactile noise was on. For Subjects 7 and 8 while the noise was on, a positive percentage was observed, 44.457% and 13.608%, respectively, meaning that the while the noise was on, the peak amplitude was bigger than the baseline. Another positive value was recorded from when the noise was off for Subject 5 (27.400%).

Table 2. Raw Intracortical Inhibition Data of Noise on vs off. The percent reduction of the peak-to-peak MEP amplitude with the conditioning stimulus compared to without determined SICI is found for each Subject.

Subject	Noise On (% decrease)	Noise Off (% decrease)
1	-78.214	-80.482
2	-3.283	-53.121
3	-55.681	-77.705
4	-87.937	-69.244
5	-13.310	27.400
6	44.457	-58.303
7	-36.437	-69.654
8	13.608	-55.516
9	-14.393	-23.467
10	-82.829	-85.824
11	-44.905	-52.280
12	-38.504	-57.148

Figure 6 below represents the average of the percent reduction from the baseline peak reading while the vibrotactile noise was on versus when it was off. Despite the values showing as positive on Figure X, the average intracortical inhibition of the MEP while the noise was on was -33.119% reduction, and the average intracortical inhibition of the MEP while the noise was off was -54.612% reduction. The paired two sample t-test showed a p-value of 0.04, meaning that a significant statistical difference was observed between the vibrotactile noise on versus when the vibrotactile noise was off. As a result, while the vibrotactile noise was on, the percent inhibition of the MEP was statistically smaller than when the noise was off.

Figure 6. Average Intracortical Inhibition of MEP. The percent change average for the on vs off condition were compared. A significant difference was found between the two values (P=0.04).



Cortical Facilitation

The percent increase of the peak-to-peak MEP amplitude with the conditioning stimulus compared to without the determined 15ms long interval for each Subject is shown in Table 3. This raw data provides a closer look to how the vibrotactile noise affected the facilitation of the MEP triggered from the TMS. Positive numbers on the table show that the peak was larger when compared to the baseline peak without the introduction of the LICF.

The largest facilitation of the MEP was observed in Subject 11 with a 118.549% increase from the baseline peak. The smallest facilitation observed was for Subject 2 where only a 2.553% facilitation from the baseline was observed while the vibrotactile noise was off. For Subjects 7, 10, and 12 while the noise was on, a negative percentage was observed, - 42.579%, -32.918%, and -6.628%, respectively. Therefore, while the noise was on, the peak amplitude was smaller than the baseline peak after the MEP. Other negative values were observed when the noise was off for Subjects 4 and 7, with -27.206% and -0.886%, respectively.

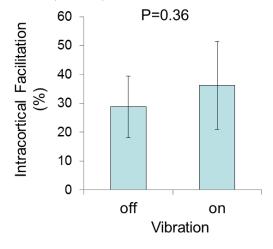
Table 3. Raw Intracortical Facilitation Data of Noise on vs off. The percent increase of the peak-to-peak MEP amplitude with the conditioning stimulus compared to without determined LICF is found for each Subject.

Subject	Noise On (% increase)	Noise Off (% increase)
1	65.850	34.305
2	7.234	2.553
3	12.438	98.889
4	43.186	-27.206
5	21.335	38.695
6	98.914	3.414
7	-42.579	-0.886
8	102.794	23.226
9	46.991	16.821
10	-32.918	88.330
11	118.549	54.302
12	-6.628	13.493

Figure 7 below represents the average of the percent facilitation from the baseline peak reading while the vibrotactile noise was on versus when it was off for all twelve Subjects. The average intracortical facilitation of the MEP while the noise was on was 36.264%, and the average intracortical facilitation of the MEP while the noise was off was - 28.828%. The paired two sample t-test showed a p > 0.36, meaning that a significant

statistical difference was not observed between the vibrotactile noise on versus when the vibrotactile noise was off.

Figure 7. Average Intracortical Facilitation of MEP. The percent change average for the on vs off condition were compared. A significant difference was not found between the two values (P=0.36).



Cortical Silent Period

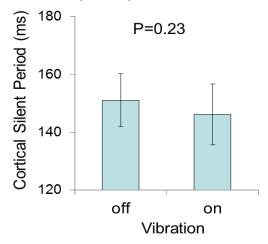
The silent period was determined as the duration from the TMS trigger until the EMG signal returned. An average of eight repetitions were taken when the vibrotactile noise was on and when it was off for each Subject. Table 4 below is the raw data of the cortical silent period of all twelve Subjects. The largest cortical silent period observed was 0.239 ms from Subject 3. In return, the smallest cortical silent period observed was in Subject 11 with a value of 0.101 ms. The longest cortical silent period in duration observed when the vibrotactile noise was on was 0.239 in Subject 3 and the shortest in duration was 0.101 ms. Conversely, the longest cortical silent period observed when the condition was off was 0.216 observed from Subject 3 and the smallest in duration cortical silent period when the noise was off was 0.104 ms from Subject 1.

Table 4. Raw Data of Cortical Silent Period. The silent period was determined as the duration from the TMS trigger until the EMG signal returned. An average of eight repetitions were taken when the vibrotactile noise was on and when it was off for each Subject under each condition (on vs off).

Subject	Noise On (ms)	Noise Off (ms)
1	0.127	0.104
2	0.152	0.154
3	0.239	0.216
4	0.154	0.127
5	0.121	0.140
6	0.153	0.165
7	0.103	0.148
8	0.147	0.178
9	0.176	0.184
10	0.143	0.141
11	0.101	0.106
12	0.137	0.148

Figure 8 below is the average duration of the cortical silent periods of all twelve Subjects. While the condition was off, the average cortical silent period observed was 0.151 ms in duration. While the noise was on, the average cortical silent period calculated was 0.146 ms in duration. The comparison between the conditions on versus off using a paired two sample t-test showed a p < 0.23. Therefore, no statistical difference was observed between the duration of the cortical silent period between when the vibrotactile noise was on and when it was off.

Figure 8. Intracortical Cortical Silent Period Duration Average. The duration average for the on vs off condition were compared. A significant difference was not found between the two values (P=0.23).



Recruitment Curve

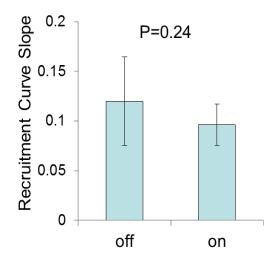
Table 5 below shows the raw data collected from all twelve Subjects during the recruitment curve protocol. The measurement obtained was the steepest slope observed during the formation of the sigmoidal curve. The steepest slope observed was 0.541 from Subject 7. The least steep slope observed was 0.0218 from Subject 1. While the vibrotactile noise was on, the steepest slope observed was 0.215 and the least steep slope observed for this condition was 0.0218. While the vibrotactile noise was off, the steepest slope observed was 0.541 and the least steep slope observed was 0.0281.

Table 5. Recruitment Curve Average Raw Data. The maximum slope of the recruitment curve was the outcome measurement obtained from each Subject (steepest slope).

Subject	Noise On	Noise Off
1	0.0218	0.0419
2	0.149	0.175
3	0.200	0.0302
4	0.0263	0.0281
5	0.0530	0.0434
6	0.215	0.292
7	0.191	0.541
8	0.0732	0.0635
9	0.0675	0.0942
10	0.183	0.0386
11	0.0392	0.0383
12	0.112	0.0691

Figure 9 below is the averaged slopes collected from each of the Subjects during the experiment. The average steepest slope data for when the condition was off was determined to be 0.121. Meanwhile, the average steepest slope data for when the condition was on was determined to be 0.111. The value obtained from the condition off seemed larger than the value obtained when the condition was on. A paired two sample t-test was used to determine if the two values were significantly different. A p < 0.24 was obtained meaning that no statistical difference was observed between the two values.

Figure 9. Recruitment Curve Average (on vs off). The average steepest slope for the on vs off condition were compared. A significant difference was not found between the two values (P=0.24).



DISCUSSION

The hypothesis of this experiment states that corticospinal motor excitability of healthy adults will increase with the wrist subthreshold vibrotactile stimulation on when compared to when the vibrotactile noise is off. When all of the variables of the corticospinal excitability are taken into account, the hypothesis must be rejected since all three variable showed no indication of a higher excitability when the vibrotactile noise was on. The only variable that showed a significant difference between the conditions of vibrotactile noise on and off was the inhibition measurement of the MEP. The CSP and the duration of the cortical silent period was used as a measure of cortical inhibition that is thought to be mediated by local GABAergic circuits, in specific GABA_B receptors (Guglietti et al., 2013; Orth & Rothwell, 2004). The average CSP of the Subjects was hypothesized to decrease once the vibrotactile noise was present on the wrist, indicating an increase in corticospinal excitability. The results indicated that the noise did not affect the CSP. In relation to the inhibition, facilitation and the CSP, the recruitment curve is the sigmoid curve that indicates a relationship between the intensity of the stimulus and the motor evoked potential (MEP) amplitude (Rossini et al., 2015). The early segment of the sigmoid curve is flat and come from stimulus intensity that corresponds to the motor threshold (MT), whereas the second portion of the curve is an ascending sigmoidal line caused by the approximation of the linear increase in the MEP amplitude with increasing stimulus intensity (Rossini et al., 2015). The results showed that the steepest slope of the condition where the vibrotactile noise was on was not significantly different than when the noise if off. An average recruitment curve steep slope was expected to indicate an increase in overall corticospinal motor excitability, but the results indicated that the vibrotactile noise did not influence this overall indicator of

corticospinal excitability.

The question that must be answered after three of the variables did not show an increase of excitability is why those variables did not change with the vibrotactile noise condition being turned on. In relation to the recruitment curve, it has been noted in the literature that the use of a stimulation intensity sufficient to generate a MEP of standard amplitude, or 1 mV, fails to provide a satisfactory basis to assess the impact of this intervention at the corticospinal tract (Burke & Pierrot-Deseilligny, 2010; Carson et al., 2013). This is explained by the considerable variation that exists across individuals and target muscles in the input-output relationship between TMS stimulation intensity and MEP amplitude (Carson et al., 2013). It has even been noted that muscles proximal to the hand exhibit poor test-retest reliability (Carson et al., 2013). In this case, the muscle being tested was the ABP, which could be close enough to this body area, making the sigmoid function of the recruitment curve not able to provide an adequate basis to assess the impact of the excitability of the corticospinal projections to this muscle.

Another factor that needs to be accounted for to explain the non-significant results between the on versus off conditions in the three variables is the fact that figure-of-8 shape coils are not focal, meaning that the ability to activate discrete brain regions or specific neural connections is relative to the accuracy of the position maintained throughout the stimulation (Burke & Pierrot-Deseilligny, 2010). The TMS pulse activates axons, and not cell bodies, and it is known that when an axon discharges, its excitability changes (Burke & Pierrot-Deseilligny, 2010). Activation of the axons of intracortical interneurons will lead to an obligatory phase or refraction, and the axons will hyperpolarize following several stimuli. Since the stimulus was the exact same strength when established by the rMT, the same

strength stimulus did not excite the same number of intracortical axons as it did at the beginning of the study (Burke & Pierrot-Deseilligny, 2010). If cortical excitability changed at the beginning of the study due to the application of the vibrotactile noise and the TMS pulse, the subthreshold conditioning stimuli did as well. It is suggested that threshold should have been recalibrated for the test MEP during the different measurements assessed (Burke & Pierrot-Deseilligny, 2010). Taking into account that all the Subjects were healthy and had no previous pathology that damaged any of the motor tracts, their bodies corrected for all of the overload of stimuli during the experiment.

Implications to Stroke Rehabilitation

Taken together with previous studies, the vibration appears to affect not only the sensory system but also the motor system of the hand even at rest (Lakshminarayanan et al., 2015; Hur et al, 2014; Enders et al., 2013; Seo et al., 2014; Seo et al., 2015). Specifically, the vibration may affect the hand function not only by improving sensation and sensory feedback-based motor control of the hand, but also by directly changing excitability of the corticospinal tract as the results from the inhibition of the MEP show. The improvement reported in this pilot study may be small, but the improvements were obtained instantaneously, and repeated use of the device may result in a greater clinical impact in stroke survivors. The results from this study also reinforces the fact that application of the noise to the wrist, as opposed to the fingers, prevents the device from interfering with object manipulation as see in other studies (Seo et al., 2014).

The focus of stroke rehabilitation is to regain or improve function for the stroke survivor (Seo et al., 2014). Improving function of the affected hand could mean an increased ability to perform activities of daily living and the confidence to be more independent as a

stroke survivor. Studies point out that manual dexterity is indicative of functional independence (Seo et al., 2014). The features of the approach taken in this study enable the potentially easy adoption of subthreshold sensory noise for home or clinic use. The approach taken in this study applied an unperceivable vibration to the wrist of healthy Subjects. Simple mechanical vibration can be produced with low-cost devices and fewer safety concerns, compared with temporary deafferentation via anesthesia, constant current electrical stimulation, which are not all accessible or have a greater side effect (Seo et al., 2014).

The application of the noise to the wrist may have increased the corticospinal excitability in two different ways. One of the theories formulated by this study states that the GABA-Aergic inhibitory activity within the primary motor cortex or corticospinal tract was affected, meaning that the inhibition of the MEP was decreased, which in return increased the excitability of the muscle. The second theory proposed by the results of this study indicated that the vibrotactile noise was affecting the corticospinal tract via stochastic resonance. If so, the increased excitability is similar to the increase in motor coordination results via somatosensory pathways.

GABA-Aergic Inhibition as Means of Increased Cortcicospinal Excitability

The vibrotactile noise was postulated to be disturbing or affecting the receptors or the function of GABA, allowing the stimulus to travel freely through the sensory pathway, in return allowing for higher corticospinal hand excitability. From several different animal studies, it is known that intracortical inhibitory circuits are involved in cortical plasticity in different ways (Russmann et al., 2009). In relation to the results obtained from this experiment, the results obtained through other *in vitro* studies showed that the decrease of local inhibitory activity supplements and stimulates the development of long-term

potentiation (LTP) synaptic remodeling and cortical receptive field expansion. LTP is defined as an increase in synaptic strength of a neuron following high-frequency stimulation of a chemical synapse, in this case the GABA-Aergic receptors in the corticospinal tract (Russmann et al., 2009). However, the results attained by this experiment meant that the imperceptible white-noise wrist vibration affected the cortical motor excitability by reducing the activation of the GABA_A receptor inhibition. In humans, indirect evidence has supported that a decrease of local GABA_A receptor inhibition in the motor cortex enhances dramatically the excitability in the intracortical circuitry during motor practice (Ziemann et al., 2001; Russmann et al., 2009). Meanwhile, the blocking of GABA_B inhibition prevents the development of a cortical plasticity artificially caused by TMS (McDonnell et al., 2007; Russmann et al., 2009).

Taken together with previous studies, the significant reduction of the inhibition of the MEP when the vibrotactile noise was applied to the wrist allowed for a sign of increased corticospinal excitability in healthy adults. Studies of the GABA_A receptor complex indicated that it facilitates an increase in membrane conductance of Cl ions with an equilibrium potential at around −70 mV (Olsen & DeLorey, 1999). The conductance increase is frequently followed by a membrane hyperpolarization, resulting in an increase in the firing threshold of the neuron (Olsen & DeLorey, 1999). Therefore, a decrease in the likelihood of an action potential initiation is observed, causing neuronal inhibition of the action potential (Olsen & DeLorey, 1999). It is suggested by the results obtained that the noise could disturb these GABA_A receptor complexes in the corticospinal tract, allowing for the motor action potentials to be carried to the hands more easily. In the context of stroke rehabilitation, the wrist vibration theoretically would increase the likelihood of a motor action potential

reaching the hands of the stroke survivor, which in return facilitates the usage of the hand. Reduction of GABA-Aergic inhibition may be beneficial for hand movement initiation of chronic stroke survivors with elevated GABA-Aergic inhibition (Hummel et al., 2009). Stochastic Resonance as Means of Increased Corticospinal Excitability

The concept of stochastic resonance has been proposed as a method of improving hand coordination in stroke survivors by affecting the somatosensory system (Seo et al., 2014). The addition of noise improves signal detection and feedback-controlled system performance, and it has been demonstrated theoretically in varieties of mammals, including humans (Duan et al., 2013; Seo et al., 2014). Subthreshold vibrotactile noise when applied to the foot has been shown to improve foot tactile sensation in stroke survivors, healthy young adults and old adults (Liu et al., 2002; Wells et al., 2005). In relation to hand function, subthreshold vibrotactile noise when directly applied to the index fingertip has been shown to immediately improve finger tip tactile sensation in stroke survivors and healthy adults, but it also reduced the amount of excess grip force for lifting objects (Liu et al., 2002; Kurita et al., 2013).

SR is broadly applied to describe neurophysiological phenomenon where the presence of this noise in a nonlinear system strengthens the output signal quality than if the noise was absent (Gammaitoni et al., 1998; McDonnell & Abbott, 2009). This effect required three components which are described as an energetic activation barrier, or threshold in the case of the somatosensory pathway, a weak coherent input, such as a periodic signal like the subthreshold vibrotactile noise, and finally a source of noise that is inherent in the system, such as an action potential fired by the neurons (Gammaitoni et al., 1998). The addition of this noise could have increased the likelihood that the motor pathway was able to fire the

action potentials via temporal summation. Temporal summation occurs when the high frequency of action potentials in the presynaptic neuron elicits postsynaptic potentials that overlap and summate each other (Inghilleri et al., 1990; Taylor et al., 1993). This effect is generated by a single neuron as a way of achieving action potentials (Inghilleri et al., 1990; Taylor et al., 1993). Therefore, the corticospinal excitability could have been increased via this mechanism. However, this would meant that the facilitation, cortical silent period, and recruitment curve should have shown significant difference as well. As explained previously, the order and lack of breaks in between measured variables may have caused the system of the healthy adults to adapt to the noise increasing the threshold of noise necessary in order to see an effect on the excitability.

Future Studies

Despite a significant result obtained from this pilot experiment, future studies are necessary to continue the understanding of how this vibrotactile noise affects the human body. Future studies may examine a potential of this vibration technique in enhancing hand therapy outcomes and abilities for activities of daily living in stroke survivors and others with sensorimotor issues. It is probable that the noise will have a significant impact not only on the inhibition of MEP, but also the facilitation, CSP and recruitment curve measurements of actual stroke survivors who have a much more debilitated motor and sensorimotor systems. In addition, to further understand the effects of the noise on the GABA-Aergic inhibition, *in vitro* and *in vivo* models could be used to measure the physical and chemical changes observed when the noise is on versus off. The method of using subthreshold vibrotactile noise as a rehabilitation technique needs to further be accessed to determine how much exposure, frequency of the treatment, and location of the noise in the hands is necessary to

positively impact the hand coordination of stroke survivors in the short-term and long-term usage of this treatment.

CONCLUSION

Vibrotactile noise was previously shown to improve touch sensation and motor function of the hand in stroke survivors and healthy adults (Collins et. al, 1997; Kurita et al., 2013; Seo et al., 2014; Wells et al., 2005). This study contributes to elucidating neural mechanisms of the vibration-based sensory stimulation approach that has a potential to enhance day-to-day hand function. Imperceptible white-noise wrist vibration could have affected the cortical motor excitability by reducing the activation of the GABA-Aergic inhibition or through effects to stochastic resonance. Specifically, the vibration may affect the hand function not only by improving sensation and sensory feedback-based motor control of the hand, but also by directly changing the GABA-Aergic inhibitory activity within the primary motor cortex. The reduction of GABA-Aergic inhibition may be beneficial for hand movement initiation of chronic stroke survivors with elevated GABA-Aergic inhibition (Hummel et al., 2009). Future studies may examine a potential of this vibration technique in enhancing hand therapy outcomes and abilities for activities of daily living in stroke survivors and others with sensorimotor issues. Therefore, this experiment allows for a potential enhancing of the vibrotactile therapeutic technique currently being studied in stroke patients.

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