Design Principles and Application of a Wearable Vibration Device for Individuals with Proprioception Deficiency

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ABSTRACT

Proprioception deteriorates as a result of both healthy aging and injuries to the nervous system. Effective and efficient limb control requires accurate feedback from the moving limbs, thus any change in proprioception has a direct impact on movement performance. In recent years muscle tendon vibration has emerged as a complementary treatment option for improving motor performance in individuals with stroke or older adults. However, it is not clear how vibration of antagonist muscle groups will affect performance of upper limb tasks and how adaptable the sensorimotor system is to such afferent input. The current thesis explored the role of proprioception on motor control processes with the goal of developing a wearable sensory assistive device.

This thesis includes 5 studies: the first two being fundamental studies focused on the role of using visual versus proprioceptive inputs in the motor control of the upper limb when one or both inputs are modified. The third study, a systematic review with meta-analysis, determined the characteristics of effective muscle tendon vibration for improving upper limb movements in individuals with stroke. The fourth study reports the design considerations and development of a novel assistive device that used muscle-tendon vibration for upper limb rehabilitation. The fifth study is a proof-of-concept study on the performance of an upper limb aiming task with muscle-tendon vibration applied at the wrist of young adults.

The results of the five studies are organized in a manuscript-style thesis. The results of the first two fundamental studies found and confirmed the significant role of proprioceptive input in online control of movements, even in the presence of visual input. A prototype of the muscle-tendon vibration device was designed based on the results of the systematic review and meta-analysis. Finally, the behavioural study using muscle tendon vibration provides proof-of-concept for future clinical trials using this novel assistive device. Based on the current findings, future research will focus on the effectiveness of the muscle-tendon vibration band for rehabilitation in individuals with stroke and older adults.

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DEDICATION

This thesis is dedicated to my parents.

For their love, support, and encouragement.

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LIST OF ABBREVIATIONS

CE	Constant error
CI	Confidence interval
CNS	Central nervous system
EEG	Electroencephalography
EMG	Electromyography
ERM	Eccentric rotating mass
FAS	Functional ability scale
FIM	Functional independence measure
IRED	Infrared light emitting diodes
HSD	Honestly significant difference
KR	Knowledge of results
MT	Movement time
MTV	Muscle tendon vibration
MVC	Maximum voluntary contraction
PEDro	Physiotherapy evidence database
PRISMA	Preferred reporting items for systematic reviews and meta-analyses
PV	Peak velocity
QuickDASH	Disabilities of the arm, shoulder, and hand
RCT	Randomized controlled trial
RT	Reaction time
SD	Standard deviation
SEPs	Somatosensory evoked potentials
SMD	Standardized mean difference
taPV	Time after peak velocity
TMS	Transcranial magnetic stimulation
ttPV	Time to peak velocity
VE	Variable error
WMFT	Wolf motor function test

CHAPTER 1

INTRODUCTION AND LITRATURE REVIEW

1.1 Preamble

Proprioception is necessary for fast, smooth and effective movement control. In particular, proprioception plays a significant role for movement control when vision is not available. Proprioception improves with both practice and development in healthy individuals. It can also be impaired or absent as a result of aging and central or peripheral nervous system deficiencies, such as stroke and diabetes, respectively. Current evidence indicates that proprioception training using various robotic rehabilitative devices and physical training methods may be effective for regaining lost sensorimotor function through promoting cortical plasticity related to proprioception. However, little attention has been given to wearable rehabilitation devices, such as a muscle tendon vibration band, that may enhance upper extremity sensorimotor function through proprioceptive stimulation. Using a wearable device is cost effective because individuals can learn to use them independently. Hence, the purpose of the current thesis was to understand the contributions of proprioception to upper limb movement control, including the adaptability of the sensorimotor system to changes in the visual and proprioceptive inputs. The findings were then used for the design of a novel rehabilitation device for individuals with somatosensory deficiencies.

The current thesis consists of 7 chapter including 5 studies (chapters 2-6). Chapter 1 is the general introduction presenting the current literature on the importance and role of proprioception in motor control, including how proprioception can be stimulated and modified. Details of studies using induced paresthesia and muscle-tendon vibration techniques are reviewed. Chapters 2 and 3 include two fundamental studies on how the accuracy and efficiency of goal-directed movements are impacted by impaired proprioception. Induced paresthesia was used to impair proprioception while vision of the limb and/or target was manipulated. Together these experiments investigated how the sensorimotor system adapts to induced paresthesia when performing a goal-directed aiming task, and if vision of the limb specifically is used to help improve movement performance. Chapter 4 presents a literature review and meta-analysis on the effectiveness of muscle tendon vibration in improving the function of the upper limb in individuals with chronic stroke. Based on the findings of this literature review, the study reported in chapter 5 addresses design considerations for the prototype of a novel muscle-tendon vibration band. The latter study also includes a validation study on a cost-effective method for measuring the characteristics of vibration for muscle tendon vibration protocols. Chapter 6 reports a proof-of-concept study on the effects of muscle-tendon vibration on motor performance of the upper limb. Motor performance was

assessed by analysis of a goal-directed aiming movement while applying the muscle-tendon vibration over the wrist. Taken together the findings of the current research contribute to our understanding of the role of proprioception in the efficiency and accuracy of functional upper limb movements and the associated effects of muscle-tendon vibration, as a method of proprioceptive input modification/augmentation, on upper limb motor performance. The findings of the current thesis lay the foundation for future studies that will examine the effects of the newly developed vibration band on patient populations and older adults. The results of the above studies have been organized in a manuscript-style thesis. Chapters 2-6 provide manuscripts reporting each study separately. The final chapter (chapter 7) includes a summary explanation of the findings of the current thesis and its contributions to the relevant scientific fields.

1.2 Literature Review

1.2.1 Proprioception

Proprioception or kinesthesia is the awareness of the position of each part of the body relative to one another. Proprioception is considered one of the major functions of the somatosensory system that allows humans to control their moving limbs efficiently and effectively, especially when visual feedback is absent (Schmidt et al., 2018a; Sherrington, 1952b). Proprioception includes i) the vestibular system and ii) the receptors within tendon muscles, joints, and skin. The vestibular system provides information about gravity acceleration and head motion that are sensed with the hair cells in vestibular labyrinths. This information contributes to postural control (Schmidt et al., 2018a). Input from mechanoreceptors of the joints, skeletal muscles, tendons, and tactile information from the body surface integrates in the body schema so that we are aware of the position and movement of our limbs and joints in space. Haggard and Wolpert (Haggard & Wolpert, 2005) defined body schema as "a neural representation of the body used for spatial sensorimotor processing" that is a higher-order cognitive representation of the body, rather than a somatotopic map of the body.

Proprioception can be interrupted anywhere along the peripheral or central pathways, including in neurologic conditions such as Parkinson's disease, stroke, peripheral sensory neuropathies, or non-neurologic conditions such as aging. Since proprioceptive feedback is necessary for fine motor control and error correction during movement (Carey et al., 1993;

Schmidt & Lee, 2011; Tyson et al., 2008), its loss will have a significant effect on the quality of the voluntary movement, especially in the upper limb.

1.2.2 Proprioceptors

Mechanoreceptors are the type of sensory receptors used for sensing proprioception. There are four major categories of senses that can be detected by mechanoreceptors: (1) skin tactile sensibilities, (2) deep tissue, muscle, and joint sensibilities, (3) hearing, (4) equilibrium, and (5) arterial pressure. The first two categories are the ones that are involved in sensing tactile and proprioceptive stimulations. Skin tactile stimulations can be detected by free nerve endings, Merkel's disks, Ruffini's endings, Meissner's and Pacinian corpuscles, and hair end organs. These mechanoreceptors sense skin deformation, motion, stretch, and vibration. Tactile stimulations on the glabrous skin of the hand and feet can be detected by four mechanoreceptors, two at the superficial and two at the deep layers of skin. The superficial layers contain small receptor cells including Meissner corpuscles and Merkel cells while deep layers of the skin and subcutaneous tissue contain large receptors such as Pacinian corpuscles and Ruffini endings. Overall, almost all tactile receptors have some role in detecting vibration, but each of the receptors are sensitive to different vibration frequencies (Kandel et al., 2013). There are four specialized muscle ending mechanoreceptors that contribute to the sense of proprioception. These receptors acquire different aspects of body movement information. These aspects include: i & ii) muscle-length, sensed by primary and secondary muscle spindles (type Ia and II fibers); iii) muscle force or effort; sensed by Golgi tendon organs (type Ib fibers); and v) tension in joints, sensed by joint capsule receptors (type II fibers) (Hall, 2015; Kandel et al., 2013)

1.2.3 Muscle and Tendon receptors

Muscle tendon mechanoreceptors are mainly in charge of the sense of limb position and limb movement. They include *primary and secondary fibers of muscle spindles* and *Golgi tendon organs* (Matthews, 1974). Primary endings are innervated by group Ia sensory fibers and are sensitive to size and speed of muscle length change. Also, primary endings may be responsible for sense of position and movement (Goodwin et al., 1972a; Matthews, 1974). Secondary endings may contribute to the sense of limb position. These receptors are innervated by II sensory fibers and are

known to be sensitive to changes in muscle length and do not have a significant role in sensing changes in velocity (Matthews, 1974).

In the general classification of nerve fibers, the nerve fiber group for muscle ending receptors are Aα, β fibers. Muscle spindle fibers are named as group Ia and II fibers and include intratubal muscle fibers that are encapsulated and placed parallel to the long muscle fibers. So, the rate of firing of these receptors are proportional to the length of the enclosing muscle. Muscle spindles can detect both active and passive changes in muscle length. Muscle spindles can also detect rapid rates of changes, which makes them suitable for detecting movement rates associated with mechanical vibration (Hall, 2015; Kandel, 2013). In contrast, Golgi tendon organs are 1mm long and 0.1 mm in diameter encapsulated structures that are located at the junction of muscle and tendon. There are several braided collagen fibers that are connected in series to the muscle fibers. Each tendon organ is innervated by a Ib afferent axon that has many branches inside the receptor capsule. These nerve endings are connected to collagen fibers in such a way that stretching the tendon organs will compress these nerves. Therefore, Golgi tendon organs can measure the load on tendons and the force generated by the muscles (Hall, 2015; Kandel, 2013). Muscle spindles and Golgi tendon apparatuses are both slowly adapting receptors. That is, both receptor types keep sending signals to the brain as long as the stimulus exists so that the brain will be aware of the status of muscle contractions and load on the tendons at all times (Hall, 2015).

1.2.4 Proprioception Pathways

All somatosensory signals, including proprioception, touch, pressure, pain, thermal sensation, tickle and itch, and sexual sensation enter the spinal cord through the dorsal roots. The neural signals are then transmitted to the brain through the dorsal column-medial lemniscal system and the anterolateral system. The medial lemniscal system transfers signals from phasic sensations (detected by different mechanoreceptors) such as vibration, sensations of movements against the skin and position of the joints to the somatosensory areas of the brain (Hall, 2015). The dorsal column-medial lemniscal system is made of large, myelinated fibers with high conduction velocities (30 to 110 m/sec). Besides the high velocity capability of these fibers, they are oriented in an organized way that makes the fibers suitable for transferring signals that need fast transmission with high temporal and spatial precision, such as position sensations from the joints and phasic sensations (i.e., vibratory sensations over the skin). The main pathway of the dorsal

column–medial lemniscal system consists of one of only three synaptic relays between the periphery and cerebral cortex: i) the synapse of the neurons ascending from the dorsal root ganglion to the Gracile and Cuneate nuclei in the medulla; ii) the synapse at the ventral posterior lateral nucleus in the thalamus (after decussation in the medulla); iii) the synapse between the thalamic neurons with the primary somatic sensory cortex (Gilman, 2002; Hall, 2015; Kandel, 2013). The projections of these third-order neurons travel mainly to the postcentral gyrus in the parietal lobe of the cerebral cortex, also known as somatic sensory area I. Additional projections travel to a smaller area in the lateral parietal cortex, known as somatic sensory area II (Hall, 2015; Kandel, 2013).

1.2.5 Motor Control and Role of Proprioception

Visual and proprioceptive sensory inputs contribute to different aspects of planning and controlling limb movements. Vision is thought to monitor the kinematics and trajectories of the movements. Proprioception is thought to evaluate the amount of muscle force and joint torques needed to adapt (update the future motor commands) for the environmental perturbations to effectively execute the planned movement (Sarlegna & Sainburg, 2009; Sober & Sabes, 2003).

Proprioceptive and tactile afferents (somatosensory inputs) provide information about changes in the immediate environment and within the body. The central nervous system uses this information for adaptations related to perturbations and changes in the environment as well as planning movements in relation to the body's surroundings. Proprioception is a key source of input that the central nervous system uses to generate and adapt motor commands. For example, it is thought that the CNS uses feedback from the mechanoreceptors within the joint capsules and muscles tendons that are responsible for locating the relative angles of the limb segments and multiple joints (Riemann & Lephart, 2002). In a simple goal directed movement using the upper limb there are several muscles that pass the shoulder, elbow, and wrist. Afferent information from all the proprioceptors within these muscles and joints will be integrated by the central nervous system and contribute to updating ongoing motor commands.

Sensory-motor and cognitive processes involved in controlling human movement have been studied for more than a century. In 1899, Woodworth defined a two-component model for controlling goal-directed aiming/reaching movements (Woodworth, 1899). The ballistic phase that is responsible for covering most of the distance from the start point to the vicinity of the target.

The current control phase includes the error corrections for the initial ballistic portion of the movement in order to land on the target. Elliott et al. proposed the multiple process model of limb control with two phases for aiming movements: impulse control, limb-target control (Elliott et al., 2001; Elliott et al., 2017). This model takes into account multiple processes such as noise in the neural-motor system, force related error as well as efficiency of energy expenditure. These components of a movement form an internal representation of expected efference and sensory consequences. According to Elliott's model, during the limb target control phase the available sensory inputs are compared to the internal representations. This comparison is used to proactively make any necessary online error corrections. Elliott also suggested that these two phases are not independent. He considers visual feedback as the main sensory driver of the impulse control phase and a combination of proprioception and vision as the main sources of information for limb-target regulation.

1.2.6 Proprioception Loss: motor consequences

Lesions and conditions that involve any of the components of the somatosensory pathways will affect proprioception. Some conditions that involve these components are: demyelination polyneuropathies, neurotoxic or nutritional neuropathies, plexopathies or radiculopathies, spinal cord lesions including dorsolateral cord lesions, Brown-Sequard syndrome, infarction in the dorsal or radicular spinal arteries, tumors that compress the dorsolateral spinal cord, and brainstem lesions, lesions of ventrolateral and ventromedial thalamus, diseases within the postcentral cortex (Gilman, 2002). Other conditions include injuries to the ligaments, joints, and muscles (Barrack et al., 1989; Lephart et al., 1994; Torres et al., 2010). Older adults have also been found to have significant decline in their somatosensory function (Adamo et al., 2009; Goble et al., 2009).

Several studies on patients with large-fiber sensory neuropathy, a condition that leads to disruption of proprioceptive pathways, have provided a clear understanding of the motor function deficits that accompany a lack of proprioception, including difficulties in maintaining consistent level of force (Rothwell et al., 1982), performing a movement task according to the defined sequence and timing without visual feedback (Rothwell et al., 1982), maintaining a specific movement amplitude of a simple repetitive task without visual feedback (Rothwell et al., 1982), fine-tuning the movement for the endpoint accuracy (Rothwell et al., 1982; Sanes et al., 1985), inter-joint coordination (Sainburg et al., 1993), maintaining the trajectory of the movement

(Sainburg et al., 1993). All these deficiencies will severely affect the quality and efficacy of movements and lead to difficulty with everyday activities such as cooking or driving. The following two sections present clinical evidence on proprioception loss in two frequent conditions: aging and stroke.

1.2.6.1 Proprioception loss and Aging

Several studies have shown that both sense of position and movement in the joints deteriorate with aging. The decrease leads to functional deficits in both upper and lower limb tasks as well as balance activities. The deterioration may be the result of parallel mechanisms such as degenerative changes in the peripheral nervous system as well as deficiencies in the central processes related to proprioceptive feedback (Goble et al., 2009). Adamo et al. conducted two studies on the static joint position sense of older adults' during both elbow (Adamo et al., 2007) and wrist (Adamo et al., 2009) single-joint position reproduction tasks. The results from the matching task for the elbow and wrist joints showed significantly higher errors and longer movement times for older adults than their younger counterparts. The older adults showed a lack of smoothness in their movements and longer movement times since they had several sub-movements that corresponded to more online corrections. In another study, the same group of researchers (Wright et al., 2011) assessed the joint motion sense (kinesthesia) in older adults (mean age: 79.5 ± 2.2 years) and measured their ability to perceive passive movement about the wrist. The results showed that the somatosensory sensation impairments related to joint position were not limited to static sense of position in the older adults, and that the ability to detect wrist joint motion was significantly impaired as well. Older participants' ability to detect passive movement threshold were two times higher than the younger participants (about 2° versus 1° in the younger group).

1.2.6.2 Proprioception Loss and Stroke

Impairment of proprioception is estimated to occur in 25 to 50% of individuals with stroke (Carey, 1995; Kessner et al., 2019). Proprioception impairment is associated with primary and secondary somatosensory cortex lesions as well as lesions in frontal subcortical areas, frontal insular cortex and the external capsule and subcortical area in the parietal associative cortex and putamen (Kessner et al., 2019). As previously mentioned, somatosensory afference makes several synapses and pathways in different areas of the central nervous system. Stroke related lesions in

any of these brain structure will impair sensorimotor function. Kenize et al., conducted a study on acute stroke patients with lesions in ventral posterior lateral nucleus of the thalamus, the posterior limb of the internal capsules, the post-central gyrus and posterior parietal cortex. The authors assessed the consequences of lesions in these somatosensory related areas on motor and proprioceptive function (Kenzie et al., 2014). To assess the sense of proprioception, active and passive robotic guided position matching tasks were used without vision of the limb. The findings of Kenize's study showed increased spatial and temporal variability in both static and dynamic position tasks in participants with stroke. In another study Scheidt & Stoeckmann studied the adaptation of reaching movements when performing a task with unpredictable environmental perturbations in stroke patients (Scheidt & Stoeckmann, 2007). The task was conducted using a robotic arm that applied unpredictable amounts of load on the handles between the trajectories of the two horizontal targets while vision of the limb was blocked. The authors showed that clinically measured proprioception loss was related to measurements of movement trajectory adaptation in response to the perturbation loads and to final hand position variability. Scheidt & Stoeckmann also found that stroke patients with proprioceptive deficiencies did not adapt their future motor plans and performance according to the experience of past perturbation as much as people with intact proprioception. These results could be explained by the fact that feedback from the proprioceptors plays an important role in evaluation of the amount of muscle force and joint torques needed to adapt (update the future motor commands) for the environmental perturbations (Sober & Sabes, 2003). Thus, stroke patient with lesions in the areas that are involved with somatosensation are not able to acquire the feedback needed for updating their existing motor programs or for online control of their movements.

1.2.7 Muscle tendon vibration method and mechanisms

Muscle tendon vibration uses a mechanical device to apply vibration stimulation over the muscle tendon units. For ease of reference in the current document, muscle tendon vibration applied simultaneously on antagonist muscle groups around one joint will be referred to as "dual muscle tendon vibration" or dual MTV, and muscle tendon vibration applied on one muscle group in a joint will be referred to as "single muscle tendon vibration" or single MTV. It is important to note that different frequencies of vibration on muscles tendons can activate different sensory receptors such as muscle spindle primary (Ia) and secondary (II) endings and Golgi tendon organs

(Ib), or cutaneous mechanoreceptors such as Pacinian corpuscles (Aman et al., 2014; Enders et al., 2013; Roll et al., 1989). The peripheral system inputs during the actual movements are similar to the response of proprioception afference to mechanical vibration. Roll et al. showed using microneurography that sensation of movement could be stimulated by selective stimulation of muscle spindles using vibration over the muscle tendons (Roll & Gilhodes, 1995; J. P. Roll & J. P. Vedel, 1982). Before that, Goodwin et al. showed that vibration over the tendon of the upper limb could be perceived as the muscle is being stretched (Goodwin et al., 1972b). This false sense of movement that is induced by vibration is called "illusory movement" sensation. Findings of several studies suggest that primary muscle endings have a major role in the illusory movement sensation (Goodwin et al., 1972a; J.P. Roll & J.P. Vedel, 1982). Moreover, Roll and Gilhodes showed that the same vibration frequency over two antagonistic muscles does not induce kinesthetic illusions (Roll & Gilhodes, 1995). There are studies suggesting that the equal vibration stimulation over antagonist muscle groups will degrade proprioception (Bellan et al., 2016; O. Bock et al., 2007). However, Gonzales and Goble showed that proprioception adaptation happened within about 10 minutes of biceps-triceps vibration as measured by an elbow angle matching task (Gonzales & Goble, 2014). The results of this study showed that the amplitude of the undershoot errors (constant error) for the matching task decreased at the later trials when compared to the early trials. However, matching variability (variable error) did not increase significantly during biceps-triceps vibration.

Brain excitability studies have shown that MTV leads to cortical level changes in healthy individuals (Forner-Cordero et al., 2008; Marconi et al., 2008; Rosenkranz et al., 2003) and in individuals with stroke (Marconi et al., 2011). These changes include excitability of the motor areas related to the vibrated muscle, as well as patterns of intra-cortical inhibition and facilitation. Marconi et al. conducted a brain excitability study using transcranial magnetic stimulation (TMS) on healthy participants (Marconi et al., 2008). They found that 30 minutes of MTV (100 Hz frequency, 0.05-0.1mm amplitude) on a contracting wrist flexor muscle can cause changes in the target muscle's cortical excitability that lasted for two weeks and returned to baseline levels within three weeks. In another study Marconi et al. used the same MTV protocol for individuals with chronic stroke (Marconi et al., 2011). The authors used TMS before and after the MTV protocol and measured the sum of averaged motor evoked potential amplitudes acquired from all of the excitable sites mapped on the scalp. The results of this study showed increased map volume for both agonist and antagonist muscles. Motor cortical excitability changes in Marconi et al.'s study

with stroke participants was also accompanied by reduced spasticity and improved functional movement (Marconi et al., 2011). In most of the MTV clinical studies the vibration frequencies were between 80Hz and up to 120Hz, with small vibration amplitudes (amplitude range: 0.2-2mm) (Mortaza et al., 2019). This range of frequency for application of MTV is appropriate because the muscle spindles, that are the target of MTV, are sensitive to this range (J.P. Roll & J.P. Vedel, 1982; Roll et al., 1989).

1.2.7.1 Clinical evidence for the benefits of MTV

In addition to the above studies that measured motor cortex excitability as a measure of the effects of MTV, there is also clinical evidence for the effects of MTV on improving muscle strength and function (Alghadir et al., 2018; Benedetti et al., 2017; Fattorini et al., 2006), reducing spasticity (Casale et al., 2014; Costantino et al., 2017; Marconi et al., 2011; Murillo et al., 2011), and consequently improving functional motor performance (Casale et al., 2014; Choi, 2017; Costantino et al., 2017; Tavernese et al., 2013). In addition, given changes in proprioception associated with aging, there are also studies showing that MTV may be beneficial for older adults experiencing healthy aging (Celletti et al., 2015; Yu et al., 2010).

1.2.7.1.1 Muscle Strength

Benedetti et al. used 150Hz low amplitude vibration over the belly of the quadriceps as an intervention for quadriceps weakness secondary to knee osteoarthritis (Benedetti et al., 2017). The treatments included 10 sessions each 20 minutes long. They mentioned that they chose higher vibration frequency to target activation of primary spindle endings (Brown et al., 1967). Following the treatment participants showed significant improvements in physical capacity according to improved scores on the Western Ontario and McMaster Universities Osteoarthritis Index score, less pain, and decreased times for both stair climbing and the timed up-and-go. Also, knee flexion range of motion was increased. The electromyography measurements revealed higher involvement of type II muscle fibers as a result of vibration that suggests a neuro-mediated muscle recruitment pattern change rather than a muscle composition change as a result of focal vibration. The authors suggested that the local vibration improved the muscle function in patients with osteoarthritis.

In another study with healthy adults, Fattorini et al. used 100 Hz low amplitude vibration on the quadriceps muscle in two conditions: with or without concomitant isometric contraction (Fattorini et al., 2006). The treatment included three 10-minute episodes of vibration per day for three consecutive days. Force development capacity of the muscular structure of the knee was

assessed using maximum voluntary contraction (MVC), isometric, and isotonic (fatiguing task) tests. Although MVC did not improve as a result of muscle vibration, force values reached at 30, 50, 100 and 200ms of MVC onset time increased for both vibration groups. The vibration with contraction training decreased time to peak force. Also, the isotonic tests showed increased fatigue resistance for both vibration groups. The authors suggest that quadriceps muscle vibration can improve force development and fatigue resistance.

In contrast, Herda et al.'s study indicated that 20 minutes of 70 Hz vibration over the Achilles tendon decreased MVC peak torque by 5% (Herda et al., 2009). Also, EMG amplitude of the soleus and medial gastrocnemius muscles were significantly reduced (9-23%) when compared to the pre-treatment values. Herda et al. suggested that the suppression of group Ia afferents, as a result of mechanical vibration, may be responsible for the decreased muscle activity. In the same study, similar results were found for the condition in which participants received prolonged stretching. One possible reason for the inconsistent result of Herd's study with the former two studies may be that in the Herda's study the immediate effect of vibration was assessed immediately before and after the intervention whereas the other studies used long term training and long intervals before and after the treatment sessions. The results of Herda et al. study seems to be consistent with the studies that have shown suppression of H-reflex (Ekblom & Thorstensson, 2011; Murillo et al., 2011; Rocchi et al., 2018; Seo et al., 2016) and reduced spasticity in conditions such as stroke and spinal cord injury (Casale et al., 2014; Costantino et al., 2017; Marconi et al., 2011; Murillo et al., 2011) as a result of MTV. The results of these studies will be elaborated in the next section.

1.2.7.1.2 Spasticity and Functional Performance

Bock et al. (O. Bock et al., 2007) applied 80 Hz tendon vibration over the tendons of either wrist extensors, wrist flexors, or over antagonist muscles at the same time. They found that all vibration conditions led to H-reflex suppression. The authors suggested that simultaneous vibration of the antagonist muscles could cause stronger reflex suppression. Please refer to chapter 4 (systematic review and meta-analysis; (Mortaza et al., 2019)) for more studies on the effect of MTV on spasticity and functional performance improvement in individuals with stroke. Although each of the studies included in this systematic review and meta-analysis showed improved function and lower spasticity in individuals with chronic stroke, the pooled results of the meta-analysis indicate that there is insufficient evidence on the effectiveness of MTV for improving the

functional performance and spasticity of the upper limb. However, the meta-analysis did find a benefit of MTV for the upper limb when function was assessed using movement time for a reaching task. So, it seems that there is a need for more research on the effectiveness of MTV on performance of upper limb reaching tasks. Also, kinematic analysis of the reaching task seems to be a sensitive measurement method to detect motor performance changes as a result of MTV treatment.

1.2.7.1.3 Aging

As explained above, proprioception sensibility declines with aging. There are a limited number of studies on the effectiveness of tendon vibration on the lower limb muscles with the goal to enhance postural control in older adults (Celletti et al., 2015; Yu et al., 2010). Yu et al. (Yu et al., 2010) applied low amplitude 90Hz vibration over the tibialis anterior and Achilles tendons at the ankle in older adults with single or dual MTV. To assess the effects of vibration, center of pressure trajectories were recorded during one-legged and two-legged stance. The results showed that when one vibratory stimulation was on, depending on the vibration site, small anteroposterior body shifts were observed, but when the antagonist muscles of the ankle were vibrated simultaneously, center of pressure sways were decreased during one legged balance compared to the no vibration condition.

In a controlled clinical trial, Celetti et al. used 100Hz low amplitude tendon vibration over the tendon of the bilateral quadriceps muscle in older women. The treatment included 30-minute sessions of vibration application for three consecutive days (Celletti et al., 2015). In order to measure the efficacy of the MTV intervention, Performance-Oriented Mobility Assessment scale was used to assess gait and balance quality as well as risk of fall prediction. The Performance-Oriented Mobility Assessment were conducted before, immediately after, one month and six months post-treatment. According to Performance-Oriented Mobility Assessment, older women who received tendon vibration showed significantly less risk of a fall at long term follow-up compared to the group who received sham vibration. The authors suggested that MTV improved motor performance and could effectively reduce risk of falls in older women. It seems that MTV may benefit older adults in terms of postural control related to improved neuromuscular performance of the lower limbs, however, to the knowledge of the author there are no studies on the effectiveness of tendon vibration on upper limb performance in an older adult population. Since, loss of proprioception as a result of aging could also impair the function of the upper limb (Adamo

et al., 2009; Adamo et al., 2007; Goble et al., 2009; Wright et al., 2011) it seems there is a gap in the literature on the effect of MTV for the upper limb performance in older adults.

1.2.8 Induced paresthesia method for Studying the Role of Proprioception

Somatosensory feedback, a combination of tactile and proprioceptive sensory feedback, (Schmidt et al., 2018b; Sherrington, 1952a), is particularly relevant for performing everyday tasks. In order to better understand the contributions of somatosensory input to movement control, researchers have used a variety of methods to disrupt somatosensory feedback in a neurotypical population. For example, the natural visual and proprioceptive relationship can be altered by rotating the visual feedback (Krakauer et al., 2000; Shadmehr & Mussa-Ivaldi, 1994). Muscle tendon vibration is another approach that has been utilized to alter proprioception (Otmar Bock et al., 2007; Goodman & Tremblay, 2018; Redon et al., 1991). A third method to alter proprioception is to induce paresthesia using direct nerve stimulation to impair somatosensory inputs (Glazebrook et al., 2020; Passmore et al., 2014; Passmore et al., 2020). Paradigms such as these allow researchers to assess the contributions of visual and proprioceptive feedback to movement control, as well as to understand the capacity of the nervous system to adapt when one of these sensory inputs are unavailable or modified (e.g., using MTV or induced paresthesia). Paresthesia can be induced by transcutaneous electrical stimulation applied over the estimated path of the chosen peripheral nerve (Zehr & Chua, 2000; Zehr et al., 1997). This method does not eliminate the tactile and proprioception inputs; it rather causes a condition that resembles a radiating paresthesia pathology or a feeling of tingling and numbness radiating along the course of the targeted peripheral nerve. The induced radiating paresthesia resembles the loss of sensory input in a neurologic injury or disease.

This induced paresthesia technique was used in the current thesis for manipulating the somatosensory inputs in the studies included in chapters 2 and 3.

1.2.9 Purpose and significance of the thesis

Sensory feedback and movement performance are intimately linked for both goal-directed reaching movements and multi-limb coordination tasks (King et al., 2009; Maslovat et al., 2009; Proteau, 1995; Proteau et al., 1992). In the natural environment both visual and proprioceptive feedback are available to plan and update goal-directed reaching movements (Elliott et al., 2017).

To date, researchers have focused on understanding the specific characteristics associated with reaching movements performed with/without vision and with/without conflicting proprioceptive and visual feedback. While disrupted visual feedback has been studied extensively, the impact of disrupted proprioceptive feedback is poorly understood in the context of movement control (Kritikos & Brasch, 2008). Proprioception is particularly relevant for performing everyday tasks. Independence may be reduced or lost if the ability to perform functional tasks is altered. Individuals with a variety of sensorimotor disorders that alter the central and/or peripheral nervous system (e.g., stroke, multiple sclerosis, Parkinson's disease, diabetes) are faced with learning and re-learning how to perform movements when somatosensory feedback has been reduced or disrupted. Therefore, it is important to understand how best to supplement reduced somatosensory feedback with other available sensory feedback, as well as which sensory modality will lead to optimal planning, execution, and learning of functional movements. There are studies that demonstrate it is possible for the appropriate or preferred modality to shift if the preferred modality becomes degraded. This adaptation is similar to what happens in neurologic injuries or diseases that affect sensory systems. The re-weighting of sensory inputs for movement control has been demonstrated both for balance and reaching tasks. For example, humans become more dependent on vision to maintain balance if the sensitivity of their somatosensory and/or vestibular systems decreases (Horak & Hlavacka, 2001; Horak et al., 1990). Burr and Alais (Burr & Alais, 2006) also showed that when visual target was blurred beyond 32° of visual angle, the auditory feedback became the preferred modality during a goal directed reaching task. Thus, the sensory input with most accurate feedback will be the preferred source of information for the movement which can change with the changes in the environment or individual. In other words, the preferred modality may change as the accuracy of the sensory input changes in different environments and for different individuals. One purpose of the current thesis was to answer the fundamental question of how the control of goal-directed movements adapt to impaired somatosensory inputs when performing a goal-directed reaching task using induced paresthesia as a technique that most closely resembles the loss of sensory input in neurologic injury or disease.

Tendon muscle vibration may also interfere with the perception of limb position sense (O. Bock et al., 2007; Goodwin et al., 1972b). However, there is evidence indicating that the human nervous system can adapt to the sensory changes caused by MTV (Gonzales & Goble, 2014; Seizova-Cajic et al., 2007). Also, it has been shown that even a few sessions of MTV may be

enough to trigger cortical plasticity in both healthy individuals (Marconi et al., 2008; Rosenkranz et al., 2003) and in individuals post-stroke (Marconi et al., 2011). MTV has also shown trends toward improving functional movements of the upper limb in individuals with stoke (Mortaza et al., 2019). Hence, individuals with proprioceptive deficiencies may benefit from a wearable assistive device with MTV that can be affordably and independently applied by the individual. None of the previous studies investigated effects of applying MTV, specifically dual MTV, during the performance of a functional upper limb task such as a goal-directed aiming movement. The results of the current dissertation will be applied in the design of a novel vibratory band for rehabilitation of functional upper limb movements in population with proprioceptive deficiencies (e.g., stoke, diabetes, older adults etc.). The results from this thesis will set the basis for the design of clinical trials on the effectiveness of the muscle-tendon vibration band for specific populations.

In summary, the purpose of the current thesis was to enhance our understanding of the contributions of proprioception to upper limb control and how upper limb dual MTV modulates motor planning and execution.

1.3 General objective

The general objective of the current thesis was to better understand the contributions of proprioception to upper limb control in order to inform the design of a novel rehabilitation device for individual with somatosensory deficiencies.

1.4 Specific Objectives

The specific objectives of the five studies of this dissertation are:

1) Study 1 (chapter 2): To determine the impact of disrupted somatosensory feedback on the accuracy and efficiency of goal directed reaching movements when online visual feedback of the target was present versus when it was removed (to induce a preplanned movement strategy).
2) Study 2 (chapter 3): To determine if vision of the limb specifically is used to help improve movement performance when participants experience induced paresthesia. Also, studies 1 and 2 sought to understand how control of goal-directed reaching movements adapts in the context of different combinations of visual and somatosensory modifications.

3) Study 3 (chapter 4): To conduct a systematic literature review with meta-analysis on the effectiveness of MTV on functional performance of the upper limb in individuals with stroke and determine the characteristics of an effective MTV protocol.
4) Study 4 (chapter 5): Based on the results of study 3, to design and implement a prototype for a novel vibration band and develop a method for measuring the characteristics of the vibration on the muscle tendon.
5) Study 5 (chapter 6): To investigate the effect of applying MTV on performance of an aiming task. A secondary objective of this experiment was to determine if there was a correlation between the perception of illusory movement sensation caused by MTV and associated changes in movement performance.

1.5 Special circumstances

The experimental work of the current thesis was originally planned to include behavioral and neurophysiologic (SEPs) studies related to the effects of MTV. As a result of the COVID-19 pandemic the university of Manitoba restricted performing experimental work that required close contact with human participants. At the time the neurophysiologic experiment set-up and SEPs experimental protocol was established, and some pilot studies were completed. However, the experimental work with human participants could not continue. Please refer Appendix 1 for details of the proposed neurophysiologic study on MTV as well as a sample of the results of the pilot experimental data. Given the ongoing restrictions, in order to finish my PhD dissertation, decision was made to work on data collected previously for two relevant studies. I analyzed the data and prepared the first two chapters which represent the fundamental work leading to the MTV related studies.

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CHAPTER 2

Study 1: Optimizing movement performance with altered sensation: An examination of multisensory inputs

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C.G. and S.P. designed the protocol of the current study and led data acquisition. N.M reduced, analyzed, and interpreted the experimental data. N.M. also prepared the first draft of the manuscript. C.G. collaborated with the data analysis. All authors critically revised the draft of the manuscript for intellectual content and approved the final draft for submission to a journal.

Preface

Proprioception is particularly relevant for performing everyday tasks, however the impact of disrupted proprioceptive feedback in the context of movement control is poorly understood. The current fundamental study investigated the impact of disruption of proprioceptive feedback on the accuracy and efficiency of functional upper limb movements. We used the method of induced paresthesia by nerve stimulation, which closely resembles the proprioceptive disruption experienced by individuals with sensorimotor deficits. The findings of the current study helped us understand modification in the control of goal-directed movements when the proprioceptive feedback was disrupted, including online control as well as how movements are preplanned. The findings set the basis for designing a rehabilitation program and/or device that supplements or modifies sensory feedback that is optimal for planning, executing, and learning of functional movements.

Abstract

Introduction: In addition to vision, somatosensory input contributes to efficient and accurate moment planning and execution. Studying clinical populations has provided some insight into the contributions of somatosensory input for movement performance. However, it may not always be possible to separate the influence of any concurrent changes in visual and/or motor pathways from how motor control processes adapt to the altered somatosensory inputs. **Aim:** The goal of the current study was to investigate the effect of induced paresthesia in an otherwise intact nervous system on the performance of a goal-directed aiming task. **Methods:** 3D kinematic data from movements of 14 healthy participants were recorded while they pointed to a target on a monitor in 4 different sensory conditions (paresthesia – i. with target vision; ii. Without target vision; no paresthesia – iii. with target vision; iv. without target vision) presented over two days. One of four possible targets was randomly assigned to each condition. One hundred trials were performed per condition and data from all conditions were analyzed by comparing early (first 20% of trials) versus late (last 20% of trials) performance to assess adaptability to the change of somatosensory inputs. **Results and conclusions:** When vision of the target was not available paresthesia adversely affected both accuracy and efficiency of motor performance. Participants adapted to the changes caused by induced paresthesia with more practice by preplanning their movements, leading to fewer online corrections. Also, the decreased movement variability observed during the later trials with paresthesia is evidence that participants decreased their initial movement impulse to compensate for the increased noise in the somatosensory input.

2.1 Introduction

Sensory feedback and movement performance are intimately linked for both goal-directed reaching movements and multi-limb coordination tasks (King et al., 2009; Maslovat et al., 2009; Proteau, 1995; Proteau et al., 1992). In the natural environment both visual and proprioceptive feedback are available to plan and update goal-directed reaching movements (Elliott et al., 2017). To date, researchers have focused on understanding the specific characteristics associated with reaching movements performed with/without vision and with/without conflicting proprioceptive and visual feedback. While disrupted visual feedback has been studied extensively, the impact of

disrupted somatosensory feedback is poorly understood in the context of movement control (Kritikos & Brasch, 2008).

Somatosensory feedback, a combination of tactile and proprioceptive sensory feedback, (Schmidt et al., 2018c; Sherrington, 1952), is particularly relevant for performing everyday tasks. Independence may be reduced or lost if the ability to perform functional tasks is altered. For example, if an individual has decreased sensory input, then they are in danger of touching a hot object unknowingly, or they are unable to reach an object without having to look at their limb. Independence may be reduced or lost if the ability to perform functional tasks, such as manipulating objects, is altered. Individuals with a variety of sensorimotor disorders that alter the central and/or peripheral nervous system (e.g., stroke, multiple sclerosis, Parkinson's disease, diabetes) are faced with learning and re-learning how to perform movements when somatosensory feedback has been reduced or disrupted. The impact of altered somatosensory input on the performance of goal-directed actions is poorly understood. Similarly, how to best supplement reduced somatosensory feedback with other available sensory feedback, and which sensory modality will lead to optimal planning, execution, and learning of functional movements have not been investigated systematically.

In order to better understand the contributions of somatosensory input to movement control, researchers have used a variety of methods to disrupt somatosensory feedback in a neurotypical population. For example, the natural visual and proprioceptive relationship can be altered by rotating the visual feedback (Krakauer et al., 2000; Shadmehr & Mussa-Ivaldi, 1994). Muscle tendon vibration is another common approach for altering proprioception (Bock et al., 2007; Goodman & Tremblay, 2018; Redon et al., 1991). A third method is to induce paresthesia using transcutaneous nerve stimulation to impair proprioception (Glazebrook et al., 2020; Passmore et al., 2014; Passmore et al., 2020). Paresthesia is a feeling of tingling and numbness radiating along the course of a peripheral nerve. While it is possible to induce paresthesia experimentally, paresthesia is experienced as a result of disorders of both the central and peripheral nervous systems. Thus, there are a variety of paradigms that allow researchers to assess the contributions of visual and proprioceptive feedback to movement control.

There are studies that demonstrate the appropriate or preferred modality will shift when the preferred modality becomes degraded. This shift in the preferred sensory modality is consistent with what happens in neurologic injuries or diseases that affect sensory systems. The sensory re-

weighting effect has been demonstrated for both balance and reaching tasks. For example, humans become more dependent on vision to maintain balance if the sensitivity of their somatosensory and/or vestibular systems decreases (Horak & Hlavacka, 2001; Horak et al., 1990). Burr and Alais also demonstrated that if a visual target is blurred beyond 32° of visual angle then the auditory modality can become the preferred modality when reaching to a target (Burr & Alais, 2006). Thus, the modality that provides the most accurate information will be the preferred modality and can change with changing individual, environmental or task circumstances.

The specific objectives of the current study were: (1) To determine the impact of induced paresthesia, in an otherwise healthy nervous system, on the accuracy and efficiency of goal-directed reaching movements; (2) To determine if disrupted somatosensory feedback results in an increased reliance on visual feedback of the moving limb. We hypothesized that individuals will be more reliant on visual feedback in the presence of a somatosensory disruption, and both accuracy and efficiency of goal- directed reaching movements would be affected only when vision of the target is unavailable (Elliott & Allard, 1985). The premise for this manipulation is that when somatosensory feedback is disrupted then the need for online visual feedback will increase. A secondary objective was to explore the effect of practice and possible adaptation with the changes in the visual and somatosensory inputs. To do so, trials from early and late performance trials were analyzed compared.

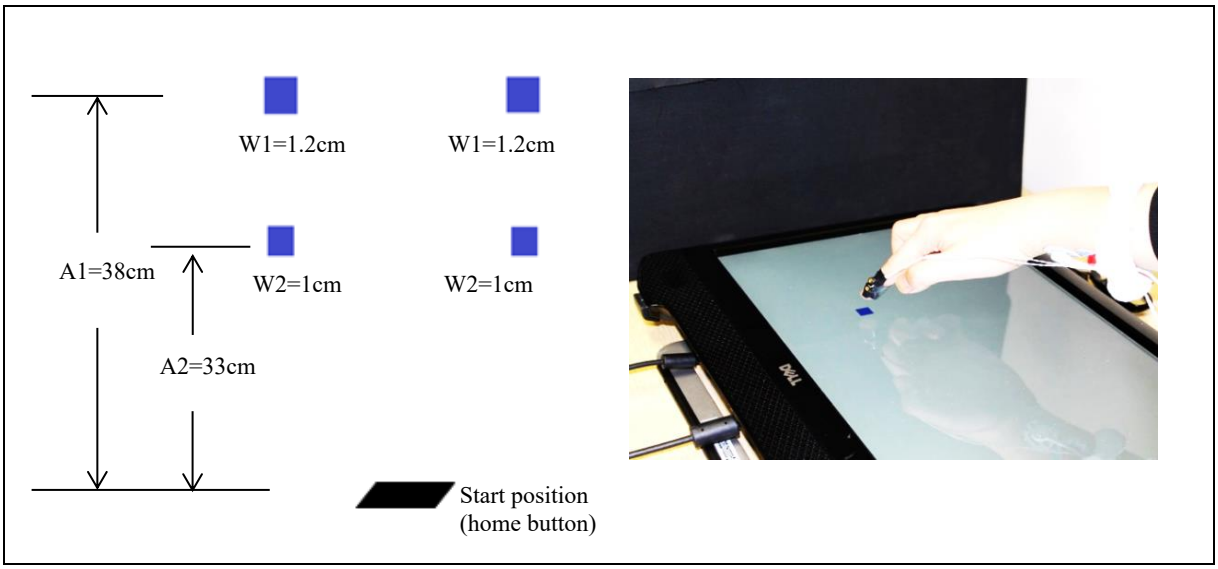


Figure 2-1 *Goal directed aiming task set up (right) and 4 possible targets (left) with different amplitudes(A) and widths(W); all targets had an index of difficulty of 6.*

2.2 Methods

2.2.1 Participants

Sixteen neurotypical (ten females, six males) young adults between 18 and 40 years-old participated in the current study (Mean age = 21.7, SD = 3.07). All participants were right-handed with normal (n=7) or corrected-to-normal vision (n=10) and no neurological condition or orthopedic injury that would interfere with their task performance. Approval by the local ethics board was granted, and informed consent was obtained from all participants. This study was carried out in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

2.2.2 Task

Participants were asked to aim "as quickly and accurately" as possible to one of four square-shaped targets (Figure 1; Index of Difficulty for all targets was 6; see Fitts & Peterson, 1964) located on a 17" computer screen that was placed horizontally on a table in front of them (see Figure 2-1). Each trial began with participants holding their index finger on the home position, which was a microswitch located at the bottom of the screen (Figure 2-1). The experimenter initiated each trial once participants were ready with their finger on the home position. Then a fixation cross appeared on the screen for a random foreperiod between 800-1400ms, after which one of the four targets appeared, and the participant moved their finger to touch the location of the target on the screen. In the "No-vision" conditions, the target disappeared at movement initiation as measured by the release of the microswitch. At the end of each trial, feedback was provided to participants, including their movement time and if they hit or missed the target. In the "Vision" conditions, participants could see the target throughout the trial. Participants were rewarded for fast and accurate movements by giving feedback about movement time to encourage them to challenge themselves to move as fast and accurately as they could. Rewards for movement times within 0.5, 1, 1.5, and 2 standard deviations of their baseline movement time (calculation described below), included being given 4 to 1 draw entries respectively to win a $100 gift card to the university bookstore (Elliott et al., 2004; Manzone et al., 2020).

2.2.3 Experimental procedure

The critical manipulation for the current experiment was the induction of paresthesia through constant current stimulation of the median nerve (Zehr & Chua, 2000; Zehr et al., 2001). The induced paresthesia method used in the current study was similar to our previous studies (Glazebrook et al., 2020; Passmore et al., 2014; Passmore et al., 2020) and was applied throughout the test session that included paresthesia. In order to create, or induce, the feeling of paresthesia, a Digitimer DS7AH constant current stimulator (IBIS Instrumentation Canada, Inc.) was used transcutaneously to generate constant stimulation along the median nerve using two Ag/AgCl disposable, adhesive, surface electrodes. The median nerve was selected because the areas supplied by this nerve (the index finger and thumb) are critical for fine motor movements. Stimulation electrodes were placed on the frontal aspect of distal forearm, over the predicted course of the median nerve. Custom E-prime (Psychology Software Tools) software externally triggered the constant current stimulator, with a pulse duration of 200μs, an interstimulus interval of 10ms, and a voltage edge of 0.2V. To achieve a consistent stimulation level, all stimulations were kept at premotor threshold level. The premotor threshold was established for each participant by systemically establishing the different stimulation threshold levels including sensory, radiating, premotor and motor. Sensory threshold was defined as the first sensation the participants reported as a result of stimulation. Radiating threshold was defined as the point when participants felt a moving sensation along the median nerve in their forearm. Premotor threshold was the highest stimulation intensity that did not cause any movement and the motor threshold was the lowest stimulation intensity that caused movement. Disrupted sensation was confirmed immediately prior to performing the test conditions that required paresthesia by assessing the tactile sensitivity of the palmar side of thumb and index fingers using a monofilament light touch test (Touch-Test® Sensory Evaluators: Semmes-Weinstein Monofilaments). These results were compared to the results of the baseline tests.

Participants attended two sessions on two separate days and performed a goal-directed aiming task in one session with induced paresthesia and one session without. Participants started the first session with 20 baseline trials with natural sensory input (full vision of their limb and target and without paresthesia); this data was used to establish the reward related criteria for the movement. The experimental conditions included: 1) vision of target and normal sensation (Vision,

No-Paresthesia); 2) no vision of target and normal sensation (No-vision, No-paresthesia); 3) vision of target and disrupted sensation (Vision, Paresthesia); 4) no vision of target and disrupted sensation (No-vision, Paresthesia). The order of the four conditions and associated target locations were blocked and counterbalanced across participants so that the participants aimed at a different target location for each condition; participants only pointed at one target per block. Participants performed 100 aiming trials toward the assigned target for each condition (200 trials per day for a total of 400 trials). Repeated movements to the same target were used to promote participants working to push the limits of how fast they could move while still acquiring the target successfully.

2.2.4 Data collection and treatment

Movement characteristics were recorded using a three-dimensional motion capture system (Optotrak 3D Investigator, Northern Digital Inc. Waterloo, ON). Two InfraRed Emitting Diodes (IRED) were taped to the participants dominant hand on the dorsal side of the distal phalanx of the index finger (Figure 2-1, left). Movements were recorded for 2 seconds for each trial at a sampling frequency of 300Hz. Motion capture system recordings were controlled and synchronized using a custom-made program designed using E-Prime (Psychology Software Tools). A customized MATLAB (the MathWorks, Inc.) program was used to process the raw displacement data acquired by Optotrak. Movement data were filtered using a 15 Hz lowpass Butterworth filter. Movement initiation was defined as the time that the speed of the IRED movement went above 30mm/sec and maintained that velocity for 30ms. Movement completion was detected when the IREDs' velocity fell below 30mm/s for 30ms. The primary axis of movement was defined as the axis with an anteroposterior direction.

2.2.5 Outcome measures

Temporal dependent measures included reaction time (RT), movement time (MT), and time to peak velocity (ttPV). Reaction time was defined as the time in milliseconds from the "go signal" until movement initiation, while MT was defined as the time in milliseconds from movement initiation until movement termination. In this way RT provides an index of movement planning and MT provides an index of the time needed to move to the target successfully. Time to peak velocity was measured as the time from movement onset until peak velocity was achieved in the primary axis of movement. Relative time to peak velocity was normalized as a percentage of the

MT for that trial. Time to peak velocity and relative time to peak velocity provide an index of the actual and relative time spent in the initial limb transport phase (Handlovsky et al., 2004; Mendoza et al., 2006).

Spatial outcome measures included measurements of movement endpoint accuracy (constant error [CE] and variable error [VE]), and movement trajectories in both primary (anteroposterior) and secondary (mediolateral) axes. Moreover, VE in the primary axis at 20%, 40%, 60%, 80% of movement time was analyzed to infer changes in online limb control (Khan & Franks, 2003; Khan et al., 2006). The measure of CE was used to determine the mean bias participants had about the location of their movement endpoints using the calculation: $CE=\Sigma (x_i - T) /n$, where x_i is the IRED location at the end of the movement on trial i, T is the target location, and n is the number of trials the participant performed. Variable error is a measure of within participant variability in aiming calculated as: $VE=(\Sigma (x_i - M)^2 / n)^{-2}$, where x_i and n were previously defined, and M was the mean of the locations of the IREDS that the participant reached (Schmidt et al., 2018b). To investigate the effect of the manipulated sensory inputs (vision and somatosensation) on participants' ability to improve the performance of their goal-directed actions, only data from the first and last 20 (out of 100 trials) trials in each condition was included in the data analyses and presented as "Early" and "Late" performance.

2.2.6 Statistical analysis

Outcomes of the monofilament testing were compared before and after induced paresthesia using Wilcoxon Signed-Rank Test to establish the efficacy of the induced paresthesia. Dependent variables for movement performance included MT, RT, normalized ttPV, as well as CE and endpoint VE in both primary and secondary axes using a 2 Target Vision (Vision, No-vision) × 2 Paresthesia (Paresthesia, No-paresthesia) × 2 Time (Early / Late Performance) repeated measures analysis of variance (ANOVA). In order to analyse changes in the movement variability (VE) along a movement trajectory a 2 Vision (Vision, No-vision) × 2 Paresthesia (Paresthesia, No-paresthesia) × 2 Time (Early / Late Performance) × 5 Movement Percent (20%, 40%, 60%, 80%, 100%) repeated measures ANOVA was performed. Significance level was set at $p<0.05$, and significant interactions were further analyzed using Tukey's HSD post hoc with alpha= 0.05.

2.3 Results

Wilcoxon Signed-Rank Test showed that the participants required a significantly thicker monofilament to detect skin deformation changes after paresthesia was induced ($Z = -3.60$, $p = 0.000$). The results of the monofilament testing at baseline and with induced paresthesia are reported in Table 1.

Motion capture data for two participants were excluded from the statistical analysis because displacement data for more than 50% of the trials were missing due to IREDs becoming obscured during the reaching movement. Therefore, data analysis is based on the remaining 14 participants.

Table 2-1 *Touch-Test® Sensory Evaluation- sensed monofilament size before induced paresthesia and after induced paresthesia right before the condition with paresthesia.*

Participant	Without Paresthesia	With Paresthesia
P01	2.83	3.61
P02	2.83	3.61
P03	2.83	3.61
P04	3.61	4.56
P05	2.83	4.31
P06	2.83	3.61
P07	2.83	3.61
P08	2.83	4.31
P09	2.83	4.31
P10	2.83	3.61
P11	2.83	4.31
P12	2.83	3.61
P13	2.83	3.61
P14	2.83	4.56
P15	2.83	4.31
P16	2.83	3.61
Median	2.83	3.61

2.3.1 Temporal measurements

For the outcome measure of RT, no significant main effect or interaction was found for the factors of vision time and paresthesia (results included in Table 2-2).

For MT, there were significant main effects for time, F (1,13) =15.48, p=0.002, η_p^2=0.54, and paresthesia, F (1,13) =8.50, p=0.012, η_p^2=0.39 (Figure 2-2a). Movement time was shorter without paresthesia than with paresthesia and during the later 20 trials than the early 20 trials (Table 2-2). There were no significant interactions between the factors of vision, time, and paresthesia.

Results of normalized ttPV showed a significant main effect for the factor of Vision, F(1,13) = 11.59; p =0.005, η_p^2 = 0.47. As shown in Figure 2b, normalized ttPV was longer in No-vision (*M* = 40.9; *SD* =7.1) than Vision conditions (*M* = 38.5; *SD* = 6.2). Also, there was a significant interaction between the factors of time and paresthesia, F (1,13) = 7.25; p =0.018, η_p^2= 0.36 (Figure 2-2c). As illustrated in Figure 2c, Tukey's HSD test showed that while normalized ttPV for the early and late practice trials were not significantly different, when paresthesia was present participants had longer ttPV for later trials (*M* = 40.2; *SD* = 7.6) versus the early trials (*M* = 39.3; *SD* = 5.8) (Figure 2-2c).

Table 2-2 *Mean and standard deviation (SD) for the temporal outcome measure of reaction time (RT), and raw ttPV, as well as temporal outcomes of variable error (VE) and constant error (CE) in the primary axis of movement for different sensory conditions at early and later trials.*

		Paresthesia				No Paresthesia			
		Vision		No Vision		Vision		No Vision	
		Early Performance	Late Performance	Early Performance	Late Performance	Early Performance	Late Performance	Early Performance	Late Performance
RT (ms)	Mean ±SD	383.0 ±56.4	375.0 ±64.6	442.5 ±169.6	404.7 ±106.7	379.5 ±43.5	386.4 ±80.1	413.5 ±141.5	377.1 ±71.8
MT (ms)	Mean ±SD	477.6 ±70.8	438.5 ±60.0	464.4 ±86.5	438.6 ±92.4	439.8 ±65.9	414.0 ±55.8	421.4 ±71.8	390.6 ±63.0
ttPV (ms)	Mean ±SD	179.6 ±35.8	172.0 ±43.2	180.6 ±36.0	181.2 ±34.3	170.4 ±23.6	157.1 ±27.6	172.0 ±33.2	159.1 ±32.4
VE (mm)	Mean ±SD	3.7 ±1.0	3.9 ±0.9	4.3 ±1.0	4.3 ±1.4	3.8 ±1.1	4.0 ±0.7	4.5 ±1.1	3.9 ±1.3
CE (mm)	Mean ±SD	1.3 ±1.7	1.3 ±1.2	1.4 ±2.9	2.0 ±3.2	1.6 ±2.6	2.7 ±1.8	1.8 ±1.7	2.5 ±1.7

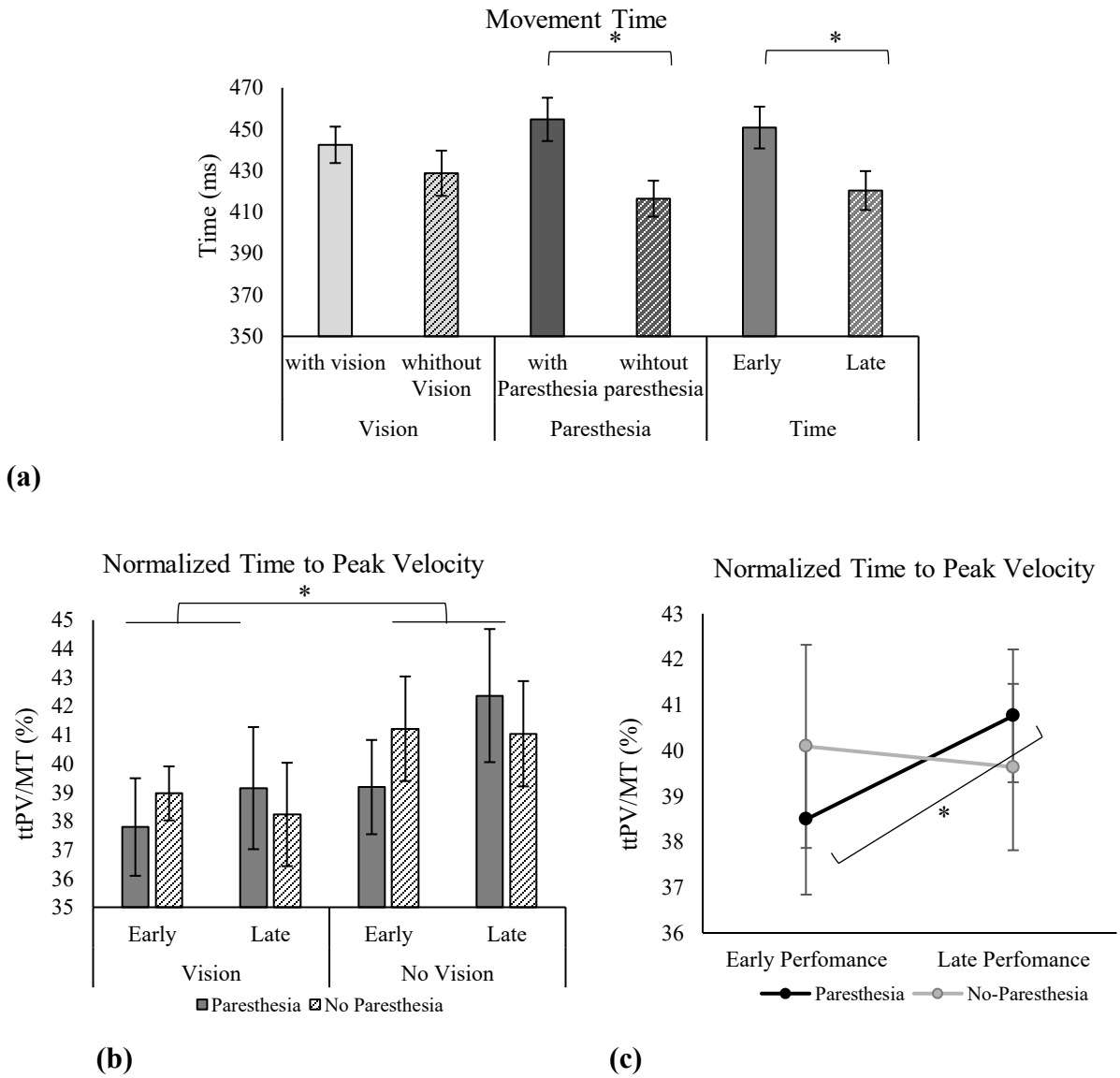


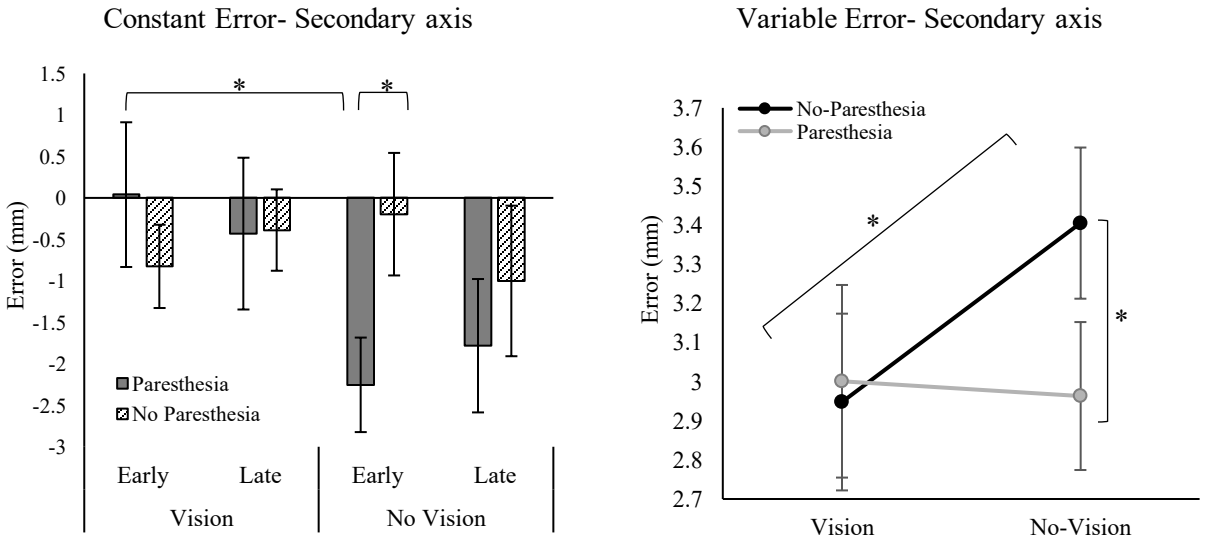
Figure 2-2 (a) *Movement time (MT) separated for factors of time, paresthesia, and vision with significant main effects for the factors of time and paresthesia.* ***(b)***, ***(c)*** *Normalized percentage of time to peak velocity (ttPV/MT%).* ***(b)*** *Time to peak velocity demonstrated separately for different conditions showing significant main effect for the factor of vision.* ***(c)*** *Interaction of the two factors of time and paresthesia showing significantly higher normalized significant main effect for the factors of time and paresthesia for the normalized ttPV. All error bars indicate standard error.*

2.3.2 Spatial Measurements

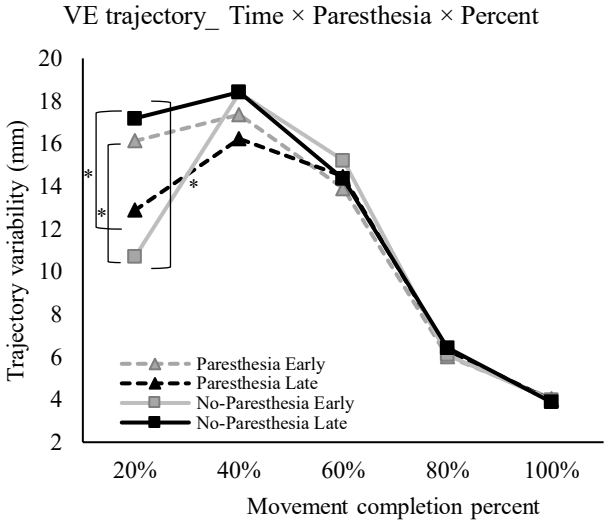
In the primary axis of movement, no significant main effects or interactions were found for the factors of vision, time, or paresthesia for CE and VE (Table 2-2).

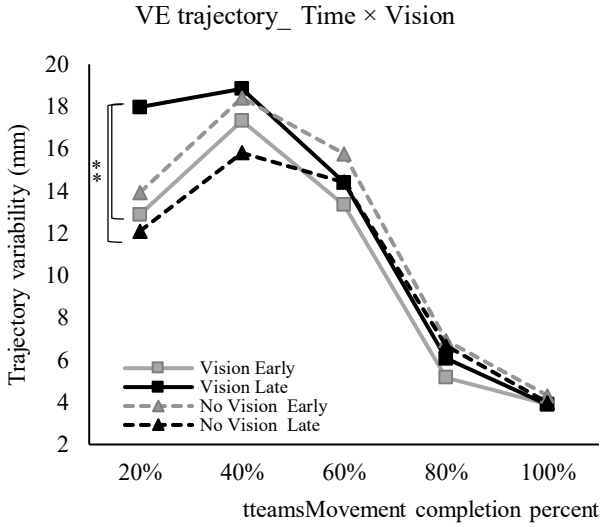
In the secondary movement axis, however there was a significant interaction between the factors of time, paresthesia, and vision for the outcome of CE, F (1,13) = 6.03, p=0.029, η_p^2=0.32, (Figure 2-3a). Post-hoc analysis showed that when vision of the target was removed, for early trials CE was significantly higher when paresthesia was induced (*M* = -2.25; *SD* = 2.1) versus without paresthesia (*M* = -0.20; *SD* = 2.8).

For VE in the secondary movement axis, there was a significant interaction between the factors of paresthesia and vision, F (1,13) = 6.48, p=0.024, η_p^2=0.33 (Figure 2-3b). Post-hoc analysis showed that in no-paresthesia conditions participants had significantly higher variability when vision of the target was removed (*M* = 3.40; *SD* = 0.9) versus when it was available (*M* = 2.95; *SD* = 0.8). Also, when vision was not available participants had significantly higher variability without paresthesia (*M* = 3.40; *SD* = 0.9) compared to with paresthesia (*M* = 2.96; *SD* = 0.7).

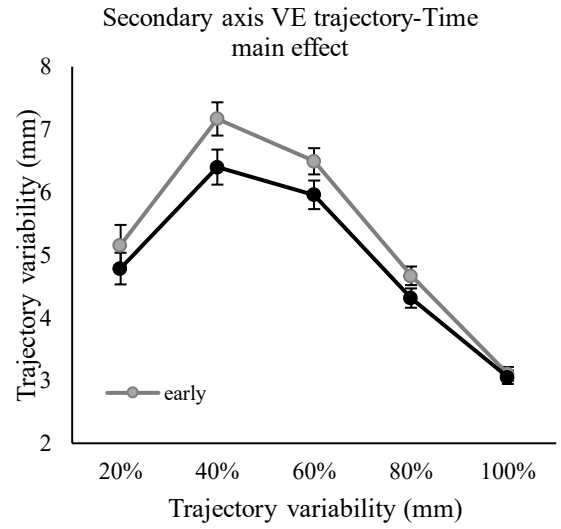


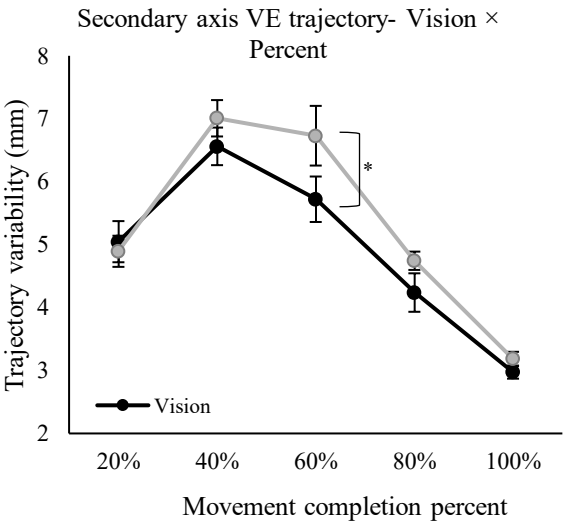
(a) **(b)**





(c) **(d)**





(e) **(f)**

Figure 2-3 (a) *The significant interaction of vision × paresthesia × time for the outcome measure of constant error (CE) in the secondary axis (medio-lateral).* ***(b)*** *The significant interaction of the two factors of vision and paresthesia for the outcome of variable error (VE) in the secondary axis.* ***(c)*** *The significant interaction of three factors of paresthesia, time, and percentage of movement.* ***(d)*** *The significant interaction of two factors of time, and vision.* ***(e)*** *VE in the secondary axis for the significant interaction of vision and percent.* ***(f)*** *Significant main effect of time for the trajectories in the secondary axis.*

2.3.3 Movement Trajectories

The repeated measures ANOVA for the variability of the movement trajectory in the primary movement axis showed a significant main effect for percentage of the movement, F (4,52) = 87.2, p=0.000, η_p^2=0.87. Also, there was a significant three-way interaction between factors of movement percent, time, and paresthesia, F (2.1,27.3) = 10.74, p=0.000, η_p^2=0.45 (Figure 3c), and another interaction between the factors of time and vision, F (1,13) = 13.25, p=0.003, η_p^2=0.50 (Figure 2-3d). Post-hoc analysis for the interaction of time, percent, and paresthesia showed that during early practice trials when paresthesia was induced, variability was significantly higher compared to the no-paresthesia condition at 20% of the movement; mean difference of early practice with paresthesia versus No-paresthesia was 5.4 mm. However, this trend was reversed during later trials. That is, following more practice without paresthesia, later trials showed significantly higher variability at 20% in the movement compared to the no paresthesia condition; mean difference of VE at 20% of the movement for paresthesia versus No-paresthesia condition for the late practice trials was 4.3 mm (Figure 2-3c). Comparison of the late versus early trials when no paresthesia was induced also showed more variability at late performance (mean difference= 6.5mm; Figure 2-3c). Post-hoc analysis for the interaction of vision and time showed that when vision was available, participants had significantly higher variability in the first 20% of movement with more practice (later trials) versus early practice trials (Figure 2-3d). Also, in late practice the VE at 20% MT in the movement was significantly higher with vision versus No-vision.

Results of the VE for movement trajectory in the secondary axis of movement showed a significant main effect for the factors of time, F (1,13) = 9.22, p=0.010, η_p^2=0.41(Figure 2-3e), and percent of movement, F (2.0,25.7) = 108.0, p=0.000, η_p^2=0.89 (Figure 2-3f); indicating higher VE at later versus early performance. Also, there was a significant interaction between percent of movement time and vision, F (4,52) = 3.01, p=0.026, η_p^2=0.19. Post-hoc analysis for this interaction showed that at 60% of movement time, with vision conditions had significantly greater variably than no-vision conditions (Figure 2-3e).

2.4 Discussion

We hypothesized that accuracy and efficiency of goal-directed reaching movements would be affected only when vision of the target was unavailable because vision is considered the dominant and most reliable source of information for spatial tasks (Ernst & Banks, 2002; Ernst & Bülthoff, 2004; Rock & Victor, 1964). As predicted, when vision of the target was available the conditions with and without induced paresthesia were not different. However, when vision of the target was not available, performance was affected more with induced paresthesia compared to without paresthesia.

2.4.1 Effect of Sensory manipulation on Endpoint Accuracy

We predicted that paresthesia would affect movements more robustly when vision of the target was not available. Only the accuracy measures in the secondary movement (i.e., mediolateral) axis were consistent with this prediction. In early performance trials, CE in the secondary axis became significantly larger with paresthesia compared to the no-paresthesia condition only when vision of the target was removed. When vison of the target was available, paresthesia did not affect end point accuracy.

Constant error early in performance, without vision and with paresthesia, was significantly larger than early performance in paresthesia condition with vision (Figure 2-3a). This pattern indicates that visual feedback was the dominant source of feedback for endpoint accuracy. Paresthesia without target vision led to participants being consistently biased towards flexion, inferred from the consistent undershoot errors (Figure 2-3a). One explanation for this bias could be the imbalance caused in the proprioception by stimulation of median nerve only. Stimulation of the median nerve only could lead to a false sense of location and tendency for overcorrection towards the midline when proprioception was distorted (Bellan et al., 2016). In a study by Goodman et al. (Goodman & Tremblay, 2018) tendon vibration before movement task was used to manipulate somatosensory input. They found that vibration application resulted in increased CE in a goal-directed reaching task when vision was also removed. Their results for CE in the primary axis showed target undershoots, similar to the finding of the current study in the secondary axis. They also found target overshoots in the anterior-posterior axis (secondary axis in that study), similar to findings of the current study for CE in the anterior posterior axis (which was the primary

axis in the current study). It should be noted that the current study was performed in the anteroposterior direction while Goodman et al.'s task was performed mostly in the mediolateral direction. Although these two studies used different methods for interrupting proprioception, there was a tendency to perceive the position of the upper limb as closer to the midline. Given the location of the stimulations used in these two studies for interrupting proprioception, and the possible tendency to position the upper limb closer to the midline, the consistent findings reinforce the result that interrupting proprioception leads to target undershoots.

Endpoint variability (VE) in the secondary axis was also affected with paresthesia only when vision of the target was removed (Figure 2-3b). However, unlike our expectation, VE was significantly higher when vision of the target was removed, compared to when target vision was available only in the no-paresthesia condition; that is, induced paresthesia did not increase endpoint variability in the secondary axis. Although statistically significant, the endpoint variability in the no-paresthesia condition increased as small as 0.5 mm when vision of the target was removed, which may make this finding negligible in everyday tasks.

2.4.2 Effect of Sensory manipulation on Movement Strategy

2.4.2.1 ttPV and Change of Movement Strategy

We found that MT was shorter after performing more trials, which replicates previous findings (Elliott et al., 2004). Movement time was also shorter when performing the task without induced paresthesia compared to the induced paresthesia condition. No significant interaction was found for the factors of vision and paresthesia. Normalized ttPV was the temporal variable that supported our hypothesis, which predicted that individuals will be more reliant on visual feedback in the presence of a somatosensory disruption. In the current study, when vision of the target was available, regardless of paresthesia condition, ttPV was shorter (see Figure 2-2b). The changes in ttPV can be interpreted using Elliott et al.'s proposed multiple process model of limb control (Elliott et al., 2010; Elliott et al., 2017). In this model, there are two early and late online control processes: the impulse control and limb-target regulation phases. Most of the impulse control phase happens before the limb reaches peak velocity and is the distance covering portion of the movement that determines the direction and velocity of the movement. Limb-target regulation happens after the peak velocity is reached and is performed by using the visual and somatosensory inputs to fine tune the landing of the limb on the target. By considering the ttPV finding in the

current study, we can interpret that when vision of the target was available participants reached to the proximity of the target quickly and spent more time for online corrections relying on the available visual information of the target location and the limb, whether or not somatosensory input was interrupted (Elliott et al., 2017; Hansen et al., 2006), However, when vision of the target was removed the time spent before PV (ttPV) was a larger portion of the movement time. Although statistical analysis did not show a significant effect of paresthesia on the ttPV in the no-vision conditions, analysis of the late versus early performance trials showed that when paresthesia was present, as more trials were performed (comparing first vs. last 20 trials) the normalized ttPV increased; that is a larger percentage of the movement time was spent in the impulse control phase, and less in limb-target regulation. One explanation for this finding could be that participants chose a different strategy for controlling their movement by preplanning their movements because they did not have proprioception or target vision available for feedback and current control. In other words, with practice they adopted a strategy that included less time on limb-target regulation (Elliott et al., 2004; Khan et al., 1998). The present findings are similar to Goodman et al.'s study where simultaneous muscle tendon vibration of elbow flexors and extensors was used to manipulate somatosensory inputs in typically developing adults (Goodman & Tremblay, 2018). These authors applied muscle tendon vibration before trials of a horizontal goal-directed aiming task while vision of the whole environment was manipulated using occlusion goggles. Similar to the current study, Goodman et al. found that when vision was removed, or when vibration was applied, participants spent less time after peak velocity for online corrections to the limb movement.

2.4.2.2 Trajectory variability and Change of Movement Strategy

According to the findings of the variability of movement trajectories, participants appear to have selected different strategies when performing the task with and without paresthesia. Variability of the movement trajectory early in the movement (~50% of the movement) is known to be associated with motor planning and offline control (Khan et al., 2006), while trajectory variability later in the movement is thought to reflect on-line corrective processes. Looking at the results of the trajectory variability in the primary axis, regardless of available visual input, when there was no paresthesia, participants were more variable at movement initiation in late trials compared to both early trials without paresthesia and late trials with paresthesia (Figure 2-3c).

Movement initiation was also more variable with paresthesia than without paresthesia for early trials specifically. We propose that with more practice participants learned to use larger initial impulses at movement initiation when there was no paresthesia. This strategy is expected to lead to higher impulse variability at movement initiation as detected with higher position variability at 20% into the movement (Schmidt et al., 1979). Although participants were asked to move as fast as they could, the average movement time for the task was long enough for participants to perform limb-target corrections and reduce endpoint error and variability (i.e., overall mean of MT= 435 ms that is higher than 200 ms, see Schmidt ,1979, for more information). On the other hand, when paresthesia was induced participants appeared to use a more conservative movement strategy after more practice with the task. Specifically, we found lower VE at 20% of movement time during later trials with paresthesia versus early trials (Figure 2-3c). One explanation for this finding could be that paresthesia may have increased neural-motor noise and affected force specification processes. So, participants chose a safe strategy with smaller impulses at movement initiation, leading to less variability at 20% of movement time. The movement time findings are also consistent with this explanation since movements became shorter with practice and longer with paresthesia.

Results of the movement trajectories in the mediolateral axis showed that with more practice, or when vision was available, movements became less variable, specifically around 40% and 60% of movement time (Figure 2-3e, f). This reduced variability of the movement around halfway into the movement time and beyond, indicates a more preplanned movement and fewer online corrections when vision of the target was not available.

2.4.3 Effects of practice and Adaptability

A secondary objective of the current study was to investigate how ongoing practice with the changed sensory inputs would affect movement performance; that is how adaptable to the altered sensory input was the motor control system. As expected, regardless of experimental condition, participants had shorter MTs with more practice (Figure 2-2a). Also, normalized ttPV in the paresthesia condition became longer with more practice. These findings indicate that when paresthesia was induced participants learned to spend more time during the preplanned impulse control phase and subsequently fewer online correction. Although not statistically significant, the trends in movement strategies seemed to be larger when vision of the target was not available,

(Figure 2-2b). In summary, the analysis of early versus late trials demonstrated that at least some of the changes in the temporal and spatial movement characteristics as a result of manipulating the sensory input were alleviated with practice.

2.4.4 Target Vision Availability and Movement Strategy

In the current study visual input was manipulated by obscuring the vision of the target only because vison of the target is necessary for limb-target control processes that are used to acquire the target accurately (Elliott, 1988; Heath, 2005; Meegan et al., 2004). Lack of target vision (or its memory) is expected to lead performers to use more preplanned movements as well as using kinesthetic or feedforward sources of information (Elliott, 1988). In the current study vision of the target was removed upon movement initiation, so the memory of the target location was not decayed and was available for memory guided limb-target regulation (Heath, 2005). Hence, in this study, target vision was removed to assess the effect of paresthesia on execution of a preplanned and memory guided aiming task. As expected, the results of this study showed that participants' aiming accuracy was significantly different in the two no-target-vision conditions with and without paresthesia (CE in the secondary axis, Figure 2-3a). A possible mechanism considered for this finding is that the memory-guided movement required more mental effort for the participants and adding induced paresthesia could have overloaded attentional resources, which would interfere with visual attention towards dynamic limb location and online limb-target control processes (Schmidt et al., 2018a). It is possible that although vision of the limb was present, and the target location memory should have been available, that participants did not engage online limb-target control processes and used a safe strategy where they pre-planned their movements. The findings of movement trajectories in the secondary axis also supports a preplanned movement strategy when target vision was obscured. Removing target vision increased movement variability at 60% of the movement time. Another explanation for the altered movement control strategy when target vision was removed could be that with memory guided movement control participants relied on their perception of the target location (Heath, 2005) which itself was likely distorted or biased as a result of inducing paresthesia by only stimulating the median nerve.

2.5 Conclusions

The most consistent finding was that movements performed in the presence of paresthesia took longer to execute, but not any longer to plan or initiate. As expected, visual input was the dominant source of information and when vision of the target was available participants' accuracy and motor control strategies did not change. When vision of the target was not available then paresthesia adversely affected accuracy and efficiency of motor performance. We found that participants learned to adapt to the changes caused by induced paresthesia with more practice by preplanning the movement more, performing fewer online corrections, as well as decreasing their initial movement impulse to compensate for the increased neuromuscular noise. The results of the present study contribute to developing our understanding of how humans adapt their motor control strategies when available somatosensory input is disrupted. The present work represents the first step towards extending this line of work to clinical populations who experience disrupted somatosensory feedback. Future work will determine the effect of vision of moving limb and the role of auditory feedback to aid movement performance.

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CHAPTER 3

Study 2: Induced Paresthesia Affects Performance of an Upper Limb Goal Directed Aiming Task, even in the Presence of Full Vision

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Contributions of Authors to The Manuscript

C.G. and S.P. designed the protocol of the current study and led data acquisition. N.M reduced, analyzed, and interpreted the experimental data. N.M. also prepared the first draft of the manuscript. C.G. collaborated with the data analysis. All authors critically revised the draft of the manuscript for intellectual content and approved the final draft for submission to a journal.

Preface

This study complements the experiment reported in Chapter 2 by addressing the specific role of the visual feedback of the upper limb on the movement performance when proprioception is compromised using induced paresthesia. Together, the results from these two experiments clarified the contribution of different components of visual feedback for movement control while paresthesia was induced. These two studies also explored how the sensorimotor system adapts to the modified visual and proprioceptive feedback.

Abstract

Purpose: The goal of the current experiment was to determine if vision of the limb is used to improve movement performance when participants experience induced paresthesia. **Method:** 12 neurotypical adults performed four blocks (100 trials/block) of a goal-directed aiming task in four different conditions: 1) with induced paresthesia and full vision; 2) with induced paresthesia and no-vision; 3) without paresthesia and full vision; 4) without paresthesia and no-vision. Each block of trials consisted of aiming to only one of the four possible target locations on a monitor placed horizontally. Vision was obscured using visual occlusion goggles and paresthesia was induced with a constant current stimulator. Results were analyzed by comparing early (first 20% of trials) versus late (last 20% of trials) performance to assess adaptability to altered somatosensory input. **Results and conclusions:** Removing vision of the limb significantly increased endpoint variability and accuracy. When compared to the early performance in the no-paresthesia and no-vision condition, induced paresthesia and no-vision of the hand caused significantly higher end-point error toward the body midline in both early and late performance. This finding reveals the importance of proprioceptive input for movement accuracy in the absence of visual feedback. Only when paresthesia was not induced the no-vision condition had longer time to peak velocity and shorter time after peak velocity compared to the full vision condition. The lack of similar results in these temporal parameters in the full vision and induced paresthesia condition signifies the role of proprioception in the movement efficacy, even when visual information of the limb, target, and environment is available. Thus, in the current study vision could not fully compensate for the disrupted proprioceptive input.

3.1 Introduction

Human movements are planned and executed by using and integrating visual, somatosensory, and auditory sensory inputs. There is extensive research on the role of vision in controlling goal-directed movement of the upper limb as vision is a dominant source of information for movements (Ernst & Banks, 2002; Ernst & Bülthoff, 2004; Rock & Victor, 1964). Somatosensory information, and more specifically proprioception, has a complementary role in the control of human movement by providing information about the location of the limb in the

space as well as relative location of limbs to each other (King et al., 2009; Maslovat et al., 2009; Proteau, 1995; Proteau et al., 1992). Thus, it is important to know how these two major sources of information are integrated for voluntary limb control.

The multiple process model of limb control proposes aiming movements are comprised of two components, but multiple processes within these two components (Elliott et al., 2001; Elliott et al., 2017). According to this model, the first component of the movement is defined by impulse control, which includes the preplanned part of the movement where the limb covers the majority of the distance to reach the vicinity of the target. The second component is the limb-target control phase where the available sensory inputs are compared to the internal representations. The multiple process model considers multiple factors, such as noise in the neural-motor system, force related error, as well as efficiency of energy expenditure. It is suggested that the two components of the multiple process model are not independent, and that visual feedback is the main sensory driver of the impulse control phase. A combination of proprioception and visual inputs are the main sources of information for limb-target regulation. Thus, effective limb control includes integration of expected and actual sensory inputs from multiple sensory sources.

Knowledge about the individual and integrative role of different sensory input is crucial for rehabilitation programs when either of these sensory inputs are deficient. Previously, we used induced paresthesia to interrupt somatosensory inputs while also manipulating visual information by removing target vision upon movement initiation (Mortaza et al., 2021). We found participants changed their movement strategy from online control to pre-planned movements when paresthesia was present, and vision of the target was removed. Also, when vision of the target was removed and paresthesia was induced, participants had significantly higher bias for errors towards the midline of their body early during practice when compared to the no-paresthesia condition, or when vision of the target was available with paresthesia. Together this pattern indicates that vision of the target and intact proprioception both contribute to limb-target corrections.

In the current experiment visual information about the environment, including the limb and the target, was removed using visual occlusion goggles. The goal of this manipulation was to determine if vision of the limb specifically is used to help improve movement performance when participants experience induced paresthesia. We hypothesized that removing vision of the entire visual environment would result in larger and more pronounced differences between the vision and no vision conditions (in comparison with our previous study; (Mortaza et al., 2021), because vision

of the limb specifically was removed. We expected proprioception information would be used to achieve some degree of online control and corrections (Elliott & Allard, 1985; Elliott et al., 2017). We also compared early versus late movement trials to investigate participants' adaptability to the sensory manipulation. Thus, a secondary objective of the current study was to investigate the adaptability of the motor control strategies to the sensory manipulations.

3.2 Methods

3.2.1 Participants

Twelve healthy young adults (4 females, 8 males) with mean age of 22.9±4.0 years participated in the current experiment. Participants had no neurological condition or orthopedic injury that would interfere with their performance of the task. All experimental procedures were approved by the local ethics board and all participants provided signed informed consent.

3.2.2 Apparatus, Materials, Design, Procedure, and Analysis

The methodology of the current experiment was identical to our previous study with the exception of the protocol used for manipulation of the visual feedback (Mortaza et al., 2021). Participants sat at a table in front of a 17" monitor positioned lengthwise and in line with the table-top. The task included upper limb goal-directed reaches to one of the four square shaped targets, all with an index of difficulty of 6 (Fitts & Peterson, 1964). The tasks were done in four sensory conditions: 1) Full vision, paresthesia; 2) no-vision, no-paresthesia; 3) Full vision, no-paresthesia; 4) No-vision, paresthesia. Order of the conditions and the specific target allocated for each condition was randomized and counterbalanced across participants. Participants performed 100 discrete reaching movements to the assigned target located on a touchscreen for each condition (total of 400 per participant). In the no vision conditions, vision of the target, limb, and the environment was obscured upon movement onset using visual occlusion goggles (Translucent Technologies, Toronto, Ontario). For the conditions with paresthesia, a constant current stimulator (Digitimer DS7A) was used to induce paresthesia in the median nerve. The protocol used for inducing paresthesia has been reported previously (Mortaza et al., 2021). To confirm that sensory perturbation was achieved, monofilament pressure sensitivity test results were compared at baseline and after induced paresthesia (Table 3-1). Data was collected on two separate days.

Movements were recorded using a motion capture system at 300Hz (Optotrak 3D Investigator, Northern Digital Inc., Waterloo, Ontario) by tracking an infrared emitting diode (IRED) attached to the participants' index finger. Data collection onset was synchronized with the computer task and lasted for 2 seconds using custom software designed in E-Prime (version 2.0, Psychology Software Tools, Inc., Sharpsburg, PA). The movement data was reduced and analyzed using a customized MATLAB program (the MathWorks, Inc.) A 15 Hz lowpass Butterworth filter was used. Movement onset was marked as the first frame that the IRED moved faster than 30mm/sec for at least 30ms and movement offset was identified as the first frame that the IRED's velocity fell below 30mm/s for 30ms (Mortaza et al., 2021).

The main outcome measure included movement time (MT), reaction time (RT), peak velocity (PV), time to peak velocity (ttPV), time after peak velocity (taPV), and normalized ttPV (ttPV/MT). Accuracy variables were calculated in the longitudinal (primary) and mediolateral (secondary) axes including constant error (CE) and variable error (VE). Moreover, variability of movement trajectories in the primary axis was calculated. That is, VE at 20%, 40%, 60%, 80% of the movement time was analyzed (Please refer to Mortaza et al., 2021, for details of the outcome measure calculations). In order to investigate the effect of practice on performance adaptability only the data from the first (early performance) and last (late performance) 20 trials were analyzed for all of the outcome measures.

Data analysis included a repeated measured ANOVA with the following designs: 2 paresthesia conditions (paresthesia, no-paresthesia) by 2 vision (vision, no-vision) conditions by 2 times (early, late performance). The factor of movement percent (20%, 40%, 60%, 80%, 100%) was added to the ANOVA in order to assess the variability throughout the movement trajectories. Significant interactions were further analyzed using Tukey's HSD. Wilcoxon Signed-Rank Test was used to compare the results of monofilament tests before and after induced paresthesia. Significance level was set at $p<0.05$ for all analyses.

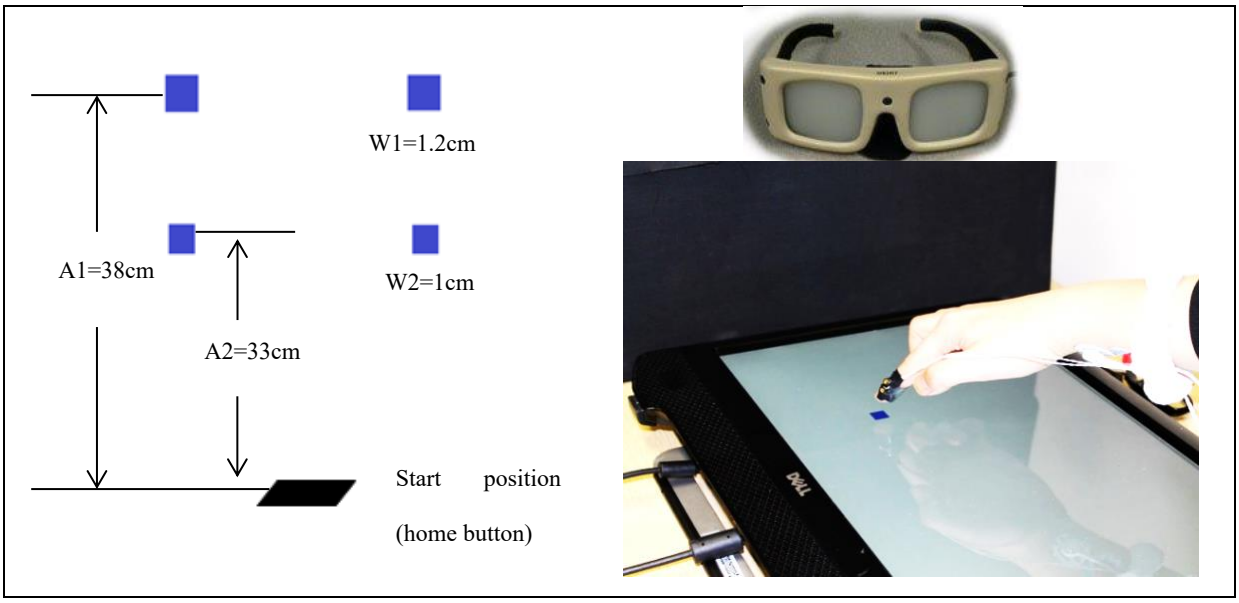


Figure 3-1 *Goal directed aiming task set up, targets locations, and occlusion goggles; figure of the goggles from: PLATO visual Occlusion Spectacles of the goggles. Translucent Technology Inc.(http://www.translucent.ca/products/plato-visual-occlusion-spectacles/plato-small/).*

3.3 Results

Monofilament test results were missing for one participant due to recording errors, so data for 11 participants was analyzed for baseline versus post stimulation comparison using the Wilcoxon Signed-Rank Test. Results showed that participants sensed thicker filaments after stimulation was applied compared to their baseline (Z=-3.21, p=0.001, Table 3-1).

Table 3-1 *Touch-Test® Sensory Evaluation- sensed monofilament size before induced paresthesia and after induced paresthesia right before the condition with paresthesia.*

Participant	Without Paresthesia	With Paresthesia
P01	2.83	3.61
P02	2.83	3.61
P03	2.83	3.61
P04	2.83	3.61
P05	2.83	3.61
P06	2.83	3.61
P07	2.83	3.61
P08	2.83	3.61
P09	2.83	3.61
P10	2.83	3.61
P11	3.61	4.31
Median	2.83	3.61

3.3.1 Temporal measurements

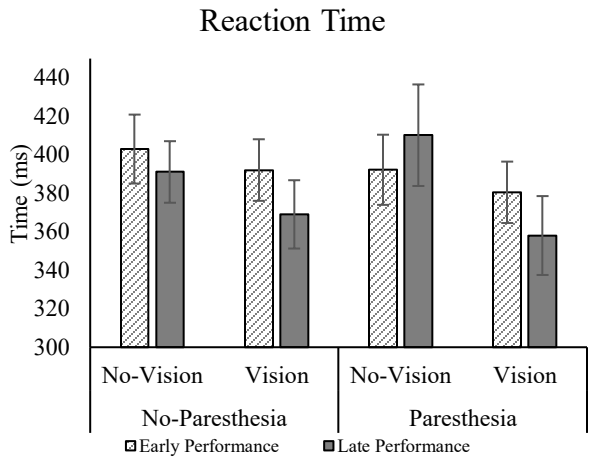
No significant interactions or main effects was found for RT (Figure 3-2a). For the outcome of MT, a significant interaction was found for vision and paresthesia, $F(1,11) = 8.85$, $p=0.013$, $\eta_p^2=0.45$. Tukey's HSD test showed that only when there was no paresthesia, participants had longer MT with vision versus without vision (Figure 3-1b).

For peak velocity (PV), there was also a significant interaction of time and paresthesia, $F(1,11) = 4.93$, $p=0.048$, $\eta_p^2=0.31$, however, post-hoc analysis did not show any significant differences between paired comparisons (none of the difference were above HSD value). Results of PV showed that when there was no paresthesia there was a trend for higher PV at the later practice trials versus early trials (Figure 3-2c).

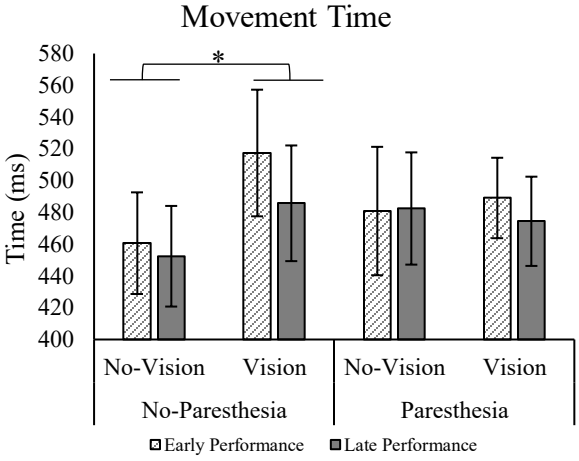
Statistical analysis for ttPV revealed a significant main effect for vision; ttPV was significantly longer when vision was removed, $F(1,11) = 5.00$, $p=0.047$, $\eta_p^2=0.31$. A significant two-way interaction for vision and time was also found, $F(1,11) =9.97$, $p=0.009$, $\eta_p^2=0.47$. Tukey's HSD test showed that showed that with full vision, late performance trials had significantly shorter ttPV than early trials. Also, at late performance when vision was removed, participants had significantly longer ttPV compared to the condition with vision. Moreover, three-way interaction for vision, time, and paresthesia was found, $F(1,11) =7.20$, $p=0.021$, $\eta_p^2=0.40$, with Tukey's HSD

test showing significantly shorter ttPV without any sensory manipulation (with vision and no paresthesia) at late performance trials when compared to early performance with the same sensory condition, and with late performance trials of both no-vision conditions with and without paresthesia (Figure 3-2d).

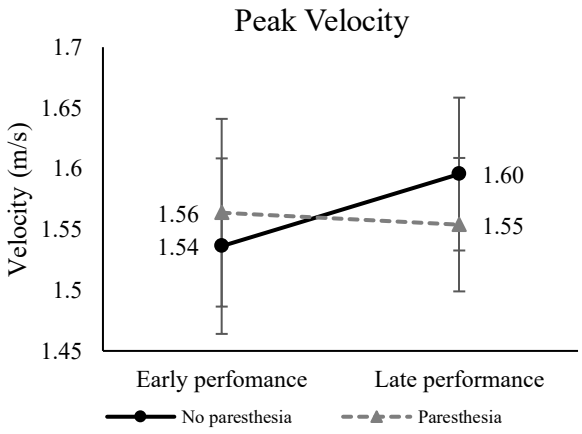
When ttPV outcome was normalized with MT, statistical analysis showed main effect of vision; that is, participants spend a larger percentage of their movement time before PV when vision was removed compared to a full vision condition, $F(1,11) = 23.82$, $p = 0.000$, $\eta_p^2 = 0.68$ (Figure 3-2f). Findings of taPV showed a significant interaction of vision and paresthesia. Post-hoc analysis showed that only in the no-paresthesia conditions, when vision was available participants spent more time after PV, while in the induced paresthesia conditions manipulating visual input did not affect taPV (Figure 3-2e).


Reaction Time
Time (ms)
440
420
400
380
360
340
320
300
No-Vision
Vision
No-Vision
Vision
No-Paresthesia
Paresthesia
Early Performance
Late Performance

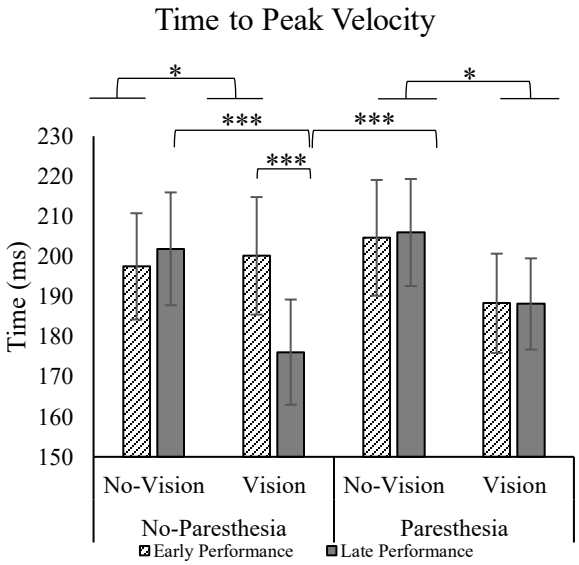
(a)


Movement Time
*
Time (ms)
580
560
540
520
500
480
460
440
420
400
No-Vision
Vision
No-Vision
Vision
No-Paresthesia
Paresthesia
Early Performance
Late Performance

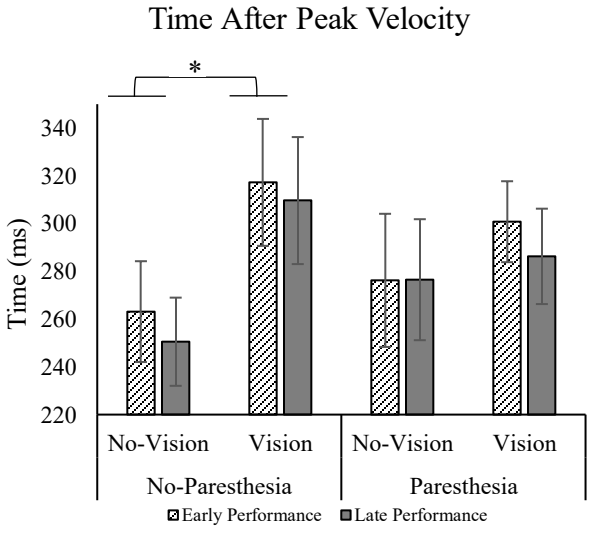
(b)


Peak Velocity
Velocity (m/s)
1.7
1.65
1.6
1.55
1.5
1.45
1.56
1.54
1.60
1.55
Early perfomance
Late performance
No paresthesia
Paresthesia

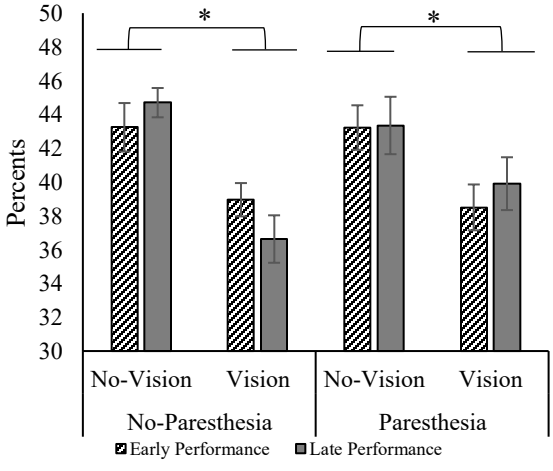
(c)


Time to Peak Velocity
*
*
***
***
***
Time (ms)
230
220
210
200
190
180
170
160
150
No-Vision
Vision
No-Vision
Vision
No-Paresthesia
Paresthesia
Early Performance
Late Performance

(d)


Time After Peak Velocity
*
Time (ms)
340
320
300
280
260
240
220
No-Vision
Vision
No-Vision
Vision
No-Paresthesia
Paresthesia
Early Performance
Late Performance

(e)


Normalized ttPV
*
*
Percents
50
48
46
44
42
40
38
36
34
32
30
No-Vision
Vision
No-Vision
Vision
No-Paresthesia
Paresthesia
Early Performance
Late Performance

(f)

Figure 3-2 ***(a)*** *reaction time* ***(b)*** *movement time with significant interaction of vision and paresthesia.* ***(c)*** *peak velocity with significant interaction of time and paresthesia.* ***(d)*** *time to peak velocity with significant main effect of vision (*), interaction of vision and time, and interaction of vision, time, paresthesia (***).* ***(e)*** *time after peak velocity with significant interaction of vision and paresthesia.* ***(f)*** *normalized time to peak velocity (ttPV) with significant main effect of vision. All error bars indicate standard error.*

3.3.2 Spatial Measurements

The ANOVA showed no significant main effects or interaction for the outcome of CE in the primary axis of movement (Figure 3-3a). Results of statistical analysis for VE showed significant main effect for vision, F (1,11) =72.35, p=0.000, η_p^2=0.87 (Figure 3-3b), indicating that participants had significantly higher VE when vision was removed.

Results of CE in the secondary axis showed significant main effect for vision, F (1,11) = 80.06, p=0.000, η_p^2=0.88, indicating larger undershoot errors when vision was removed (Figure 3-4c). There was also a significant two-way interaction of paresthesia and time, F (1,11) = 8.45, p=0.014, η_p^2=0.43, as well as a three-way interaction of paresthesia, time, and vision, F(1.72,18.89) = 116.77, p=0.000, η_p^2=0.91. Tukey's HSD test for the two-way interaction showed that at early performance induced paresthesia caused significantly larger undershoot errors comparing to the no-paresthesia condition. Also, when there was no-paresthesia, with more trials participants had significantly larger undershoot errors towards body midline, that is they performed similar to the paresthesia condition. The three-way interaction showed that CE in the secondary axis for the no-vision and no-paresthesia condition was significantly smaller than all other no vision conditions, including late performance blocks. Results of VE in the secondary axis was similar to the primary axis; that is, there was a significant main effect for vision indicating more variability when vision was removed (Figure 3-3d).

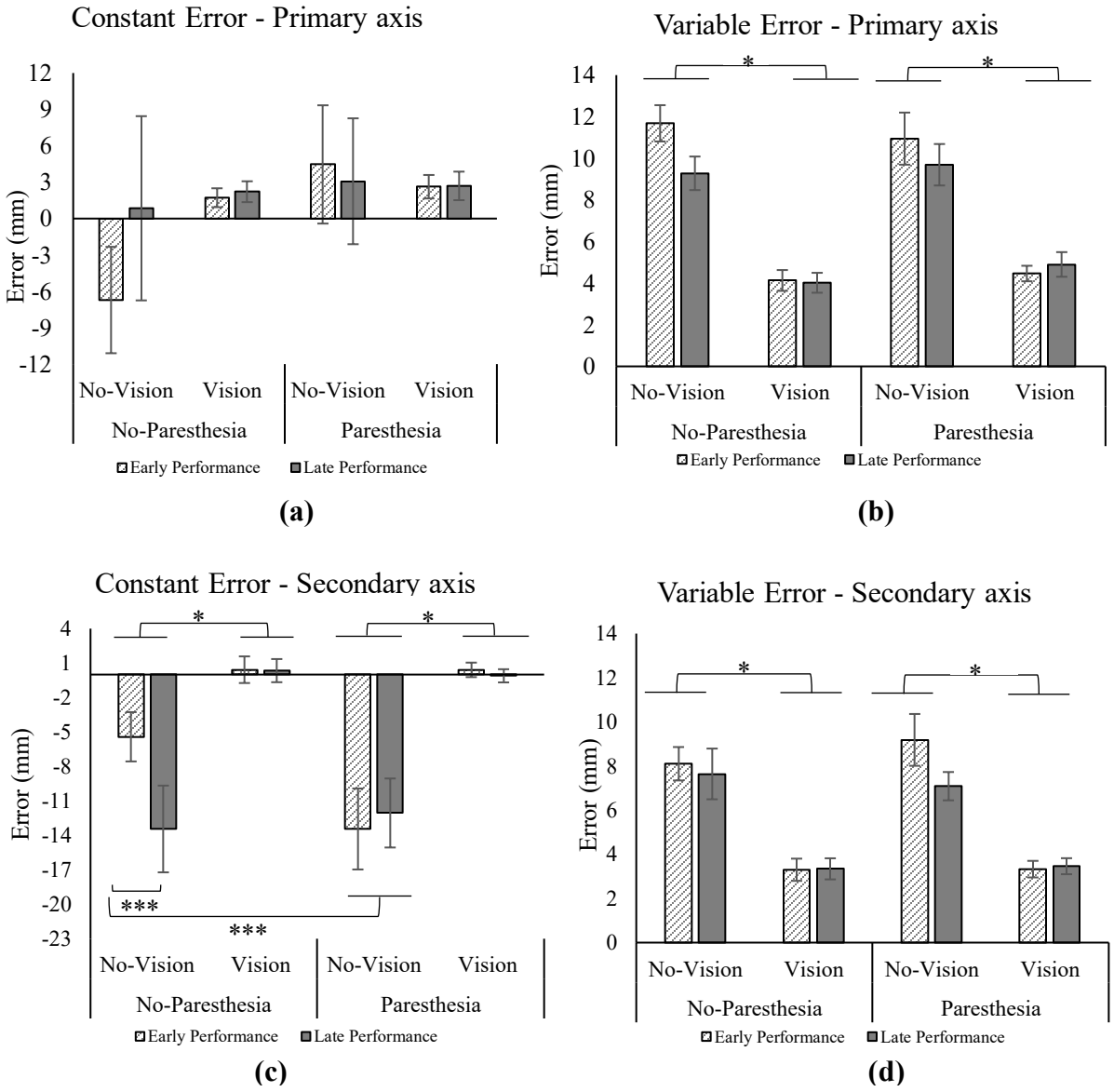


Figure 3-3 (a) *constant error in the primary axis.* ***(b)*** *variable error in the primary axis with significant main effect for vision.* ***(c)*** *constant error in the secondary axis with significant main effect of vision (*), interaction of paresthesia and time, and interaction of paresthesia, time and vision (***). (d) variable error with significant interaction of vision. All error bars indicate standard error.*

3.3.3 Movement Trajectories

Primary axis movement trajectory: There was significant main effect for factors of vision F (1,11) = 11.93, p=0.005, η_p^2=0.52 (Figure 3-4a), time, F (1,11) = 9.96, p=0.009, η_p^2=0.47 (Figure 3-4b), and percent of movement, F (1.7,18.9) =116.77, p=0.000, η_p^2=0.91(Figure 3-4a, b). Trajectories were more variable when vision was removed compared to full vision conditions and at early performance compared to the late trials. Post-hoc analysis for the significant main effect of percent of movement showed that variability was significantly higher at 40% compared to 20% and 80% of movement time.

There was a significant two-way interaction of vision and percent of movement, F(2.3,25.2) =33.48, p=0.000, η_p^2=0.75 (Figure 3-4a). Post-hoc analysis showed that when vision was not available at 60 and 80% of MT, trajectory variability was significantly higher than the conditions with full vision. Another significant interaction was time and percent of movement F(2.1,23.2) =63.88, p=0.038, η_p^2=0.25 (Figure 3-4b). Post-hoc analysis showed that only at 40% of MT did trajectory variability decrease significantly at late performance when compared to early performance.

There was a significant three-way interaction of vision, paresthesia, percent MT, F(2.1,23.2) =7.00, p=0.004, η_p^2=0.39 (Figure 3-4a). Post-hoc analysis showed that in the no-vison and no-paresthesia condition, at 60% of MT there was significantly more variability than the two vision conditions (VP and VNP). This was not the case for the no-vision with paresthesia condition at 60% into the movement, although there was a trend for higher variability with paresthesia and no-vision compared to the vision conditions. Comparison of the trajectory variability at 40% versus 60% of movement in both no-vision conditions showed significantly higher variability at 40% (Mean difference =8 mm and 6mm for no-paresthesia and paresthesia conditions, respectively).

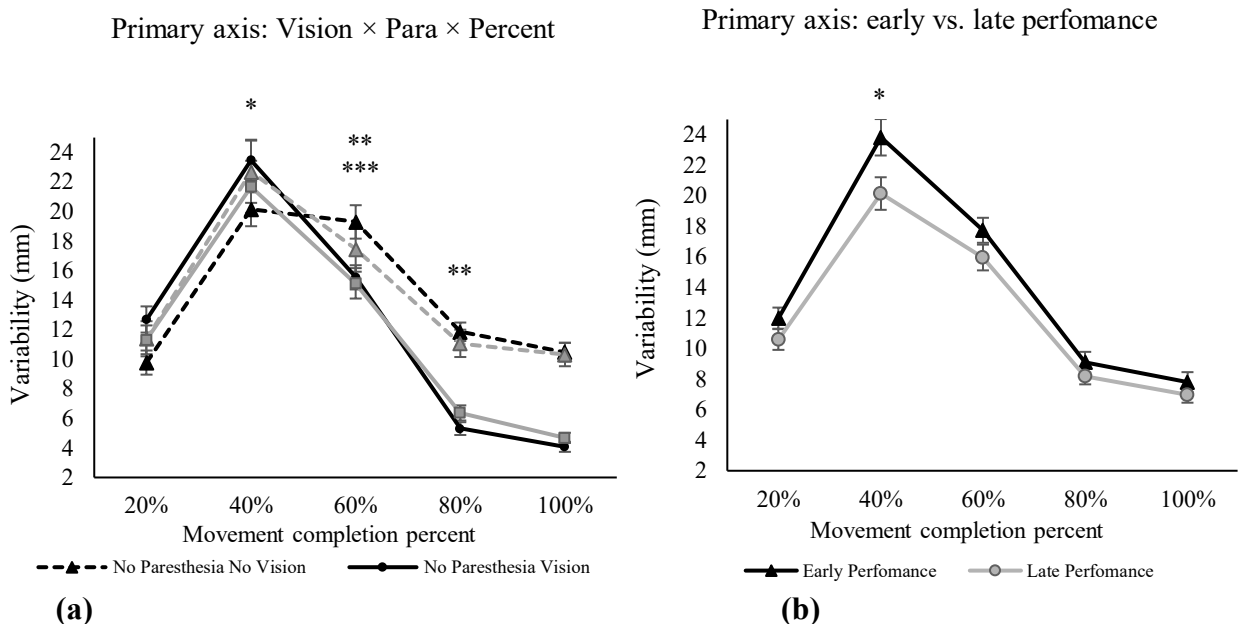


Figure 3-4 *Variability of the movement trajectory at different percentage of movement time in the primary axis of movement. Trajectory variability with significant main effects of vision and percent of movement* ***(*, a)*** *and interaction of vision and percent of movement* ***(**, a)****; significant main effect for the factor of time* ***(*, b)****, two-way interaction of time and percent of movement* ***(**, b)****, and three-way interaction of vision, paresthesia and percent of movement* ***(***, a)****. All error bars indicate standard error.*

3.4 Discussion

The aim of the current study was to understand the role of the vision of the limb in the presence of induced paresthesia (i.e., altered proprioception) on movement planning and execution. As we predicted removing vision of the limb and environment resulted in significant changes in motor control and performance characteristics of a goal-directed aiming task compared to the full vision condition. Also, as predicted these changes were greater when the no-vision condition was combined with interrupted proprioception using induced paresthesia.

3.4.1 Effect of Sensory manipulation on Endpoint Accuracy

Removing vision of the environment increased endpoint variability in both the primary and secondary axes, regardless of the paresthesia condition. There was no significant movement bias

(CE) in the primary axis, however descriptive results showed that when vision was removed the average CE indicated undershot for the no-paresthesia condition (mean= -3mm) and an overshoot for the paresthesia condition (mean=4mm; Figure 3-3a). In the secondary axis there was a significant movement bias towards the midline in both early and later performance in the condition with the most sensory disruption (i.e., no-vision, with paresthesia) when compared to the early performance of the no-paresthesia condition. This finding could signify the role of proprioception in the online correction and limb-target regulation which led to less movement bias in the no-vision, no-paresthesia condition (i.e., with intact proprioceptive inputs). Late performance in the no-vision and no-paresthesia condition also had a significant bias towards body midline when compared to the early performance. One explanation for these findings could be the bias of sense of limb position towards the attended side of the body in the absence of visual input of the limb. That is, several studies have reported that (Ghilardi et al., 1995; Haggard et al., 2000; Jones et al., 2010) in the absent of visual input of the right or left hand, individuals tend to overestimate their limb location further towards right or left, respectively. In the current study participants seemed to overcorrect this bias by moving the upper limb more towards the midline which led to undershoot errors specifically in the condition with paresthesia. Despite availability of the intact proprioception feedback, without vision during a block of 100 aiming movements, the amount of exposure to visual information was reduced such that by the final 20 trials of the block of trials a similar overcorrection phenomenon may have occurred. The above findings are consistent with the results of our previous study (Mortaza et al., 2021) in the condition without vision of the target and no-paresthesia. However, there were some differences with this previous study in that with vision of the limb and environment the movement bias (CE) in the secondary axis for late versus early performance was not statistically significant. The tendency of the participants to undershoot the target in the no-vision and paresthesia condition in the secondary axis (Figure 3-3c) could also be caused by the stimulation of the median nerve that was used to temporarily induce paresthesia. Isolated stimulation of the median nerve may have caused illusory sensation leading to a biased sense of limb position towards elbow and wrist extension and tendency for overcorrection towards the midline (elbow and/or wrist) flexion when vision feedback was not available to correct. This explanation is in agreement with the finding of Rangwani et. al. (Rangwani & Park, 2021), where they used transcutaneous electrical muscle stimulation over the synergist flexor muscles of the elbow. They found that all participants experienced proprioceptive illusory sensation towards

elbow extension according to the results of an arm-matching test. This illusory sense of limb position towards the movement of the antagonist muscle groups of the stimulation side is also seen in tendon muscle vibration that targets the muscle spindles (Goodwin et al., 1972; Roll & Vedel, 1982). In summary, induced paresthesia exacerbated the movement bias in the absence of vision, possibly by illusory sense of position towards wrist/elbow extension, when consistency (VE) was primarily impacted by vision only.

3.4.2 Effect of Sensory manipulation on Movement Strategy

The MT results showed that the lack of vision only affected MT in the no-paresthesia condition. Specifically, participants' MT became 45ms slower when vision was removed, however this was not the case for the paresthesia conditions. In the no-paresthesia and full vision condition participants had the maximum amount of sensory information available for online correction, which led to a movement strategy of using the available feedback, which led to longer MTs. The longer MT for the full vision and no-paresthesia condition was also accompanied by significantly smaller CE in the secondary axis and well as smaller VE in both axes. Together, these results indicate successful online corrections of the aiming movement.

The above results are consistent with the MT findings for previous research (Hansen et al., 2006) where participants spent a significantly longer time after PV when vision was available (Figure 3-2c). Time to PV results also showed shorter ttPV for full vision conditions and least amount of ttPV spent in the late performance of full vision and no-paresthesia condition compared to late performance of the no-vison conditions, regardless of presence of paresthesia. Also, consistent with other temporal variable findings, normalized ttPV showed a smaller percentage of movement time was spent before PV when vision was available, compared to no-vision conditions. In summary, the results of the temporal outcomes indicate that when vision was not available participants spent most of their MT time on the distance covering portion of the movement and performed fewer online corrections as they did not have visual feedback for limb-target regulations (Elliott et al., 2010; Elliott et al., 2017).The main difference that paresthesia made on movement performance was on the time spent after peak velocity. That is, in full vision conditions, when paresthesia was not applied, significantly more time was spent on the online correction portion of the movement. In contrast, when paresthesia was applied participants did not engage in the same amount of time in the online corrective phase (Elliott et al., 2017; Hansen et al., 2006). This finding

indicates that when proprioception was compromised (by induced paresthesia) participants had less sensory input to process as they were focused on visual feedback alone for online correction, which lead to a shorter time spent on limb-target regulation.

As expected, participant trajectories were most variable at 40% of MT as well as at movement end when vision was not available. In the no-vision and no-paresthesia condition at 60% of movement, there was significantly more variability than the two vision conditions (VP and VNP), while both vision conditions were significantly more variable at 40% of MT compared to 60% of MT (Figure 3-3a). Forty percent of MT corresponds to the time that PV was achieved (PV at ~38% of MT for vision conditions) and is expected to be close to the end of the initial impulse phase of the movement (Elliott et al., 1999; Elliott et al., 2010; Elliott et al., 2017; Soechting, 1984). The above finding suggests a shorter and forceful initial impulse phase in the condition with vison such that the limb reached closer to the target location and more time was spent for online corrections when visual input was available. This strategy led to more variability earlier during MT in the vision condition (at 40% of MT) compared to the no-vision and no-paresthesia condition (at 60% of MT). This finding is also in agreement with the taPV results for the condition with no-vision and no- paresthesia. That is, this condition had the shortest taPV (i.e., less time spent on online corrections). The vision conditions stayed significantly less variable than no-vision conditions for the rest of the movement (at 80% of MT).

3.4.3 Adaptability and practice

As a secondary objective of the current study, in order to assess the adaptability of the motor control processes to the changes of sensory inputs, early and late 20% of trials were also analyzed separately. The only significant effect of the factor of time on the accuracy outcomes was in CE in the no-vision and no-paresthesia condition. CE in the secondary axis was significantly greater in the later performance trials compared to the early trials. As discussed earlier, this finding can be explained by an overcorrection in the movement as a result of the biased sense of limb position in the prolonged absence of vision of the hand (Ghilardi et al., 1995; Haggard et al., 2000; Jones et al., 2010).

An effect of practice was seen with a significant decrease in trajectory variability with more trials. This difference was the most pronounced at 40% of MT (mean difference= 4mm, Figure 3-4b) which can be explained but more consistent and refined force generation profiles with repeated

movements towards the same target (Schmidt et al., 1979). Specifically, 40% of MT corresponds to the time at which peak velocity is typically reached (Khan et al., 2006). However, the difference in available sensory inputs did not have a significant effect on changes in trajectory variability with practice. In the secondary axis, during the early performance of the no-vision conditions, movement variability was significantly greater compared to the full vision conditions. This difference was reduced with more practice. The above pattern of results indicates there was some adaptation that happened with the lack of visual input that led to improved consistency of the movement trajectory with more practice.

Results of ttPV for early and late performance showed that when vision was available, participants performed the movements with longer ttPV after practice when compared to their early performance (mean difference=12ms). This change of movement strategy when vision was available was most noticeable when paresthesia was *not* applied (mean difference= 22ms). From the findings of the effects of practice on the length of ttPV we inferred that a change of movement control strategy and planning from a more pre-planned movement to using more online control occurred when participants had all intrinsically available sensory information. In contrast, participants did not update their movement control strategy when somatosensory input was altered, which indicates the critical role of proprioception in online corrections even when full visual input was available. Also, it seems that the participants could not adapt to the distorted proprioceptive input and did not use it with more practice.

3.5 Conclusion

The combination of induced paresthesia and no visual feedback led to a significant movement bias towards the body midline. The findings also support the idea that the contribution of proprioceptive input for movement accuracy is indeed larger in the absence of visual feedback. Specifically, the bias was greater with paresthesia when vision was removed. With intact sensory processing (i.e., without paresthesia and with full vision), participants had the longest MTs. In conjunction with improved endpoint accuracy, this pattern indicates that participants used the available sensory information and spent more time implementing online corrections to the limb trajectory. Notably, vision in the presence of induced paresthesia did not lead to longer MT since the participants had less sensory feedback to use for online movement corrections. The longest MT in the intact sensory input condition was associated with the shortest time to peak velocity specially

with more practice. In summary, all of the temporal movement findings are in agreement that with more practice and full sensory information available, participants developed a new movement strategy. The differences in the temporal parameters in paresthesia versus no paresthesia conditions with full vision condition signifies the role of proprioception for informing both the movement strategy and efficacy, even when visual information of the limb, target, and environment is available. We conclude that visual information of the limb had a significant role on endpoint accuracy and variability, however paresthesia or lack of intact proprioceptive input, contributed to a pre-planned movement strategy for goal-directed reaching, even when full visual feedback was available.

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CHAPTER 4

Study 3: Upper Limb Tendon-muscle Vibration in Persons with Subacute and Chronic Stroke: a systematic review and meta-analysis

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Contributions of Authors to The Manuscript

N.M. designed and prepared the literature review protocol. A.A.S., R.Z, and C.G. supervised and revised the literature review protocol. N.M and H.M ran the literature review search. N.M and R.R. design the meta-analysis method. N.M. and C.G independently extracted relevant trials from the literature review search results. N.M. extracted and analyzed the data from the included trials. N.M. prepared the first draft of the manuscript. All authors critically revised the draft of the manuscript for intellectual content and approved the final draft submitted to the European Journal of Physical and Rehabilitation Medicine.

Preface

The previous two studies presented in the current thesis provide further evidence on the importance of proprioceptive input on planning and online control of functional movements. Impairment of proprioception is one of the sensory complications of individuals with stroke, and as mentioned in the literature review section of the current thesis there are studies that showed benefits of using MTV (as a method of proprioceptive feedback modification) in improving functional movements in individuals with stroke. So, the current study is a literature review with meta-analysis that assessed and pooled the available clinical evidence on the effectiveness of MTV for rehabilitation of individuals with chronic stroke. We used the findings of this literature review for determining the parameters of an effective vibration protocol as well as the outcome measures that are sensitive enough to detect changes as a result application of muscle-tendon vibration in the last two studies included in the current thesis.

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Abstract

INTRODUCTION: Results of several recent studies suggest that tendon/muscle vibration treatment may improve motor performance and reduce spasticity in individuals with stroke. We performed a systematic review and meta-analysis to assess the efficacy of tendon/muscle vibration treatment for upper limb functional movements in persons with subacute and chronic stroke.
EVIDENCE ACQUISITION: We searched MEDLINE (Ovid), EMBASE (Ovid), and the Cochrane Central Register of Controlled Trials (Wiley) from inception to September 2017. We included randomized controlled trials comparing upper limb tendon/muscle vibration to sham treatment/rest or conventional interventions in persons with subacute and chronic stroke. Our primary outcome was upper limb functional movement at the end of the treatment period.
EVIDENCE SYNTHESIS: We included eight trials enrolling a total of 211 participants. We found insufficient evidence to support a benefit for upper limb functional movement (standard mean difference -0.32, 95% confidence interval (CI) -0.74 to 0.10, I^2 25%, 6 trials, 135 participants). Movement time for reaching tasks significantly decreased after using tendon/muscle vibration (standard mean difference -1.20, 95% CI -2.05 to -0.35, I^2 65%, 2 trials, 74 participants). We also found that tendon/muscle vibration was not associated with a significant reduction in spasticity (4 trials). CONCLUSIONS: Besides shorter movement time for reaching tasks, we did not identify evidence to support clinical improvement in upper limb functional movements after tendon/muscle vibration treatment in persons with subacute and chronic stroke. A small number of trials were identified; therefore, there is a need for larger, higher quality studies and to consider the clinical relevance of performance-based outcome measures that focus on time to complete a functional movement such as a reach.

Key words: vibration, upper-limb, stroke, rehabilitation, systematic review, meta-analysis.

4.1 Introduction

Stroke is the third most common cause of living with a disability-adjusted situation (Feigin et al., 2014). Annually, 15 million people worldwide suffer a stroke. Of these, five million are living with permanent disabilities (Mackay & Mensah, 2004). Two thirds of stroke survivors are

living with motor deficiencies that are associated with deteriorated quality of life (Langhorne et al., 2009). Motor impairments are a widely recognized consequence of stroke and are defined as loss or limited motor control or movement (Langhorne et al., 2009). Given the necessity of proprioceptive feedback for fine motor control, sensorimotor loss associated with stroke (specifically proprioception and tactile sensation deficiencies) can significantly affect upper limb motor control (Carey et al., 1993; Schmidt & Lee, 2011; Tyson et al., 2008).

Proprioception is included in many rehabilitation programs because of its importance for effective motor control. Studies have shown that persons with stroke who completed proprioception training showed improvement in upper limb sensorimotor function (Aman et al., 2014; Cordo et al., 2009). In training modalities engagement of the proprioceptors could be done by somatosensory stimulation using vibration of a muscle-tendon unit (Rosenkranz et al., 2008; Rosenkranz et al., 2009). Segmental tendon/muscle vibration treatment uses a mechanical device to apply vibration stimulation over the tendon-muscle unit. It is important to note that different frequencies of vibration on muscle/tendons can activate different sensory receptors such as muscle spindle primary (Ia) and secondary (II) endings and Golgi tendon organs (Ib) (Aman et al., 2014; Enders et al., 2013; Roll et al., 1989), or cutaneous mechanoreceptors such as Pacinian corpuscles. The peripheral system inputs during the actual movements are similar to the response of proprioception afferents to mechanical vibration and applying it during movements can cause kinematic illusions. However, in 1995 Roll et al. (Roll & Gilhodes, 1995) showed that the same vibration frequency to two antagonistic muscles does not induce kinesthetic illusions, instead it induces the feeling that the position of the joint in question has been stabilized. Also, vibration has shown to mask tactile sensation and interfere with the signals coding the tactile stimuli characteristics (Costantino et al., 2017; Ribot-Ciscar et al., 1989) that could lead to sensorimotor changes. These changes could persist for several minutes after the vibration is withdrawn. An explanation for this alteration as a result of vibratory input could be a suppression in the excitability of cutaneous mechanoreceptors (Lundstrom & Johansson, 1986). Brain excitability studies have shown the potential of tendon muscle vibration to lead to cortical level changes in healthy individuals (Forner-Cordero et al., 2008; Marconi et al., 2008; Rosenkranz et al., 2003) and in individuals with stroke (Marconi et al., 2011).These changes include excitability of the areas related to the vibrated muscle as well as patterns of intra-cortical inhibition and facilitation. Marconi et al. (Marconi et al., 2008) conducted a brain excitability study using transcranial

magnetic stimulation (TMS) on healthy participants. The authors found that 30 minutes of muscle/tendon vibration (100 Hz frequency, 0.05-0.1mm amplitude) on a contracting wrist flexor muscle can cause long lasting changes in the target muscle's cortical excitability that lasted for two weeks and returned to baseline levels within three weeks. In another study Marconi et al. (Marconi et al., 2011) used the same tendon/muscle vibration protocol for individuals with chronic stroke. The results of this study showed increased map volume for both agonist and antagonist muscles. Motor cortical excitability changes in Marconi et al.'s study (Marconi et al., 2011) with stroke participants was also accompanied by reduced spasticity and improved functional movement.

Based on the observed changes in the excitability of the representations of the upper limb muscles in the brain as a result of tendon/muscle vibration Paoloni et al. (Paoloni et al., 2014) predicted this intervention also modulates the pattern and coordination of the activity of upper limb agonist and antagonist muscles. The authors applied ten sessions of tendon/muscle vibration (120 Hz frequency, 0.01mm amplitude) over the wrist and elbow flexors of patients with chronic stroke. Electromyography assessments during an upper limb reaching movement were done to find the effects of vibration treatment on voluntary muscle contraction and movement control. The comparisons of the muscular activity before and after the intervention indicated that participants could activate some of their flexor muscles faster and had lower levels of agonist/antagonist co-contractions in the elbow and shoulder musculature. In an immediate effect study Conrad et. al (Conrad et al., 2011a) found similar results with application of tendon muscle vibration during and after an upper limb movement task. They applied 70Hz vibration on wrist flexor muscles during a planar robotic tracking upper limb task for individuals with chronic stroke. The results of this study showed that when compared with the no-vibration condition the tracking movements of the upper limb were significantly smoother and the shoulder musculature electromyography activity was reduced during and after application of muscle vibration. Taken together the above results indicate improved stability in the arm and enhanced movement control (Conrad et al., 2011a, 2011b). In summary, the above studies have used a range of outcome measures and demonstrated plausible neural mechanisms that could be helpful in explaining the results of clinical trials that have found improvements in motor performance as a result of muscle/tendon vibration treatment.

To the best of our knowledge, there are only a few small clinical trials on the effects of tendon or segmental muscle vibration on functional movement and sensorimotor recovery of functional upper limb movement in individuals with subacute and chronic stroke (more than three months

since stroke). These separate studies have reported that tendon/muscle vibration on the upper limb of persons with chronic or subacute stroke leads to improved functional movement (measured by standardized clinical scales) (Caliandro et al., 2012; Costantino et al., 2017; Marconi et al., 2011; Sim et al., 2015; Tavernese et al., 2013), reduced spasticity (Ageranioti & Hayes, 1990; Caliandro et al., 2012; Costantino et al., 2017; Marconi et al., 2011), pain, and subsequently enhanced quality of life and independence (Costantino et al., 2017). However, the efficacy, or possible adverse effects of tendon or segmental muscle vibration, as well as the effective vibration intensities, frequencies, and protocol of application for the upper limb in persons with subacute and chronic stroke have not been addressed in a meta-analysis of the available results. Hence, the purpose of the current systematic review was to identify, critically appraise, and meta-analyze data from prospective, randomized, controlled trials that compared muscle/tendon vibration in persons with subacute and chronic stroke (time since stroke incident >3 months) to sham treatment/rest or conventional interventions.

4.2 Research question

Our primary research question was "Does upper limb tendon/segmental muscle vibration effectively improve upper limb motor performance in persons with subacute and chronic stroke when compared to rest, sham, or conventional treatment?" We included prospective randomized controlled trials (RCTs) of adult participants (at least 18 years of age) who had experienced any type of stroke incident at least three months prior to the beginning of the study. The three-month cut-off was chosen to define subacute and chronic stroke as the majority of rapid recovery and intensive rehabilitation programs happen during this time period. The intervention of interest was tendon/muscle vibration of the upper limb, including local vibration of a single muscle-tendon segment. The primary outcome measure was upper limb functional movement assessed by any of the various multi-dimensional, validated, ordinal and continuous scales (Appendix 2). The upper limb functional movement was selected as the primary outcome measure because it provides a more holistic perspective on the possible effects of the intervention that interests patients and clinicians.

Secondary Outcomes included movement time of an upper limb reaching movements and upper limb spasticity. The Modified Ashworth Scale was used in all of the included studies to

measure spasticity of the upper limb. The safety outcome was defined as the number of participants with reported pain (as a result of muscle/tendon vibration).

4.3 Evidence acquisition

Using an a priori published protocol (CRD42017074095, https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=74095) , we conducted our systematic review in accordance with the Methodological Expectations of Cochrane Intervention Reviews guidelines (Chandler et al., 2011) and reported our results as per the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines for systematic review and meta-analysis (Moher et al., 2009). A review team including experts from multiple fields (physical therapy, clinical engineering, physical medicine and rehabilitation, research methodology, library sciences, and biostatistics) formulated the research question, reviewed the search strategy and review methods, and provided input throughout the review process.

4.3.1 Search strategy and study selection

We searched MEDLINE (Ovid), EMBASE (Ovid), and the Cochrane Central Register of Controlled Trials (Wiley) from inception to September 2017 using individualized search strategies prepared for each database using the Cochrane Highly Sensitive Search Strategy as a model for searching (Higgins & Green, 2011). The original search strategy was designed for MEDLINE (Appendix 3) with input from an information specialist and then translated for other databases. The following subject headings and keywords were used: 'cerebrovascular disorders, stroke, cerebral or brain infarction, vibration, vibrotactile, oscillation, tapping'.

The grey literature search consisted of three searches: a search for conference proceedings in EMBASE (January 2013 to March 2017), a search of the World Health Organization International Clinical Trials Registry Platform (to identify ongoing or planned trials), and a forward and backward search of randomized controlled trials selected for the systematic review and meta-analysis in Scopus and Web of Science to identify additional relevant citations. The conference search in EMBASE searched the following terms and phrases in the text word, keyword, conference information, conference publication, publication type fields: annual meeting,

conference, symposium, workshop, proceeding, poster*, paper*, or abstract*. These terms were added to the search used for "stroke" and "vibration".

Reference Management was performed in EndNote™ X8 (Clarivate Analytics, New York City, NY, USA). At the end of the review, we constructed a PRISMA flow diagram illustrating the number of records and full-text reports reviewed and either excluded or included. Two reviewers (NM and CG) independently reviewed the title and abstract of each citation to determine whether a study generally met the inclusion criteria. The full text of all citations listed as 'include' or 'unsure' by either reviewer at this stage were retrieved for formal review. The full text of each potentially relevant citation was then independently assessed to determine whether the trial met the predetermined inclusion and exclusion criteria.

The inclusion criteria were trials that: (1) included adults (18 years of age or greater) with subacute and chronic stroke (> 3months since stroke event); (2) applied upper limb tendon/muscle vibration; (3) assessed functional movement of the upper limb; (4) was a prospective randomized, controlled trial. Exclusion criteria were studies that: (1) applied whole body vibration; (2) included other somatosensory stimulation inputs besides vibration for the vibration intervention group (e.g., electrical stimulation or pressure); (3) included healthy controls as the only comparison group; (4) all participant groups received muscle/tendon vibration as treatment; (5) had an observational study design, were quasi-randomized, crossover, or cluster-randomized trials; (6) involved animals.

4.3.2 Data abstraction and management

Two reviewers (NM and CG) independently extracted data from the included trials, using standardized and piloted data extraction forms. Discrepancies were resolved through consensus. The following data were extracted from each study: study demographics (author, year of publication, language of publication, source of funding, publication status and country); risk of bias criteria (using the Cochrane Collaboration Risk of Bias tool) (Higgins et al., 2011; Higgins & Green, 2008); study quality criteria (using Physiotherapy Evidence Database Scale) (*PEDro Scale*, 1999), participant characteristics (number in each group, time since stroke incidence, stroke type, age, co-interventions), intervention (number and duration of treatment sessions, amplitude and frequency of vibration, target muscle/tendon) and its comparator, and results reported for the outcomes of interest. We contacted study authors to request clarifications or for missing data. The data was entered into a Microsoft Excel™ database (Microsoft Corp., Redmond, WA).

4.3.3 Study Quality and Risk of Bias Assessment

The internal validity of trials was assessed using the Cochrane Collaboration Risk of Bias tool (Higgins et al., 2011; Higgins & Green, 2008). This tool consists of six domains (sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting, and other sources of bias) and a categorization of the overall risk of bias. Each separate domain was rated low risk, unclear risk, or high risk. The overall assessment was based on the responses to individual domains. If one or more individual domains were assessed as having a high risk of bias, the overall judgment was having a high risk of bias. The overall risk of bias was considered low only if all components were judged as having a low risk of bias. The overall unclear risk of bias was chosen when there was a combination of low risk and unclear risk for different components. In addition, information on the source of funding was collected for each study. Information regarding risk of bias was used to guide sensitivity analyses and explore sources of heterogeneity. Moreover, the methodological quality of the included trials was evaluated using the Physiotherapy Evidence Database (PEDro) scale (*PEDro Scale*, 1999). The risk of bias and PEDro scale assessments were performed by two assessors independently (NM and CG). Any discrepancies in the conclusions of the risk of bias and quality analysis were then jointly examined by the two assessors, who came to consensus regarding the most appropriate score according to the criteria from the scales.

4.4 Data analysis

We conducted meta-analyses for the first measurements at the end of the treatment using Cochrane Review Manager (RevMan, version 5.3.5, 2014; The Cochrane Collaboration, Copenhagen, Denmark). For the primary outcome measure of upper limb functional movement, data were derived from validated, multi-item, ordinal and continuous rating scales. For the purpose of analysis all scales were treated as continuous data as suggested in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins & Green, 2011). We used mean difference, or standardized mean difference (SMD, where multiple scales were used to measure the same outcome) and 95% confidence intervals (CI). A random-effects model was used for all analyses. Statistical heterogeneity of the data was explored and quantified using the I^2 test (Higgins & Thompson, 2002). When significant heterogeneity was suspected further analyses, including

subgroup and sensitivity analyses, were conducted. We planned to test for publication bias using funnel plots, but did not do so because so few trials were available for the given analysis (Ioannidis & Trikalinos, 2007).

4.4.1 Subgroup Sensitivity Analysis

To investigate potential statistical heterogeneity, we performed subgroup analyses in several pre-specified groups, including vibration amplitude (0.2-0.5 mm versus above 0.5mm), vibration frequency (below 80 Hz versus 100Hz or above), and number of treatment sessions (5 sessions or less versus above 5 sessions).

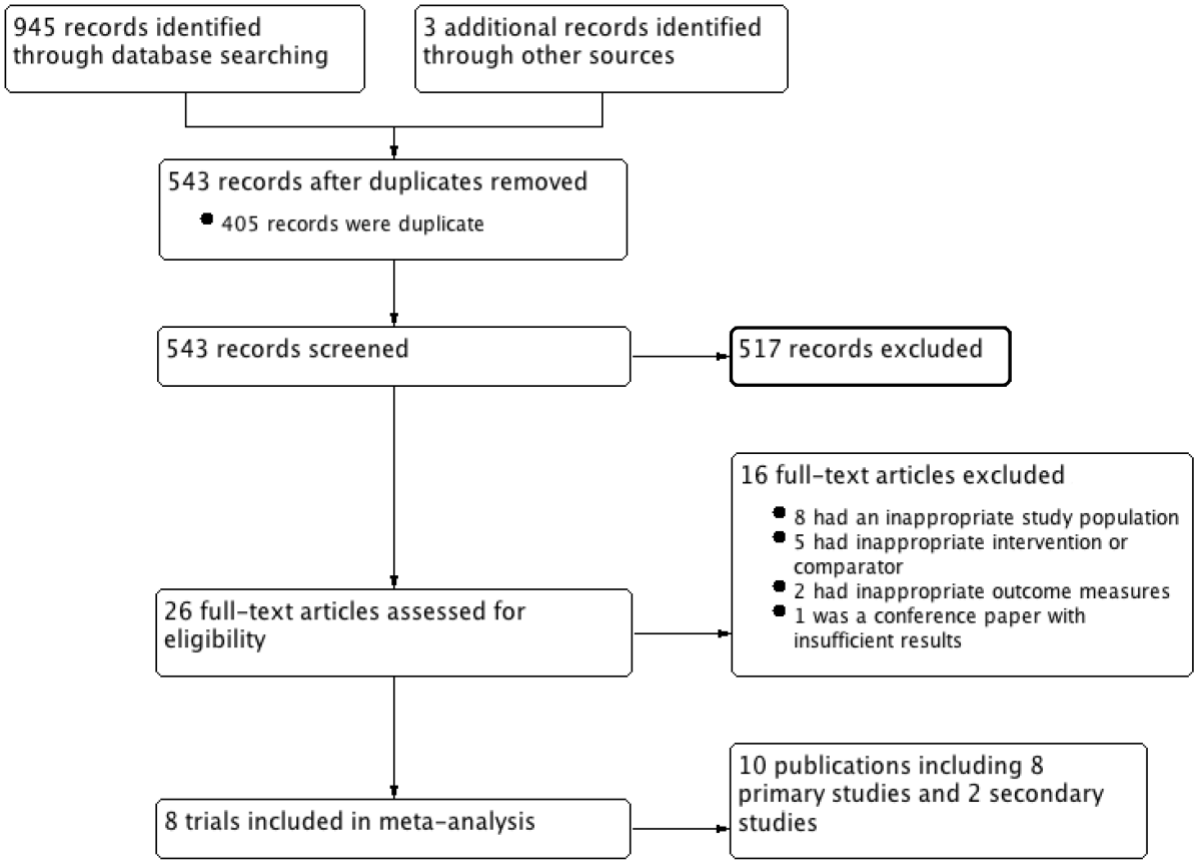

Figure 4-1 *PRISMA flow diagram.*

4.5 Evidence synthesis

We identified 945 records through our database searches and one record (full article) by contacting the author of an included conference paper and two records by grey literature search (Figure 4-1). After screening the titles and abstracts, we obtained the full text of 26 full-text articles. After further assessment, we determined that 10 publications (eight primary publications (Caliandro et al., 2012; Casale et al., 2014; Celletti et al., 2017; Choi, 2017; Costantino et al., 2017; Liu et al., 2011; Marconi et al., 2011; Tavernese et al., 2013) and two companion publications (Liu et al., 2009; Mandic et al., 2012)) were eligible according to our inclusion criteria. Details of excluded studies and reasons for exclusion are reported in in supplementary file1 (Appendix 4).

The included trials were all published in peer-reviewed, English-language journals (Table 4-1). None of the trials were industry funded. Six of the trials were conducted in Europe (Italy) (Caliandro et al., 2012; Casale et al., 2014; Celletti et al., 2017; Costantino et al., 2017; Marconi et al., 2011; Tavernese et al., 2013), one in the United States (Liu et al., 2011), and one in Korea (Choi, 2017). All trials were at unclear (Casale et al., 2014; Choi, 2017; Costantino et al., 2017) or high risk of bias (Caliandro et al., 2012; Celletti et al., 2017; Liu et al., 2011; Marconi et al., 2011; Tavernese et al., 2013) (Figure 4-2). The reason for most of the cases of high risk of bias (five trials) was due to a lack of blinding for the participants and personnel that applied the treatment. The results of the PEDro quality assessment can be accessed in supplementary file 2 (Appendix 5). The range for PEDro scores was 4 to 10. Similar to the results of the risk of bias assessment, the most common methodological issues were lack of blinding of therapists (seven trials) (Caliandro et al., 2012; Casale et al., 2014; Celletti et al., 2017; Choi, 2017; Costantino et al., 2017; Liu et al., 2011; Tavernese et al., 2013), and lack of blinding of participants (five trials) (Celletti et al., 2017; Choi, 2017; Liu et al., 2011; Marconi et al., 2011; Tavernese et al., 2013). Also, allocation concealment was not done in five of the trials (Casale et al., 2014; Choi, 2017; Costantino et al., 2017; Liu et al., 2011; Marconi et al., 2011). Considering the nature of the tendon/muscle vibration treatment, even with applying sham vibration, there was a chance for unmasking the intervention by the participants. For the same reason therapists could not be blinded for the treatment. Considering these inherent methodological challenges, we included two trials (Choi, 2017; Liu et al., 2011) with PEDro scores as low as four.

Two trials used sham vibration for the control group (Caliandro et al., 2012; Casale et al., 2014; Costantino et al., 2017) and the other trials used robot assisted training (Liu et al., 2011) and

physical therapy (Celletti et al., 2017; Choi, 2017; Marconi et al., 2011; Tavernese et al., 2013) as the comparison groups. In seven of the selected trials the participants in the treatment group received co-interventions including physical therapy (Caliandro et al., 2012; Casale et al., 2014; Celletti et al., 2017; Marconi et al., 2011; Tavernese et al., 2013) and robot-assisted training (Liu et al., 2011), and in two trials tendon/muscle vibration was the only reported treatment (Choi, 2017; Costantino et al., 2017).

Altogether the included trials recruited 211 participants. For one of the trials the author provided data on the number of participants in the control and intervention groups (Liu et al., 2011), and for another study the author provided the raw data for the upper limb functional test scores (Caliandro et al., 2012) via personal communication.

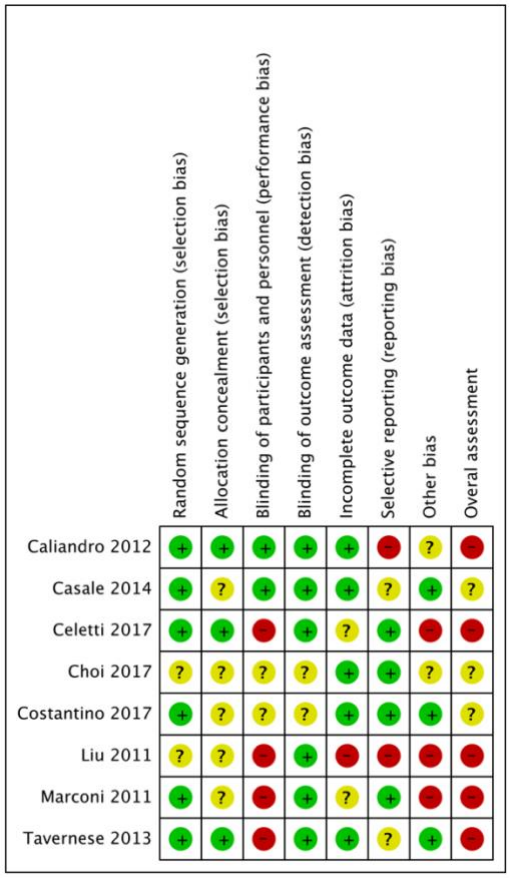

Figure 4-2 *Risk of bias summary: review authors' judgments about each risk of bias item for each included study*

4.5.1 Primary Outcomes and Subgroup Analyses

Among the six included trials for the primary outcome measure of upper limb functional movement (Caliandro et al., 2012; Celletti et al., 2017; Choi, 2017; Costantino et al., 2017; Liu et al., 2011; Marconi et al., 2011), one of them reported Motor Status Score (Liu et al., 2011), three reported the Wolf Motor Function Test - functional ability (Caliandro et al., 2012; Celletti et al., 2017; Marconi et al., 2011), one reported the Box and Block test (Choi, 2017), and finally the sixth reported the Jebsen-Taylor hand function test (Costantino et al., 2017). For the primary outcome, there was no evidence of a significant effect of tendon/muscle vibration regarding upper extremity functional movement (standardized mean difference -0.32, 95% CI -0.74 to 0.10; I^2 25%; 6 trials; 135 participants; Figure 4-3). Similar results were found in the subgroup analyses (Table 4-2).

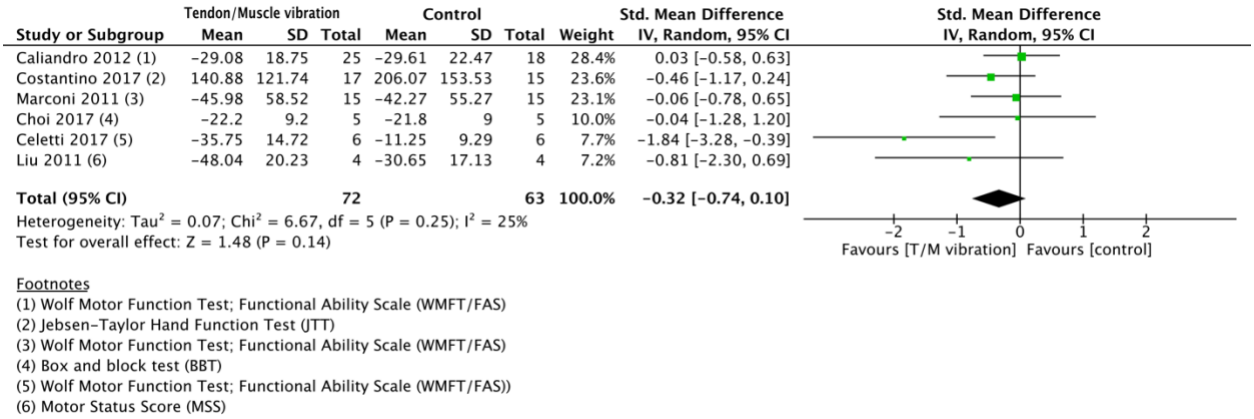

Figure 4-3 *Changes in the measurements of functional movement according to the tendon/ muscle vibration treatment for six included trials (Caliandro et al., 2012; Celletti et al., 2017; Choi, 2017; Costantino et al., 2017; Liu et al., 2011; Marconi et al., 2011).*

Boxes and horizontal lines represent point estimates, varying in size according to the weight in the analysis, and 95% confidence intervals. SD: standard deviation; Chi^2 = Chi-squared; df = degrees of freedom; CI = Confidence interval; I^2 = I-squared; IV = Inverse Variance; P = P value; Std = Standardized; risk ratio; Tau^2 = Tau-squared; Z = Z score. The footnotes indicate the type of clinical tests that were used for the primary outcome of upper limb functional change. The reported mean and SDs are the end-of-treatment measurements for the functional scores for control and treatment groups. The section under "Total" indicates the number of subjects included in the analysis.

Table 4-1 *Characteristics of selected randomized controlled trials.*

Study reference number	No of participants	Age(yr) Mean ± SD	Months since stroke Mean ± SD	Intervention	Control	Co-interventions	Outcome(s) of interest
	T-Mv / Ctrl	T-Mv / Ctrl	T-MV / Ctrl				
(Liu et al., 2011)	4 /4	Overall: 57.3 ±13.9	Overall: 94.9±116.1	-Vibration in hands during robotic assisted training. - Amp/freq.: 2mm/20 Hz - No./Length of sessions: 20/40 mins	Robot-assisted training	Robot-assisted training	MSS
(Marconi et al., 2011)	15/15	63.6 ±7.6 / 66.3 ±11.0	39.9 ±28.8/ 40.6 ±25.1	- On flexor carpi radialis & biceps brachii muscles; during contraction - Amp/freq.: 0.2-0.5 mm/100 Hz - No./Length of sessions: 3/ 30 mins	3 sessions (60 mins) of PT	3 sessions (60 mins) of PT	WMFT (FAS); MAS for elbow & wrist
(Caliandro et al., 2012)	25/20	57.4 ±12.8/ 61.8 ±15.7	100.7±82.8 /96.4 ±66.8	- Near tendon of pectoralis minor, biceps brachii , flexor carpi muscle; during contraction - Amp/freq.: 0.2-0.5 mm/100 Hz - No./Length of sessions: 3/ 30 mins	sham	All the participants continued to undergo their rehabilitation program (3d/wk for 1h/d)	WMFT (FAS); MAS for shoulder, elbow & wrist
(Tavernese et al., 2013)	24/20	58.9 ±14.7/ 58.3 ±12.4	19.1 ±18.9/ 25.9 ±21.8	- On tendon of biceps brachii & flexor carpi ulnaris (muscle contraction status: NR) - Amp/freq.: 0.01 mm/120 Hz - No./Length of sessions: 10/ 30 mins	60-mins general PT, (5d/wk)	All participants underwent 60-mins general PT, (5d/wk)	Movement time in reaching movement
(Casale et al., 2014)	15/15	64.7±5.4/ 65.1± 5.8	NR	- On belly of triceps brachii (muscle contraction status :NR) - Amp/freq.: 2mm/100 Hz - No./Length of sessions: 30min, 5d/wk, for 2 weeks	sham	60-mins PT, 5d/wk, for 2 weeks	Movement time in reaching movement; MAS for elbow
(Costantino et al., 2017)	17/15	62.6 ±15.4/ 60.5 ±16.1	Overall: 37.8 ±17.7	- On triceps brachii, extensor carpi radialis longus & brevis; during contraction - Amp/freq.: 2mm/100 Hz - No./Length of sessions: 12/ 30 mins	sham	did not perform any additional rehabilitative treatment program during the study period	JTT; MAS for shoulder, elbow & wrist

(Celletti et al., 2017)	6/6	43.2±7.8/ 60.0±6.8	33.0 ± 7.1/ 60.0 ± 17.7	- on pectoralis minor, biceps brachii; during contraction - Amp/freq.: 0.2-0.5mm /100 Hz - No./Length of sessions: 3/ 30 mins	60-mins PT, (2d/wk) for 6 weeks	60-mins PT, 2d/wk, for 6 weeks	WMFT (FAS)
(Choi, 2017)	5/5	62.0 ± 9.0/ 59.0 ± 10.1	11.0 ± 4.3/ 9.2 ± 1.9	- on biceps brachii & flexor carpi radialis; during 20% of maximal grip power contraction. - Amp/freq.: 1.00mm mm/91 Hz - No./Length of sessions: 12/ 20 mins -3d/wk	30-mins PT, (3d/wk) for 4 weeks	NR	BBT

T-MV= Tendon/Muscle vibration; Ctrl= Control group; MSS =Motor Status Score; MAS= Modified Ashworth Scale; PT= physiotherapy; WMFT= Wolf Motor Function Test & FAS= Functional Ability Scale ; JTT= Jebsen-Taylor Hand Function Test; BBT= Box and block test; freq.=frequency; Amp.=amplitude; NR= not reported.

Table 4-2 *Subgroup analyses for the primary outcome of upper limb functional movement.*

Subgroup	Trials	Participants	Effect Estimate: Std. Mean Difference (IV, Random, 95% CI)
Functional test(Caliandro et al., 2012; Celletti et al., 2017; Choi, 2017; Costantino et al., 2017; Liu et al., 2011; Marconi et al., 2011; Tavernese et al., 2013)	6	135	-0.32 [-0.74, 0.10]
1. Sub-grouped by: number of sessions			
1.1. more than 5 sessions(Choi, 2017; Costantino et al., 2017; Liu et al., 2011)	3	50	-0.42 [-0.99, 0.14]
1.2. less than 5 sessions(Caliandro et al., 2012; Celletti et al., 2017; Marconi et al., 2011)	3	85	-0.38 [-1.20, 0.43]
2. Sub-grouped by: amplitude of vibration			
2.1 0.2-0.5mm(Caliandro et al., 2012; Celletti et al., 2017; Marconi et al., 2011)	3	85	-0.38 [-1.20, 0.43]
2.2 0.5mm<(Choi, 2017; Costantino et al., 2017; Liu et al., 2011)	3	50	-0.42 [-0.99, 0.14]
3. Sub-grouped by: frequency of vibration			
3.1. <80Hz(Liu et al., 2011)	1	8	-0.81 [-2.30, 0.69]

3.2. 80Hz ≤(Caliandro et al., 2012; Celletti et al., 2017; Choi, 2017; Costantino et al., 2017; Marconi et al., 2011)	5	127	-0.29 [-0.76, 0.18]

CI = Confidence interval; I^2 = I-squared; IV = Inverse Variance.

4.5.2 Secondary Outcomes

For the secondary outcome of spasticity, two trials reported Modified Ashworth Scale as the endpoint for the shoulder (Caliandro et al., 2012; Costantino et al., 2017), and four trials reported Modified Ashworth Scale for the elbow (Caliandro et al., 2012; Casale et al., 2014; Costantino et al., 2017; Marconi et al., 2011) and three studies reported Modified Ashworth Scale for the wrist (Caliandro et al., 2012; Costantino et al., 2017; Marconi et al., 2011). While there was no significant change in spasticity following tendon/muscle vibration stimulation, compared to a control treatment as measured by the Modified Ashworth Scale (Figure 4-4), there was a trend towards lower spasticity after the vibration intervention.

Only two studies included the secondary outcome of movement time for a reaching task. The results of the comparison between the tendon/muscle vibration versus control group showed statistically significant shorter time for task performance after the intervention. The groups that received the tendon/muscle vibration treatment performed 9.5% and 34.8% faster than the control group in the Tavernese et al.(Tavernese et al., 2013) and Casale et al.'s (Casale et al., 2014) studies respectively. However, there is no established minimally clinical important difference for movement time to further interpret the clinical importance of this finding. Overall, the tendon/muscle vibration group performed the task faster than the control group (standardized mean difference -1.20, 95% CI -2.05 to -0.35; I^2 65%; 74 participants; Figure 4-5).

None of the trials reported adverse effects, defined as the number of reported cases of pain exacerbation.

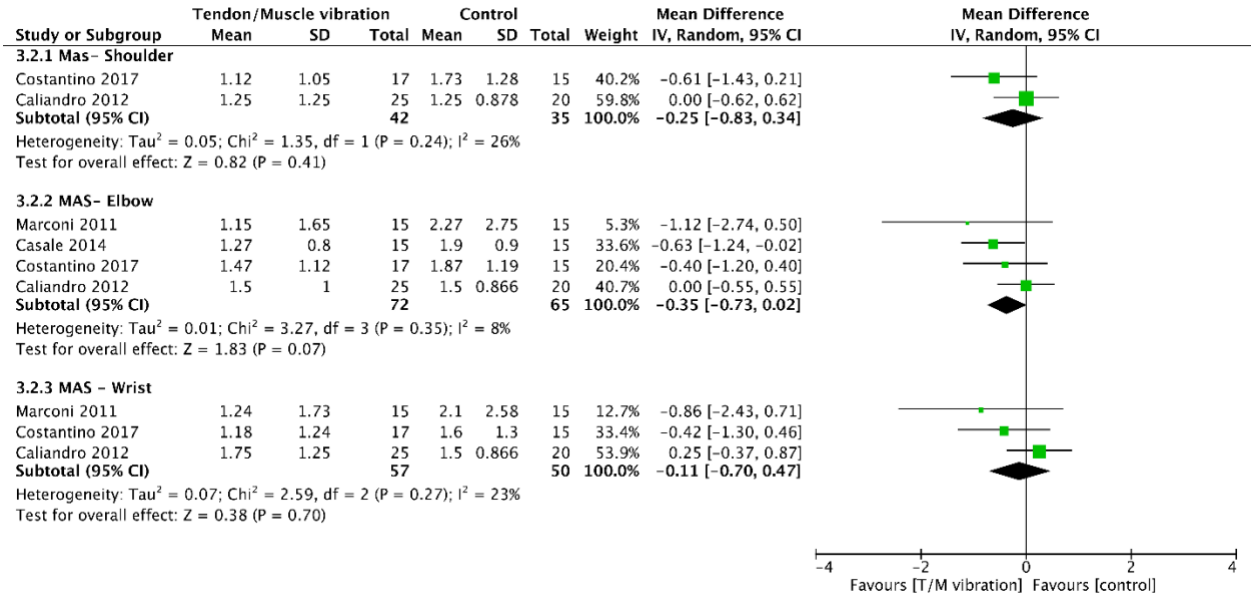

Figure 4-4 *Changes in the MAS score for shoulder, elbow, and wrist according to the tendon/ muscle vibration treatment for four included trials (Caliandro et al., 2012; Casale et al., 2014; Costantino et al., 2017; Marconi et al., 2011).*

Boxes and horizontal lines represent point estimates, varying in size according to the weight in the analysis, and 95% confidence intervals. SD: standard deviation; Chi^2 = Chi-squared; df = degrees of freedom; CI = Confidence interval; I^2 = I-squared; IV = Inverse Variance; P = P value; risk ratio; Tau^2 = Tau-squared; Z = Z score. The reported mean and SDs are the end-of-treatment measurements for MAS scores for control and treatment groups. The section under "Total" indicates the number of subjects included in the analysis.

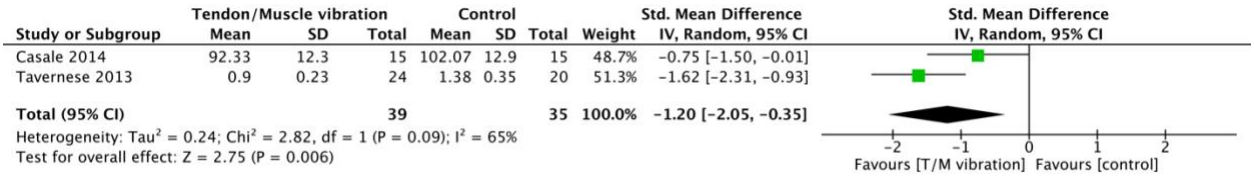

Figure 4-5 *Changes in movement time for an upper limb reaching task according to the tendon/ muscle vibration treatment for two included trials (Casale et al., 2014; Tavernese et al., 2013).*

Boxes and horizontal lines represent point estimates, varying in size according to the weight in the analysis, and 95% confidence intervals. SD: standard deviation; Chi^2 = Chi-squared; df = degrees of freedom; CI = Confidence interval; I^2 = I-squared; IV = Inverse Variance; P = P value; Std = Standardized; risk ratio; Tau^2 = Tau-squared; Z = Z score. The reported mean and SDs are the end-of-treatment measurements for the movement time measurements for control and treatment groups. The section under "Total" indicates the number of subjects included in the analysis.

4.6 Discussion

The present literature review and meta-analysis included studies that used tendon/muscle vibration both at rest and/or during contraction, regardless of amplitude, frequency of vibration and number of treatment sessions. Overall, the results of the meta-analysis for the primary outcome of functional movement showed no effect of tendon/muscle vibration at the end of treatment and no significant effect of treatment on the secondary outcome of spasticity. The reason for not finding significant effects of this treatment on functional movement measures could be the small number of trials that met the inclusion criteria (only six trials for the primary outcome), the small number of enrolled participants and the lack of consistent outcome measures used in the included trials.

In contrast to the primary outcome and secondary outcome of spasticity, analysis of the two included trials that assessed the secondary outcome of movement time showed tendon/muscle vibration led to significantly shorter (faster) movement times when performing a reaching task. The latter movement time results are also consistent with Paoloni et al.'s (Paoloni et al., 2014) electromyography study. Paoloni et al. suggested that the changes in muscular activity they observed may be indicative of an improved ability to produce voluntary movements and therefore facilitate motor performance. That is, improved quality of muscle activity could be one explanation for faster and smoother reaching movements following vibration treatment. That said, the overall findings of the meta-analysis for the primary outcome of functional movement did not support the outcome of movement time for a reaching task. This inconsistency could be explained by the fact that not all functional measures use time as the measured outcome. In addition, the functional assessments that use time to complete the movements include a broad range of upper limb functional tasks (e.g., Jebsen–Taylor hand function test). In contrast, movement time for an upper limb reaching task measures a single type of functional upper limb movement that may be more affected by any improvements related to tendon/muscle vibration. In other words, tendon/muscle vibration may be more effective for specific upper limb functional movements (i.e., reaching task) more than others. Moreover, measures of reaching task performance (e.g., movement time, reaction time) of the upper limb may be less susceptible to variability due to the objectivity of the assessor as well as the continuous nature of the dependent measure (time). Additional research is needed to establish the most reliable and sensitive tasks for assessing upper limb functional movement performance of individuals with subacute and chronic stroke. In the following sections

we examine possible explanations for the lack of significant effects for the primary and secondary outcomes(Ribot-Ciscar et al.).

To the best of our knowledge the current literature review is novel as it is the only literature review and meta-analysis that is focused specifically on a single somatosensory input (tendon/muscle vibration) as a treatment for a specific patient population (stroke). We did find one systematic literature review (Aman et al., 2014) that addressed the effects of somatosensory inputs such as whole-body vibration, magnetic stimulation and acupuncture as well as tendon/muscle vibration for rehabilitation in persons with neurophysiologic diseases. Aman et al. (2015) (Aman et al., 2014) found that when changes from pre- to post-test were analyzed for persons with a range of neurological diseases there was a 35% mean improvement in motor performance with somatosensory stimulation. In contrast, the results of the present meta-analysis found that the vibration treatments used in the included trials did not have any significant effect on the functional movement of persons with subacute and chronic stroke. The major difference of the current review is that we specified a particular somatosensory treatment and patient population, which may explain the contradictory findings. At this time, it is unclear if the lack of significant findings in the present analysis is due to the smaller number of included trials or the type of somatosensory treatment.

A second possible reason for the null findings for the primary outcome measure is that the trials that we included in the current meta-analysis used various protocols with different parameters for frequency, amplitude and location of tendon/muscle vibration and length of treatment. To further explore the subgroup analyses we excluded the study (Celletti et al., 2017) that led to the heterogeneity in the pooled data. After removing the heterogeneity, results of the subgroup analysis for the primary outcome of the upper limb functional movement revealed some trends toward different vibration protocol parameters; however, none of these trends were statistically significant. Subgroup analyses for the length of treatment protocol showed trends towards better motor performance after longer tendon/muscle vibration protocols (more that 5 sessions). Also, functional movement assessments showed trends toward better performance when vibration amplitude was higher than 0.5mm. Most of the reviewed studies used vibration frequencies above 80Hz and up to 120Hz. This range of frequency for application of muscle/tendon vibration is appropriate because the mechanoreceptors (mainly Ia afferents) that are the target of muscle/tendon vibration are sensitive to this range (Roll & Vedel, 1982; Roll et al., 1989).

Another variable when considering the possible benefits of tendon/muscle vibration for individuals with subacute and chronic stroke is the location of application of the vibration (i.e., flexor versus extensor muscles of the upper limb). Once again, there is variability from trial-to-trial. Two of the studies (Casale et al., 2014; Costantino et al., 2017) that are included in the current systematic literature review applied vibration on the extensor muscles (antagonist to the spastic muscle group in the upper limb) and the rest of the included papers used vibration over the flexor muscle groups (agonist or spastic). There is evidence showing that application of the vibration on both the agonist (spastic) (Marconi et al., 2011; Noma et al., 2009; Noma et al., 2012) and the antagonist (Binder et al., 2009; Cody et al., 1998) muscles of the upper limb may be beneficial for reducing spasticity. These two vibration application protocols have quite different action mechanisms but almost the same clinical results. Moreover, except one trial (Liu et al., 2011; Liu et al., 2009), most of the included trials in the current meta-analysis used vibration during voluntary isometric contraction of the vibrated muscle. However, the effectiveness of tendon/muscle vibration intervention during different muscle contraction states, or during movement versus stationary states, has not been addressed in the current meta-analysis and also was not considered in the included trials. Hence, it seems that there is a need for more RCTs to investigate the most beneficial location of application and vibrated muscle movement/contraction status. Although the results of the current meta-analysis showed a trend for appropriate amplitude of vibration and length of treatment, there is a need for RCTs with more participants to examine the evidence base before recommending tendon/muscle vibration treatment protocols.

Finally, 6 out of 8 of the included trials, and 4 out of 6 selected trials for the primary outcome, were conducted in Italy. To explore the possibility of cultural bias toward using tendon/muscle vibration as a method of rehabilitation based on the country of origin (Italy vs. elsewhere), we have performed a subgroup analysis for the primary outcome measure. This analysis revealed no significant differences between trials conducted in Italy and elsewhere.

4.7 Study Limitations

Evaluating scientific evidence on the effectiveness of tendon/muscle vibration treatment was challenging given the heterogeneity in treatment protocols performed and assessments used. The clinical outcome measures used for assessing the functional movement after the tendon/muscle vibration intervention were variable, including Functional Ability Scale of WMFT, Jebsen-Taylor

Hand function test, Box & Block test, and Motor Status Score. Two of these standard clinical scales (i.e., Box & Block test and Jebsen-Taylor Hand function test) are time-based and continuous scales and two of them (i.e., Functional Ability Scale of WMFT and Motor Status Score) are ordinal score-based scales. Wolf motor function test also has a timed scale, but we were not able to use timed score as half of the included studies (Caliandro et al., 2012; Celletti et al., 2017; Marconi et al., 2011) for the primary outcome of measures of functional movement had the ordinal Functional Ability Scale (FAS) results in common. Hence, one limitation of the current study was that the ordinal and continuous scales were pooled together and treated as continuous for the statistical analyses and this variability could be one reason that a significant effect of tendon/muscle vibration was not found.

With respect to the treatment protocols used by the included trials, there were a wide range of vibration protocols (amplitude range: 0.2-2mm; frequency range: 20-120) and number of treatment sessions (3-20 sessions) that made detecting the contribution of different parameters for improving hand motor performance or reducing spasticity difficult.

Despite these challenges, we addressed the effect of these parameters on the assessed upper limb motor performance by subgroup analyses; however, subgroup analyses on length of intervention, frequency and amplitude of vibration revealed no significant effects. Another limitation of the current review is the small number of included trials, so results must be interpreted cautiously.

4.8 Considerations for Future Research

In the following section we outline a number of considerations for future research in order to develop a more complete understanding of the possible benefits of tendon/muscle vibration. Based on the studies reviewed we have identified three areas in which there was either minimal, or no, consideration in the studies published to date. Specifically: quality of life, long term impact/time course of the treatment and individual patient characteristics, including proprioceptive sensibility.

Arguably, recovered motor performance is only relevant if stroke patients are able to return to activities that are meaningful to them. The addition of a quality of life assessment would provide a more holistic picture of the effects of physical rehabilitation (Kim et al., 1999). Among the included studies only Costantino et al.(2017)(Costantino et al., 2017) included a quality of life

assessment to investigate the possible benefits of using tendon vibration as a rehabilitation method for individuals with chronic stroke. Specifically, Costantino et al included the Functional Independence Measure (FIM)(Ottenbacher et al., 1996) as a measurement tool for assessing the effects of tendon vibration treatment on the cognitive and physical disability and QuickDASH Score (The Disabilities of the Arm, Shoulder and Hand Score)(Gummesson et al., 2006) to measure upper limb related disabilities during activities of daily living. The results of these two assessments showed that the group of participants who received tendon/muscle vibration had more improvement in their quality of life as it relates to performing activities of daily living when compared to the group that received sham therapy. Hence, in addition to motor performance assessments, we also encourage adding clinically relevant assessment of quality of life in future studies.

A significant aspect of any rehabilitation intervention is the long-term effects of the treatment. Among the included studies in the current meta-analysis, only a few studies reported follow-up assessment results (Caliandro et al., 2012; Marconi et al., 2011; Tavernese et al., 2013). These long-term follow-ups were done at one-week to one-month post-treatment periods. Overall, it seems that a brief treatment period as short as three 30-minute sessions has the potential for a long-term improvement in upper-limb function (i.e., up to one month as reported in (Caliandro et al., 2012)). To fully understand the role of tendon/muscle vibration in post-stroke rehabilitation, we suggest future studies include longer periods of follow-up.

Another important issue for designing future clinical trials regarding application of tendon/muscle vibration in individuals with stroke is the proprioceptive sensibility of the patients. While tendon/muscle vibration is applied with the capacity to stimulate the mechanoreceptors that are in charge of proprioception sensibility, it seems that baseline proprioception impairments in stroke patients could be an important factor in their potential to benefit from this treatment. Hence, future studies should have inclusion criteria or baseline data based on impairments in proprioception. Finally, given the current interest in using wearable technologies (Shull & Damian, 2015), future studies can investigate the possible benefits of integrating the appropriate vibratory stimulation in a wearable device and the benefits to perceptual and motor performance in individuals post stroke.

4.9 Conclusion

We are confident that our extensive search strategy across multiple databases identified all relevant trials to date. We made multiple contacts with investigators to obtain additional information on published studies and performed thorough assessments of bias and quality of the included trials. Also, we explored potential sources of clinical and statistical heterogeneity with a priori defined subgroup analyses. We found that the use of tendon/muscle vibration in individuals with subacute and chronic stroke was not associated with significant improvement in functional movements of the upper limb and did not reduce spasticity. The results of the secondary outcome of movement time to complete a reaching task showed statistically significant faster movements for the group that received the tendon/muscle vibration treatment. However, these results must be interpreted cautiously due to the small number of trials contributing to the meta-analyses. Larger randomized controlled trials with the purpose of clarifying the most beneficial location of vibration, muscle contraction/movement status while vibration is being applied, amplitude of application of vibration as well as the optimal length of treatment will add clarity to possible benefits of tendon/muscle vibration. Finally, investigating patient-related outcomes are required to further explore the benefits and harms of this intervention. At this time, there is insufficient evidence and a need for more data from RCTs before recommending tendon/muscle vibration as routine therapy for persons with subacute and chronic stroke.

Conflicts of interest. —The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript

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CHAPTER 5

Study 4: Vibration for stimulating limb proprioceptors: Measurement, characteristics, and challenges

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Contributions of Authors to The Manuscript

N.M. designed the study protocol and designed and manufactured the muscle-tendon vibration device with the accelerometer for vibration characteristics measurements. N.M. also collected, reduced, and analyzed, the experimental data. C.G collaborated with data analysis. N.M. prepared the abstract and the poster for presentation at the Canadian Society for Psychomotor Learning and Sport Psychology (SCAPPS) 2019 conference. N.M. and C.G. critically revised the draft of the abstract and the poster for intellectual content and approved the final draft for submission to the SCAPPS 2019 conference.

Preface

The first two studies included in the current thesis highlighted and clarified the contribution of proprioception in the control of functional upper limb movements, and the literature review in the third study determined the effectiveness of MTV on improving the efficacy of functional movements as well as characterized the optimal therapeutic MTV in terms of amplitude and frequency. So, in the current study a wearable rehabilitation device was designed and manufactured.

Also, a practical method has been established to measure the characteristics of the muscle tendon vibration using affordable accelerometers in order to maintain the therapeutic MTV in the frequency range that targets the muscles spindles. This measurement method was applied in the last study for adjusting and keeping the MTV stimulation at the optimal level. The abstract of the preliminary findings of the current study was published at the Journal of Exercise, Movement, and Sport (SCAPPS refereed abstracts repository). The following abstract is presented as submitted to the SCAPPS conference in 2019. The completed report of this study was presented as a poster in the SCAPPS 2019 conference.

Abstract

Using muscle-tendon vibration to stimulate mechanoreceptors (mainly Ia afferents) in rehabilitation research is increasing in popularity. Muscle-tendon vibration can also be used to stimulate the mechanoreceptors with the goal of attenuating proprioception. For therapeutic purposes vibration must be within known amplitude(~0.5mm) and frequency(80-120Hz) ranges. However, there is no standard and portable method established for measuring vibration characteristics. The aim of the current study was to describe the characteristics of the movements of a vibration motor and explore the feasibility of using an affordable accelerometer to measure vibration characteristics. Movements of a small vibration motor mounted on a participant's wrist were simultaneously measured using an Optotrak 3D Investigator and accelerometer. Five vibration intensities (55%,65%,75%,85%,100% motor capacity) were measured for five 30-second trials each. The main outcome measures were frequency, displacement, and peak acceleration of the vibration from the Optotrak and accelerometer. Pearson correlations showed a strong positive relationship between accelerometer and Optotrak measurements and t-test showed no significant differences between the frequency measurements of the two methods. Although Pearson correlation also showed strong correlation between displacement measurements of the accelerometer and Optotrak for higher vibration intensities, *t*-tests revealed a significant difference ($p<0.05$) between the displacements measured by accelerometer and the Optotrak. Hence, the results of the current study showed that accelerometer measurements could only be validated for vibration frequency measurements, but accelerometer measurements for vibration amplitude could not be validated with the Optotrak measurements.

5.1 Background and Objectives

There has been an increase in the evidence in the past ten years for using muscle tendon vibration (MTV) to stimulate Ia afferents for rehabilitation of conditions with proprioception deficiency and muscular spasticity (Aman et al., 2014; Mortaza et al., 2019). The findings of a literature review and meta-analysis by Mortaza et al. showed that for therapeutic purposes the amplitude and frequency of MTV should be about 0.5mm or higher and 80-120 Hz respectively (Mortaza et al., 2019). These MTV characteristics are appropriate because muscle spindles, that

are the main target of vibration treatment, have shown to be sensitive to vibration within the mentioned amplitude and frequency ranges (Roll & Vedel, 1982; Roll et al., 1989). Most of the studies that used MTV have not reported a quantitative method to measure the vibration parameters before or during the experiments. Also, there is no standard and portable method established for measuring vibration characteristics. Hence, the objectives of the current study were to: i) design a portable vibration device with adjustable vibration frequency and amplitude; ii) describe the characteristics of the movements of the vibration motor; iii) explore the feasibility of using an affordable accelerometer to measure vibration characteristics. The tightness of the contact of an eccentric rotating mass (ERM) vibration motor against the skin can easily affect the vibration amplitude and frequency. In order to be certain that the vibration experienced is within a therapeutic range, in the present study an affordable method was developed to measure vibration parameters using an accelerometer. To validate the accelerometer method, acquired vibration parameters using the accelerometer were compared with the outcomes measured by a gold standard method using a high-precision motion capture system.

5.2 Material and methods

5.2.1 Vibration Device

In this study a novel muscle tendon vibration band was designed. In order to generate the vibration that stimulates the muscle spindles, two ERM vibration motors were mounted on the participant's wrist with elasticized tape (Leukotape® P). A wearable Arduino-compatible microcontroller along with a motor driver (Adafruit Industries, New York, NY, USA) was used to control the vibration motors. An appropriate vibration motor was selected by testing different vibration motors, with different voltage inputs, using an Optotrak motion capture system (Northern Digital Inc., Canada) until the precise vibration parameters were acquired.

5.2.2 Experimental Procedure and Measurement Tools

The accelerometer used in the current study was ASXL326 analogue accelerometer with a sensitivity of ±16 g. Acceleration data was read and recorded at sampling rate of 10000 Hz using CED Power1401data acquisition interface (Cambridge Electronic Design, UK). In order to calibrate the accelerometer a level was used to align the accelerometer in the positive and negative

Z-axis directions to acquire the accelerometer voltage output for positive and negative $1g\ m/s^2$. An Optotrak 3D Investigator motion analysis system was used as the gold standard measurement method to compare and validate the measurements of the accelerometer. In order to be able to measure small vibration amplitude (i.e., <1mm) of the motor using the Optotrak, the motor had to be placed at the optimal angle and distance to the Optotrak position sensor. That is, the vibration movement must occur in the Z-axis and in front of the Optotrak measurement volume, which is 1.5 meter from the cameras. Optotrak data was sampled at 900Hz. Both infrared light emitting diode (IRED) sensors of the Optotrak and the accelerometer were secured to the vibration motor. The vibration motor was mounted on one participant's wrist using the elasticized tape. The participant's wrist was supinated, with their limb perpendicular to the Optotrak (Figure 5-1). The Optotrak recorded the position data of the vibration movement in the Z-axis. The motor vibrated at five different intensities presented as percentage of the maximum input voltage capacity for the motor: 55%, 65%, 75%, 85%, 100%. Five sets of 30-second trials were conducted for each of the five intensities (total of 25 trials) while the Optotrak and CED simultaneously recorded the vibration data.

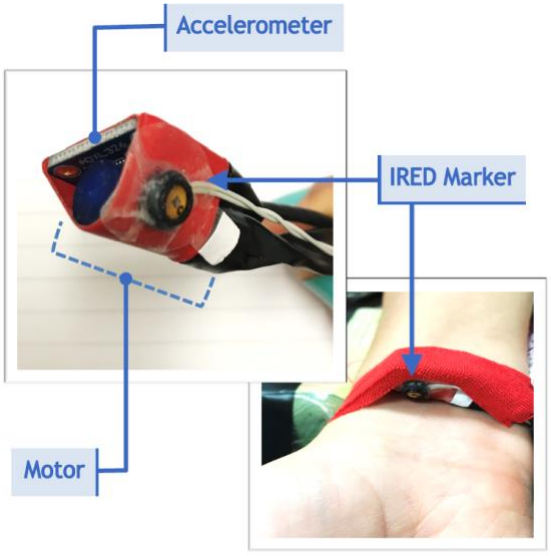

Figure 5-1 *Both accelerometer and IRED attached to the ERM motor on the participant's wrist.*

5.2.3 Data Analysis

The acceleration data from the accelerometer was filtered and double integrated to acquire the amplitude of vibration. After each integration, bandpass Butterworth filters (50-150Hz) were used to minimize noise and DC component in the accelerometer signal. The bandwidth of the filter was determined based on the frequency content analysis of three minutes of recording at 0-100% vibration intensities. Moreover, the frequency content of the vibration was assessed using the acceleration data. Filtering, data reduction and analysis were performed using a custom software designed in MATLAB (The MathWorks Inc., US). Please see details of the software in Appendix 6. The main dependant variables were peak-to-peak amplitude of vibration and frequency of the vibration measure by both Optotrak and accelerometer. The average vibration frequency and amplitude data from each 30-second trial was used for data analyses. That is, the amplitude and frequency data from the total of 25 trials for the five vibration intensities (55%-100%) were used for statistical analyses. To compare and validate the accelerometer method with the Optotrak, an independent sample t-test was used to compare the mean of the variable acquired with these methods. Moreover, Bland-Altman plots were generated. In these graphs the difference between the measurements of the two methods is plotted against the mean of these measurements using the two methods (Bland & Altman, 1986). Bland-Altman plots help evaluate the bias of the mean difference of the two methods and to define an agreement interval within which 95% of these differences fell (Bland & Altman, 1986; Giavarina, 2015). Upper and lower levels of agreement were calculated as ±1.96 standard deviation from the mean difference (Giavarina, 2015).

Pearson coefficient was also used in order to assess the correlation of the parameters obtained from the two methods. All statistical analyses were performed with SPSS v23 (Armonk, NY: IBM Corp) and Excel.

5.3 Results and Conclusion

Table 5-1 presents means and standard deviations of vibration amplitude and frequency, using the data from five trials for each vibration intensity, measured by both accelerometer and Optotrak. Pearson correlation, t-test, and Bland-Altman plots were used to assess the agreement of the means of vibration amplitude and frequency calculated using the accelerometer versus calculations from the gold standard (Optotrak) measurement.

5.3.1 Vibration Frequency.

Pearson correlations showed a strong positive relationship between accelerometer and Optotrak measurements. A *t*-test showed no significant difference between the means of the measurements using the two methods (Table 5-2). The measurement bias was calculated as the mean of the differences between Optotrak and accelerometer measurements (Giavarina, 2015). The bias between the two measurements methods was as small as - 0.013 Hz (Figure 5-2); the negative sign indicates that the accelerometer measurements were slightly higher. The interval between the upper and lower levels of agreement for frequency measurements was 0.24Hz and the range of the vibration frequency measure by the Optotrak was 75-105Hz. So, it seems that sensitivity of accelerometer measurements for vibration frequency is acceptable.

5.3.2 Vibration Amplitude

Pearson correlation showed strong correlation between displacement measurements of the accelerometer and Optotrak for 65%, 75%, and 100% vibration intensities, however *t*-tests revealed a significant difference ($p < 0.05$) between the accelerometer and Optotrak measurements (Table 5-2). The measurement bias for vibration amplitude was 0.162mm (Figure 5-3); the positive sign for the bias indicates that the accelerometer measurements were lower than the Optotrak. The interval between the upper and lower levels of agreement for the vibration amplitude measurements using the accelerometer was 0.684 mm. So, given that the range of displacement measured for the current vibration motors (as measured with the Optotrak) were as small as 0.1-0.6mm, sensitivity of accelerometer measurements for amplitude of vibration does not seem acceptable. Figure 5-3 presents the Bland-Altman plots for vibration amplitude. Since there is a linear pattern for the vibration amplitude measurements from the two methods, the next step will be to model the linear relationship between the displacement measurements with the two methods and use this model for estimating the actual vibration amplitude using the accelerometer measurements to minimize the measurement error.

Table 5-1 *Means and standard deviations (SD) of vibration amplitude and frequency, using the data from five trials for each vibration intensity, measured by the accelerometer and Optotrak*

	Frequency (Hz, Mean ± SD)		Amplitude (mm, Mean ± SD)	
Vibration intensities	Optotrak	Accelerometer	Optotrak	Accelerometer
55%	77.3 ± 1.3	77.3 ± 1.2	0.175 ± 0.059	0.197 ± 0.026
65%	83.8 ± 1.8	83.8 ± 1.8	0.257 ± 0.038	0.208 ± 0.014
75%	85.7 ± 0.5	85.7 ± 0.6	0.365 ± 0.137	0.207 ± 0.036
85%	90.4 ± 3.1	90.5 ± 3.0	0.444 ± 0.182	0.172 ± 0.028
100%	102.1 ± 3.2	102.1 ± 3.2	0.553 ± 0.119	0.197 ± 0.015

Table 5-2 *Results of the T-test and Pearson correlation statistical analyses.*

	t-test (p-value)		Pearson correlation (r)	
Vibration intensities	Amplitude (mm)	Frequency (Hz)	Amplitude (mm)	Frequency (Hz)
55%	0.39	0.996	-0.14	0.999
65%	0.04*	0.999	0.72	1.000
75%	0.95	0.415	0.89	0.999
85%	0.03*	0.979	0.36	0.999
100%	0.00*	0.997	0.75	1.000

* $P < 0.05$ indicating significant difference between the results of the two measurement methods.

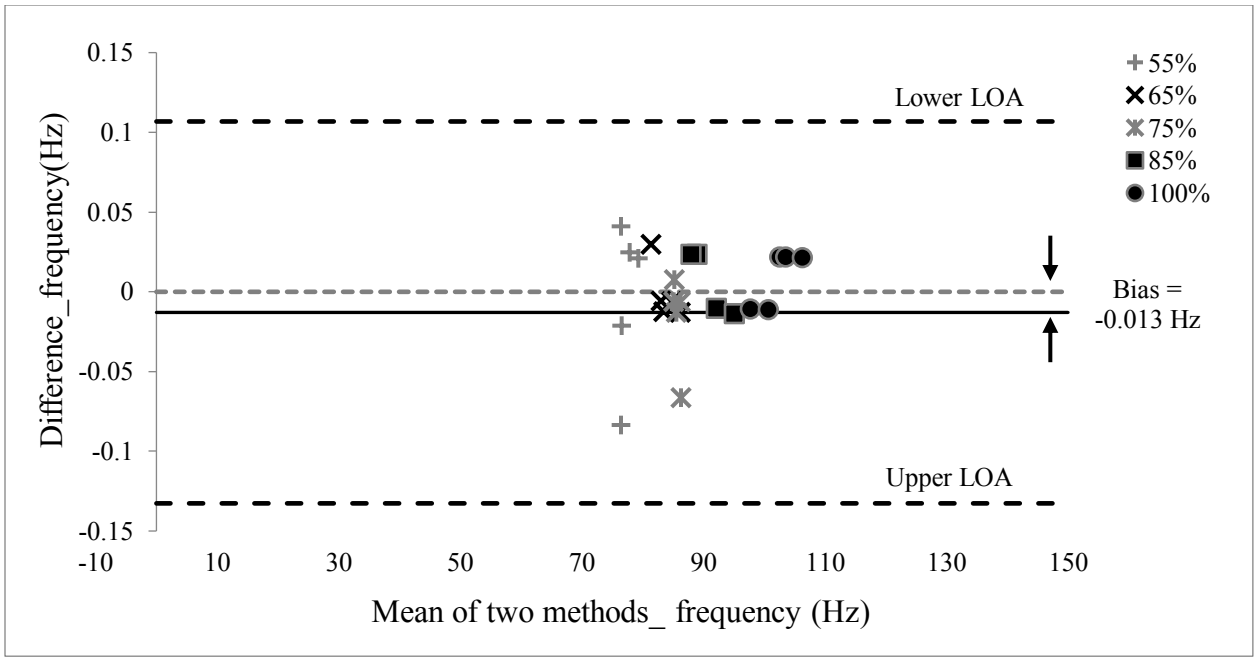

Figure 5-2 *Bland-Altman plot for vibration frequency. LOA: level of agreement.*

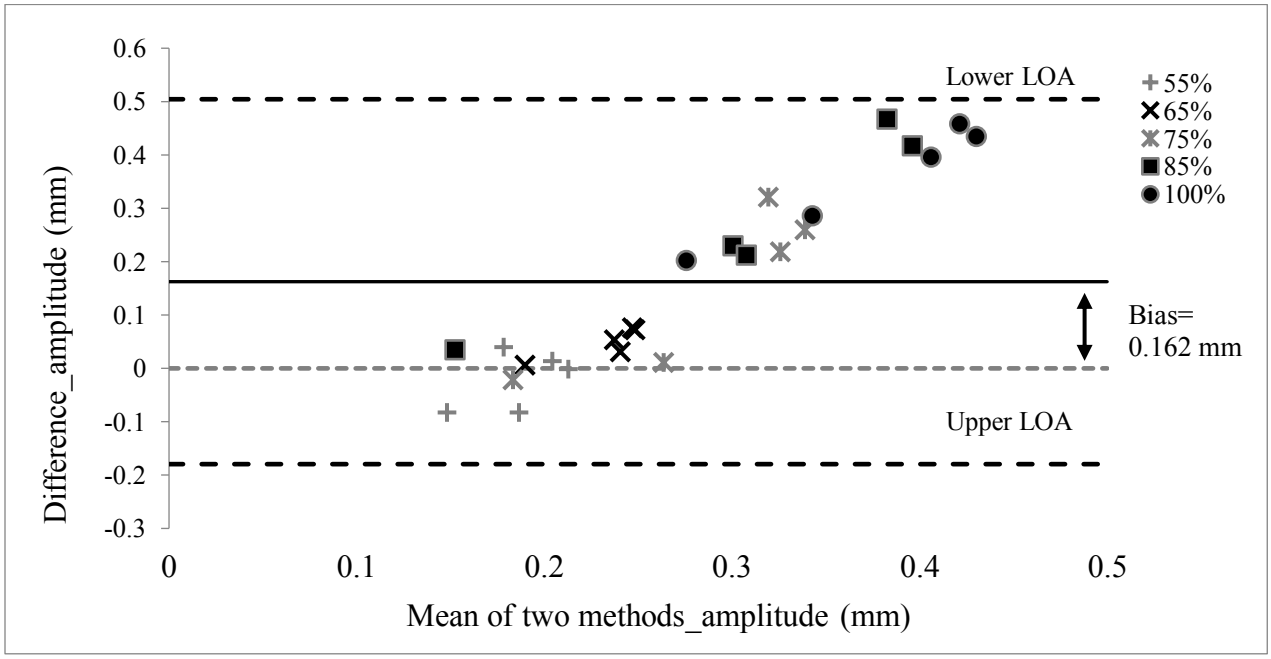

Figure 5-3 *Bland-Altman plot for vibration amplitude. LOA: level of agreement.*

5.4 Conclusions

The results of the current study showed that accelerometer measurements could only be validated for vibration frequency measurements, but accelerometer measurements for vibration amplitude could not be validated with the Optotrak measurements.

In order to use Optotrak for measuring the characteristics of MTV during an experiment, the vibration motor must be in a stationary position in an optimal position relative to the camera, which makes it a difficult posture for participants to maintain. Moreover, equipment such as Optotrak is not available, nor is it feasible in a clinical setting. An alternative method could be using an accelerometer to measure vibration characteristics. Besides lower costs and availability, accelerometers are light weight, small, and can be easily embedded within the methods used for installing the vibration motors on the participant limb. The results of the current study showed that affordable accelerometers are capable of measuring vibration frequency with high precision, however additional modelling is needed to verify that the accelerometers can estimate the vibration amplitude.

Future work will model the relationship between the vibration amplitude measurements with the accelerometer versus the Optotrak measurements. This model will then be used to estimate the actual vibration amplitude using the accelerometer measurements to minimize the measurement error.

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CHAPTER 6

Study 5: Dual Muscle Tendon Vibration Does Not Impede Performance of a Goal-Directed Aiming Task

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Contributions of Authors to The Manuscript

N.M designed the study protocol. C.G, S.P. and K.S collaborated with N.M in refining the study methodology. N.M acquired the ethics approval for the study protocol. N.M recruited the participants, reduced, analyzed, and interpreted the experimental data. N.M. prepared the first draft of the manuscript. All authors critically revised the draft of the manuscript for intellectual content and approved the final draft.

Preface

The previous four studies laid the foundation for designing and implementing the last study of the current thesis. From the previous studies we understood the important role of proprioceptive input in movement control and the adverse effects of its disruption, as a result of paresthesia, on a functional movements (Study 1 and 2), the potential benefits of using MTV as a method of stimulating the proprioception mechanoreceptors and augmenting the proprioceptive input (study

3), as well as the optimal MTV protocol for augmenting the proprioception (study 3) and the method to control MTV within the effective frequency range (study 4). The follow study is a proof-of-concept study that investigated the effects of applying MTV on performance of a goal-directed aiming task. The findings of the current study, along with a future neurophysiologic experiment on the effects of MTV on the corticospinal excitability (Appendix 1), will contribute to a comprehensive understanding of the effects of MTV on the sensorimotor system.

Abstract

The application of low amplitude muscle-tendon vibration within the frequency range of 70-120Hz has been studied over the last decade as a tool to stimulate somatosensory afferents with the goal of studying motor control in humans and improving motor performance in individuals with proprioception deficiencies. However, there is limited evidence on the effects of muscle-tendon vibration on the speed and accuracy of functional upper-limb movement. The current study applied muscle-tendon vibration over the wrist flexors and extensors and investigated its effects on: i) performance of a computer goal-directed aiming task and ii) the perceived hand location. Twenty healthy participants were randomly assigned to the vibration or control group. The aiming task included acquiring targets by moving a cursor on a screen, without the vision of the cursor or hand for four blocks. Task performance was assessed using absolute, constant, and variable error measures as well as reaction time and movement time. The perceived location of the hand was assessed using a questionnaire and a computerized conscious perception task. The two groups performed equally well in terms of end-point error and variability. However, the vibration group showed significantly shorter reaction times compared to the control group, which may indicate more attention capture and efficient movement planning with vibration. Participants in the vibration group reported less illusory movement sensation after block4. This study did not find any adverse effects of dual muscle-tendon vibration on the performance of aiming movements. These findings support the potential of the somatosensory system to adapt to vibrotactile input with associated changes in perception and motor performance.

Keywords: proprioception, wearable device, motor control, muscle tendon vibration, vibrotactile

6.1 Introduction

Proprioception is necessary for humans to control their moving limbs efficiently and effectively, especially when visual feedback is unavailable (Schmidt et al., 2018; Sherrington, 1952). Proprioception is one of the major functions of the somatosensory system and includes information about where and how the body is moving from a variety of receptors including

mechanoreceptors of the joints, skeletal muscles, tendons, and tactile receptors from the body surface. Proprioceptive feedback is necessary for successful fine motor control including error correction during movements (Carey et al., 1993; Schmidt & Lee, 2011; Tyson et al., 2008). Its loss has a significant effect on the quality of voluntary movement, especially for fine movements of the upper limb. Proprioception impairments have been reported in about 25 to 50% of individuals with stroke (Carey, 1995; Kessner et al., 2019). The application of muscle tendon vibration (MTV) has been studied over the last decade as a potential tool to stimulate somatosensory afferents with the goal of improving motor performance (Aman et al., 2014; Mortaza et al., 2019). Therapeutic MTV protocols have been applied using a mechanical device that produces vibration with specific amplitude and frequency characteristics to stimulate muscle spindles. These protocols are based on the seminal findings of Roll and Vedel (1982) who showed that low amplitude (0.2-0.5mm) vibration within the frequency range of 70-120Hz could stimulate Ia afferents in the upper limb. This stimulation was perceived as an illusory movement, similar to the feeling that the vibrated muscle was being stretched (Goodwin et al., 1972; Roll & Vedel, 1982). Clinical evidence for the effectiveness of MTV has been reported, including improved muscle strength and function (Alghadir et al., 2018; Benedetti et al., 2017; Fattorini et al., 2006), reduced spasticity (Casale et al., 2014; Costantino et al., 2017; Marconi et al., 2011; Murillo et al., 2011), and consequently improved performance of upper limb fine motor tasks (Casale et al., 2014; Choi, 2017; Costantino et al., 2017; Tavernese et al., 2013).

Roll and Gilhodes (1995) established that the same vibration frequency over two antagonistic muscle groups of the wrist (i.e., dual MTV) does not induce kinesthetic illusions (Roll & Gilhodes, 1995). That said, dual MTV still activates the somatosensory cortex (Romaiguère et al., 2003). These two characteristics of dual MTV may make it a valuable tool for rehabilitation programs through the possibility of stimulating neuroplasticity in the somatosensory pathways and sensorimotor areas of the cortex. On the other hand, there are studies that report an immediate effect of dual MTV that includes a distortion of proprioception (Bellan et al., 2016; Bock et al., 2007; Longo et al., 2009). These studies measured changes in proprioception caused by dual MTV using the contralateral limb to perform a pointing task toward different locations on the vibrated limb (Longo et al., 2009). Bellan et al. (2016) measured the effects of biceps-triceps dual MTV on perceived upper limb joint location by asking the participants to use their contralateral index finger to point at the perceived location of their vibrated side without touching it while they were

blindfolded. The authors found that the fingertip and wrist were perceived to be closer to body, but this was not the case for elbow (elbow was perceived to be at its actual location (Bellan et al., 2016). Bock et al. showed that dual MTV increased error in an angle matching task for wrist when the vibration was applied to the forearm (Bellan et al., 2016; Bock et al., 2007), but other studies that included an elbow angle matching task did not report an increase in error (Bellan et al., 2016; Longo et al., 2009). The different methods used to assess the effects of MTV may be the reason for the mixed findings. Also, none of these studies focused on the effects of MTV during an active functional task, such as a goal directed aiming movement.

The somatosensory system has also been shown to adapt to changes in proprioceptive input (DiZio et al., 2014; Gonzales & Goble, 2014; Holcombe & Seizova-Cajic, 2008; Ruttle et al., 2016). Gonzales and Goble found that proprioception adaptation happened within about 10 minutes of biceps-triceps vibration as measured by an elbow angle matching task. The authors also reported that the amplitude of the undershoot errors (constant error) for the matching task decreased on later trials when compared to early trials (Gonzales & Goble, 2014). In summary, the findings from different studies regarding the effect of proprioception distortion as a result of dual MTV are equivocal. Overall, there is limited evidence on the effect of dual MTV on the performance of a functional upper limb task (e.g. goal directed aiming movement) (Bock & Thomas, 2011; Bock et al., 2005) as well as the adaptability of the central nervous system with this sensory input change (i.e. dual MTV) for upper limb motor control.

The purpose of the current study was to investigate the effects of applying MTV on performance of a goal-directed aiming task over a series of practice trials. A secondary objective was to determine if there is a correlation between the conscious perception of any illusory movement caused by the MTV and associated changes in movement performance. We predicted that when MTV is applied to the wrist tendons the performance of an upper limb aiming task will be negatively impacted at first, but performance will become similar to the control group (no MTV) after less than 100 trials of practice. In order to address the above objectives, we measured both temporal and spatial movement parameters of goal-directed aiming task using flexion and extension movements of the wrist, with and without dual MTV on the tendons of the wrist. The perceived illusory sensation was also measured using subjective and objective assessments of the perceived limb position.

6.2 Material and Methods

Twenty neurotypical right-handed young adults with normal or corrected-to-normal vision and no known neurological conditions participated in this study. Mean age of the participants of the control group was 24.1±1.9 years (4 females), and the mean age of the MTV group was 25.5±3.5 (5 females). Approval by the University of Manitoba (Education and Nursing) research ethics board was granted, and informed consent was obtained from all participants. This study was carried out in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki. Participants were randomly assigned to the vibration group or the control group using sealed envelopes (10 in each group). The participants of both groups came to the lab for one session and performed five blocks (4 performance and 1 transfer blocks) of a computer aiming task and illusory sensation assessments. Details of the task and the flow of the experimental procedure can be found in the next section.

For the vibration conditions (MTV group), an Eccentric Rotating Mass (ERM) vibration motor was placed over each of the flexor and extensor muscle tendons of the wrist. The motors were installed above the participants' wrist with a strapping tape (Leukotape® P). To control the tension of the tape over the motors and maintain the vibration amplitude the tape was measured to 75% of the circumferences of the forearm above the wrist plus 4 cm extra length for overlap. The vibration frequency of the two motors were monitored to maintain a speed of about 80Hz using a pair of ASXL326 analogue accelerometers with a sensitivity of ±16g; the acceleration data was recorded using a CED Power1401 data acquisition interface (Cambridge Electronic Design, UK). Both motors were on during blocks 1-4 of the movement task trials for the MTV group. The vibration motors and the band were also placed as above for the control group, except that the vibration motors were not on during the aiming trials (blocks 1-4).

6.2.1 Computer aiming task

The computer aiming task was developed using Pygame library in Python and included acquiring targets by moving a cursor toward one of six possible targets displayed on a computer screen. All targets were white circles (diameter=10mm, chosen based on the feasible level of difficulty measured in a pilot study) on a black background (Figure 6-1b). One of six targets randomly appeared along a horizontal line (target distances from start point: 63.5, 127, 191 mm)

on the left or right side of the monitor. The participant held a vertical mouse (3M, USA) and used flexion and extension movements of the wrist to move the cursor. The participant's forearm was secured in a splint in a neutral position so that the extension and flexion of the wrist was possible to move the cursor; the cursor movement was constrained to only move on a horizontal line across the monitor. Participants could not see the location of their upper limb during the task because their limb was placed under the monitor as described above (Figure 6-1c). Participants were instructed to move to the targets as accurately as possible at a comfortable pace. A trial started when a fixation cross appeared in the middle of the screen with instruction to "align wrist" to the neutral position. Then, the cursor was aligned and appeared over the middle of the fixation cross. After a 3-5 second random fore-period the target appeared. The cursor disappeared as soon as the target appeared on the screen and became visible again when the target was reached, regardless of trial success. Movement completion was detected when the cursor did not move for more than 1 mm for 500 milliseconds. Movement initiation was defined as the time that the speed of the cursor went above 10mm/sec. The sampling frequency for tracking the cursor movement was 100Hz.

Movement performance was measured through analysis of both speed and accuracy. Specific dependent variables included constant, variable, and absolute error measures to assess movement bias, variability and overall accuracy respectively. Constant error (CE) was used to determine the mean bias participants had about the location of their hand using the calculation: $CE=\Sigma (x_i - T) /n$, where x_i is the horizonal cursor location on trial i, T is the horizontal target location, and n is the number of trials the subject performed. Variable error is a measure of within participant variability in aiming calculated as: $VE=(\Sigma (x_i - M)^2 / n)^{-2}$, where x_i and n were previously defined, and M was the mean of the horizontal locations of the cursor that the participant reached as the target. Absolute error (AE) was also calculated to capture the mean accuracy of the movement: $AE=\Sigma |x_i – T| /n$.

Reaction time was defined as the time between target appearance and movement initiation. Reaction time indicates the amount of preparation time needed for the movement (Henry & Rogers, 1960). Movement time was defined as the time between movement initiation and movement completion. Since the focus of the aiming task in the current study was accuracy, decreased movement time with more accuracy at reaching the targets may indicate improved task performance.

Participants relocated their own hand to a neutral position at the start of each trial. The 3D Investigator motion capture system (Northern Digital Inc., Canada) was used to check for the neutral position in real time, and also to measure any changes in the perceived neutral position of the hand. One infra-red emitting diode (IRED) was placed on the vertical mouse and second on the midline of the edge of the screen (Figure 6-1c). The consistency of the start position of the hand for different trials for different blocks was assessed using the standard deviation (SD) of the start position within each block. Perception of the neutral wrist position was measured at the end of each block. Participants were asked to align their wrist to their perceived neutral position. The motion capture system recorded the location of the IRED on the vertical handle of the mouse for 3 seconds. These locations were normalized to the midline location recorded for the first block.

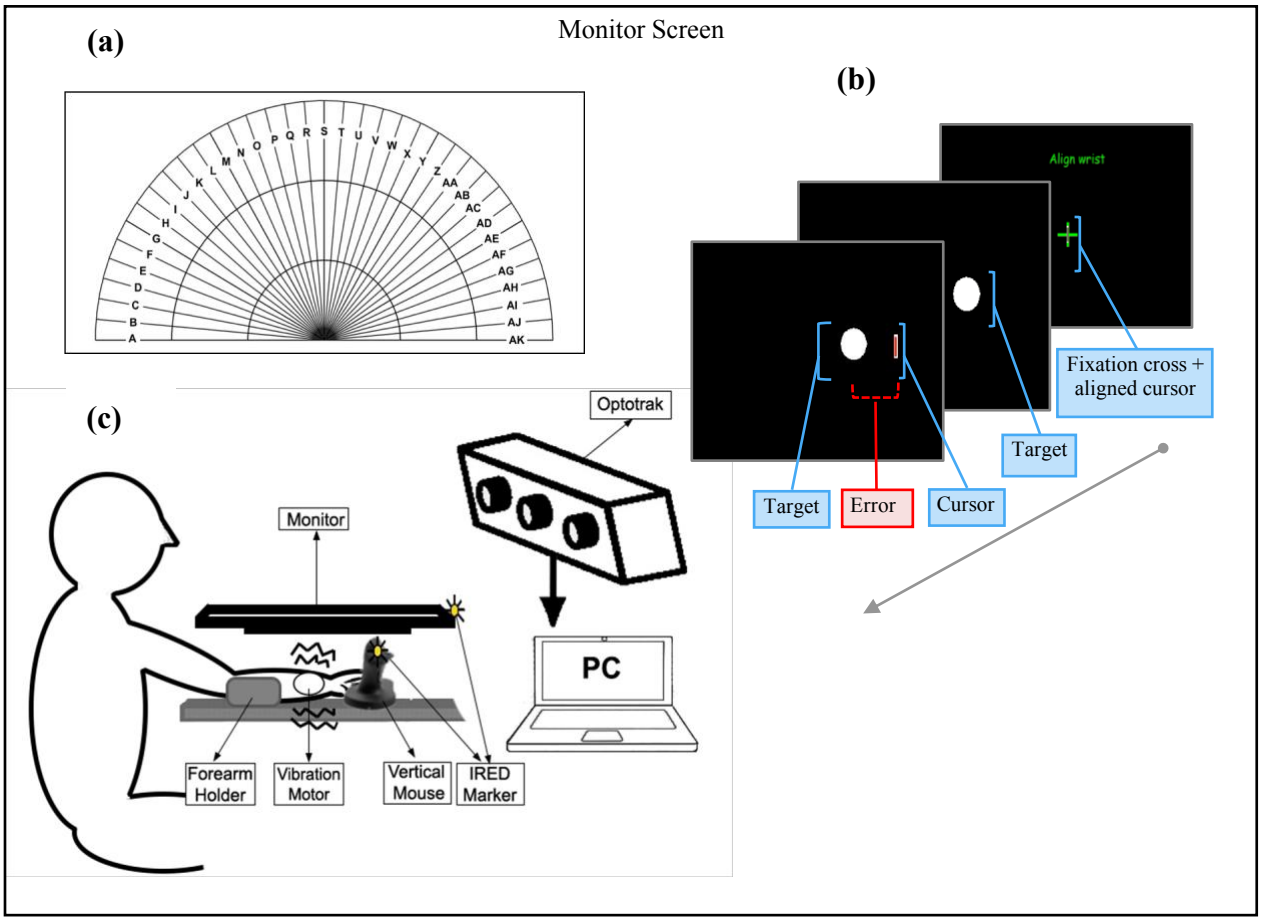

Figure 6-1 *Overview of the experimental set up and tasks.* ***(a)*** *Polar plot task screen for illusory movement sensation assessment.* ***(b)*** *Overview of the aiming task. Six targets randomly appeared along a horizontal line to the left and right side of the screen; cursor location became visible at*

the end of each trial. ***(c)*** *Overview of the experimental set-up. Vertical mouse was used to move the cursor on the horizontal monitor by flexion and extension movements of the wrist. Two vibration motors were placed over the wrist flexors and extensors. Motion capture system was used to check for neutral wrist alignment at trial onset using two markers, one placed on the vertical mouse and one in the middle of the edge of the screen.*

6.2.2 Illusory movement sensation assessment

To facilitate the objective measurement of illusory movement sensation a monitor was placed on a shelf over the participants' hand, parallel to the table, in order to obstruct vision of the moving limb (Figure 6-1c). The monitor displayed a polar plot with 37 radial lines (Figure 6-1a) with the angle between every two lines being five degrees. Each line was marked with one or two unique letter(s), allowing participants to report a maximum range of 90 degrees for wrist flexion and extension. In order to encourage attention to the perceptual task, the first five degrees on the left alternated randomly between A, B, and C. Prior to each block of trials, the wrist was aligned with the zero line on the polar plot. Then, for each trial the participants saw the polar plot on the screen and had four seconds to verbally report the letter that corresponded to their perceived current wrist angle. The polar plot disappeared after four seconds. According to the instructions on the screen, participants were asked to close their eyes and turn their head to left or right randomly during seven seconds of rest between trials. This was done to remove any bias for the reported angle from previous trials (Fuentes et al., 2012). Participants were notified of the next trial with a beep sound. Upon hearing the beep participants were instructed to open their eyes and look back to the monitor. The vibration motors were turned on according to the test condition (see the next section). The duration of the vibratory stimulus before each trial in a vibration condition was 30 seconds and was chosen based on previous work indicating that dual MTV increases position uncertainty and decays "proprioceptive memory" after only 12 seconds of sustained vibratory stimulus and this uncertainty reaches higher levels after 20 seconds (Fuentes et al., 2012). For each block of illusion assessment, participants saw the polar plots three or five times (see next section). The mean of the reported degrees of wrist flexion or extension (i.e., the degrees associated with the reported letter) was obtained. The results of the polar plot trials were corrected for any baseline bias in order to account for any bias participants may have for reporting their wrist position without vibration. This normalized score was used as the outcome measure for perceived wrist

flexion/extension. In line with Steyvers et al. (Steyvers et al., 2003), after each position test participants were asked the following three questions (the psychological questions) to quantify the continuance, vividness and strength of the vibrations on a scale from 0 to 10:

Q1: Continuance: How long was the illusory movement was felt during the vibration period? (Score 10 if the illusion was perceived during the whole block)

Q2: Vividness: Was the illusory movement sensation as if the wrist was actually moving (away or toward your midline)? (Score 10 if the illusion was perceived as if the wrist was actually moving)

Q3: Strength: What was the amplitude of the wrist movement that you felt toward or away from your midline? (Score 10 if the wrist was perceived to be maximally flexed or extended)

6.2.3 Procedure

At the beginning of the experimental session two-point discrimination and mono-filament sensory assessment were performed to establish participants' somatosensory thresholds. The baseline polar-plot assessment was done without vibration for all participants. Next, the baseline illusion assessment with vibration was performed in three vibration conditions: i) vibration on wrist flexors, ii) vibration on extensors, and iii) vibration on both muscle groups. This baseline assessment included five polar-plot trials per vibration condition, while the psychological questions were asked once per condition. Each experimental block of the illusion assessment began with 30 seconds of the assigned vibration condition. The order of the conditions was randomized and counterbalanced such that the same number of participants received each possible order. There was a minimum one-minute rest without vibration to washout the vibration aftereffects for each condition (Kito et al., 2006; Seizova-Cajic et al., 2007). Next, participants performed five familiarization trials of the aiming task. Familiarization trials were performed without vibration and with vision of the cursor throughout the trials. After 30 seconds of dual MTV (both flexors and extensors), participants performed the aiming task in four blocks that each included 24 trials (i.e., four repetitions for each of the 6 target locations). The participants took about 5 minutes to perform each block. Knowledge of results (KR) were presented with the location of the cursor becoming visible at the end of each trial for blocks 1-4. An illusion assessment with three polar plot trials and the psychological questions was repeated after blocks 2 and 4 of the aiming practice trials. Following the fourth block there was a 10-minute rest with the vibration off. Then, an immediate transfer block of the aiming task was performed which included 18 aiming trials (3

repetitions per target location), with knowledge of results presented as in the previous four blocks. For the transfer block, each group performed in the opposite condition such that vibration was off for the vibration group and on for the control group. All other test procedures, including vision of the cursor and KR, were identical for the vibration and control groups.

6.2.4 Data Analysis

The Mann-Whitney U test was used to compare the results of the overall score of psychological questions regarding illusory perception, calculated as the mean of the three vibration conditions over three items of the questionnaire, between the two experimental groups. The Wilcoxon Signed Rank test was used to compare the results of psychological questions between different assessments (baseline versus block 2 and block 4). Polar plot test results were compared at three timepoints (at baseline and after blocks 2 and 4) as well as between the two groups (MTV versus control) using a 2 Group × 3 Timepoint mixed-design ANOVA. An ANOVA with the factors of 2 Group (MTV, Control) × 5 Trial (T1-T5) was used to investigate the effect of longer vibration time on the reported illusion. A mixed between-within subject ANOVA was conducted to assess the impact of MTV (MTV, control groups) on participants' CE, VE, AE, RT, and MT, across 4 blocks of trials. The above-mentioned variables were compared across the last performance block (Block 4) and the transfer block to assess if any improvements in task performance transferred between vibration conditions. In order to explore the possible different effects of MTV on the direction of the movement (i.e., away versus towards body midline), another ANOVA was performed with the factors of 2 Direction (flexion, extension) × 2 Group (MTV, Control). Tukey's HSD post-hoc test was used to further analyze signification main effects or interactions involving more than two means. Significance for all statistical tests was set at $p < 0.05$.

6.3 Results

For the mono-filament sensory assessment, all participants received full intact sensation (5 grade points) for the 7 sensory points on the dorsal and plantar surface of their dominant hand. For the two-point discrimination test, the average two points that could be discriminated for the 7 locations on the hand was within the normal range for both groups: 4.5±1.5mm for the MTV group and 4.5±0.3mm for the control group (Dumontier & Tubiana, 2010).

6.3.1 Illusory movement sensation assessments

The illusory movement sensation result was analyzed for 10 participants in the MTV and 9 participants in the control group; one participant was removed from the illusion assessment analyses due to their misunderstanding of that test procedure.

6.3.1.1 Illusory movement sensation and direction according to questionnaire

Table 6-1 includes the results of the question regarding the perceived direction of illusory movement sensation at baseline, after two blocks and after 4 blocks of performing the aiming tasks for each group separately. With MTV on the flexor muscle tendons, extensor muscle tendons and with dual MTV, most participants felt movement toward wrist extension (n=8), wrist flexion (n=11), and both directions (alternating between flexion and extension, n=7) respectively. The most frequently reported sensation for the MTV group was "no illusion" for the illusory assessment after block 2 (n=5) and block 4 (n=6, Table 6-1).

Table 6-1 *Results for answers to the question regarding the perceived direction of illusory movement sensation at the baseline, after two blocks and after 4 blocks of performing the aiming tasks; the numbers indicate the number of participants; Flex= Flexion; Ext.= Extension*

		Perceived Illusory Movement Sensation Direction									
	MTV Location	MTV group					Control group				
		Flex.	Ext.	Ext. & Flex.	No illusion	Other	Flex.	Ext.	Ext. & Flex.	No illusion	Other
Baseline	Flexion	4	5*	0	1	0	2	3*	1	2	1[a]
	Extension	7*	2	0	1	0	4*	1	0	4	0
	Dual	3	1	4*	1	1	2	1	3*	3*	0
Post-Block2	Dual	3	0	1	5*	1[b]	-	-	-	-	-
Post-Block4	Dual	2	0	1	6*	1[b]	-	-	-	-	-

[a] *supination,* [b] *wrist radial deviation;* * *perceived sensations with highest frequencies.*

According to the results of the questionnaire at baseline, the illusory movement sensation seemed to feel more real (i.e., more vivid) and continuous in the MTV groups than the control group, however a Mann-Whitney U test showed that the difference of the overall scores of the two groups was not statistically significant (MTV Median [Md]=5.9, Control Md=2.0 U=25.5, Z=-1.6, p=0.11, r=3.66) (Figure 6-2). Moreover, the MTV group reported significantly lower ranks of illusory movement sensation with dual MTV under almost all three categories of the questionnaire when comparing the baseline results for dual vibration with block two (vividness: baseline Md=6.5, block2 Md=1, Z=-2.7, p=0.01, r=0.85; Continuance: baseline Md=8, block2 Md=0.5, Z=-2.1, p=0.03, r=0.67; Strength: baseline Md=2, block2 Md=0.5, Z=-1.71, p=0.09 r=0.54) and comparing results of baseline for dual vibration with block four (vividness: Md=0.0, Z=-2.53, p=0.01, r=0.80; Continuance: Md=0.0, Z=-2.12, p=0.03, r=0.67; Strength: Md=0.0, Z=-2.05, p=0.04, r=0.65) as assessed using Wilcoxon Signed Rank Test, a pattern that indicates they adapted to the vibration (Figure 6-2).

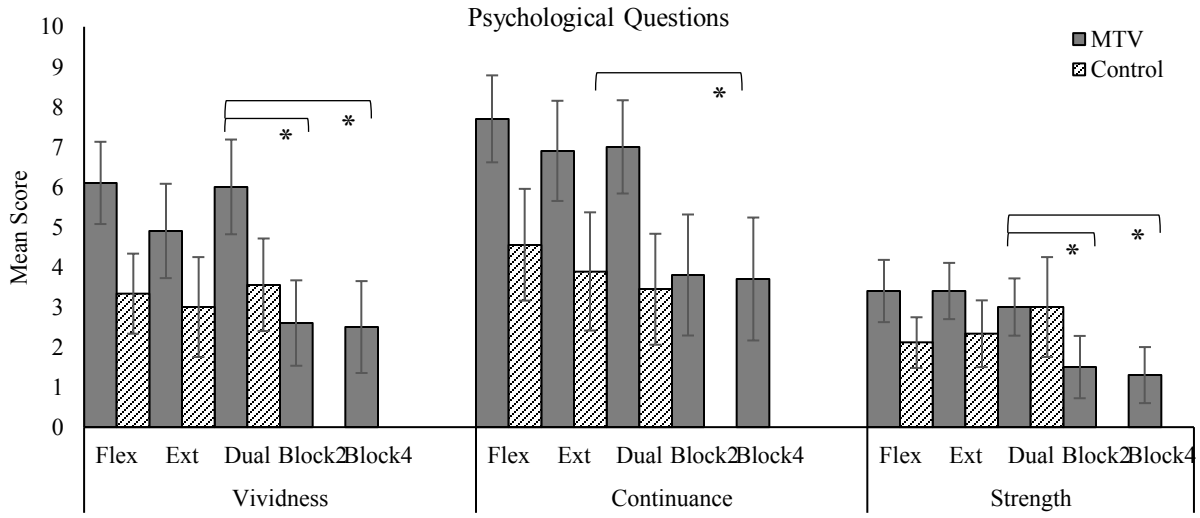

Figure 6-2 Results of the psychological questions about illusory movement sensation at baseline; including three vibration conditions (vibration over extensors, flexors, and both muscle tendons) and after blocks 2 and 4 when only MTV group received dual MTV. Error bars are standard error

6.3.2 MTV- induced illusion assessed by polar plot test

The mixed ANOVA did not reveal any significant interactions or main effects for the factors of group, MTV location, or trial number for reported angle in the polar plot test at baseline. During the condition with MTV over the wrist extensors only, most participants reported flexion (mean [M] for both groups=6.1±7.4 degrees, Figure 6-3a), and for the condition with vibration on the flexors only, participants reported some extension (M=-0.2±8.4 degrees). For Dual vibration, participants also reported flexion (M=4.2±8.5). As shown in plots (a) and (b) in Figure 6-3, the MTV group tended to report flexion throughout the experiment and the illusory sensation was reduced after block2 and block4. This pattern of results is consistent with the findings of the subjective assessments of illusory movement sensation using the self-report questionnaire.

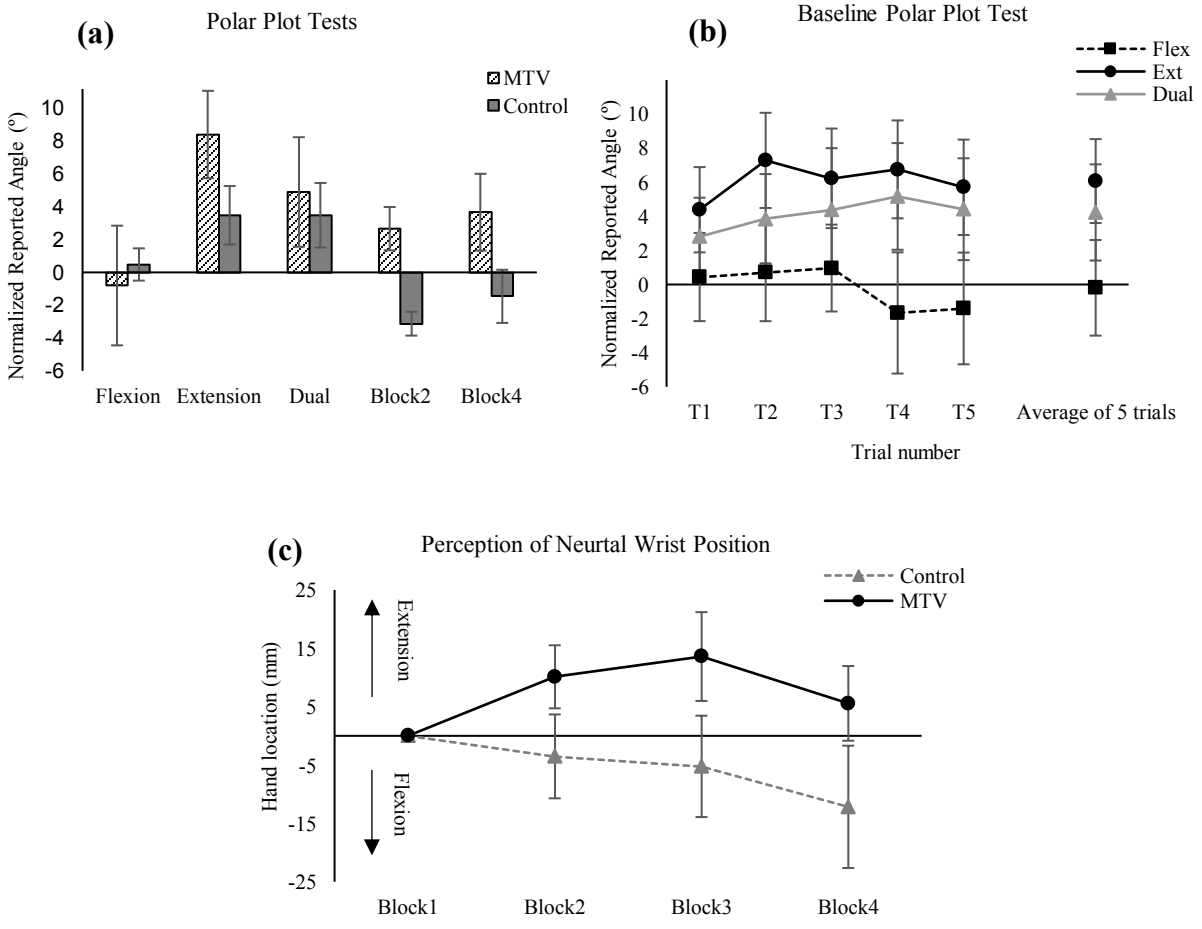

Figure 6-3 *Illusion and perceived wrist angle measurement results.* ***(a, b)*** *Positive angles indicate flexion and negative angles indicate extension; all of the reported angles were normalized to the reported baseline bias from vertical line when vibration was not presented. Plot* ***(a):*** *the bars indicate means of the perceived angles of the wrist from polar plot assessment for five trials (T1-T5) per each flexion, extension, and dual MTV conditions at baseline, as well as means of the three trials at blocks 2 and 4. Plot* ***(b):*** *data points indicate the average across 19 participants for each trial at the baseline to explore the trend of changes in the perceived angle of the wrist as the length of time with different MTV conditions increases. The Control group did not have Vibration on at block 2 and 4 assessments. Error bars indicate standard error (SE).* ***(c)****Results of normalized perception of neutral wrist position recorded by motion capture system. Positive direction indicates a change of hand location towards extension normalized to the first block; error bars are SE.*

6.3.3 Perceived neutral position versus motion capture measurements

Position data from the motion capture system was recorded and analyzed for 8 participants from each of the control and MTV groups (total n=16, data for two participants of each group could not be analyzed due to technical errors during data collection). The variability (SD) of the start position of the hand for four blocks of the aiming task and transfer block was about 1cm (mean variability: Control group=9.4±3.3 mm, MTV group=9.1±2.6mm)

A mixed ANOVA with Group (MTV, Control) x Block (Blocks1-4), to assess the normalized perception of neutral wrist position measured at the end of each block, did not indicate any significant interaction or main effect. That is, the perceived midline between different blocks was not significantly different for the two groups (Figure 6-3c).

6.3.4 Cursor movement outcomes of computer aiming task

For the variables related to movement accuracy (CE, VE, AE), the between group comparison showed that the two groups were not significantly different; AE: $F(1,18) = 2.993$, $p = 0.101$, partial eta square=0.143; CE: $F(1,18) = 0.066$, $p = 0.800$, partial eta square=0.004; VE: $F(1,18) = 0.306$, $p = 0.587$, partial eta square=0.017 (Figure 6-4a, b).

For the temporal variables, the two groups were not significantly different in MT and RT; RT: $F(1,18) = 2.038$, $p = 0.171$, partial eta square=0.102; MT: $F(1,18) = 0.878$, $p = 0.361$, partial eta square=0.047 (Figure 6-4c, d).

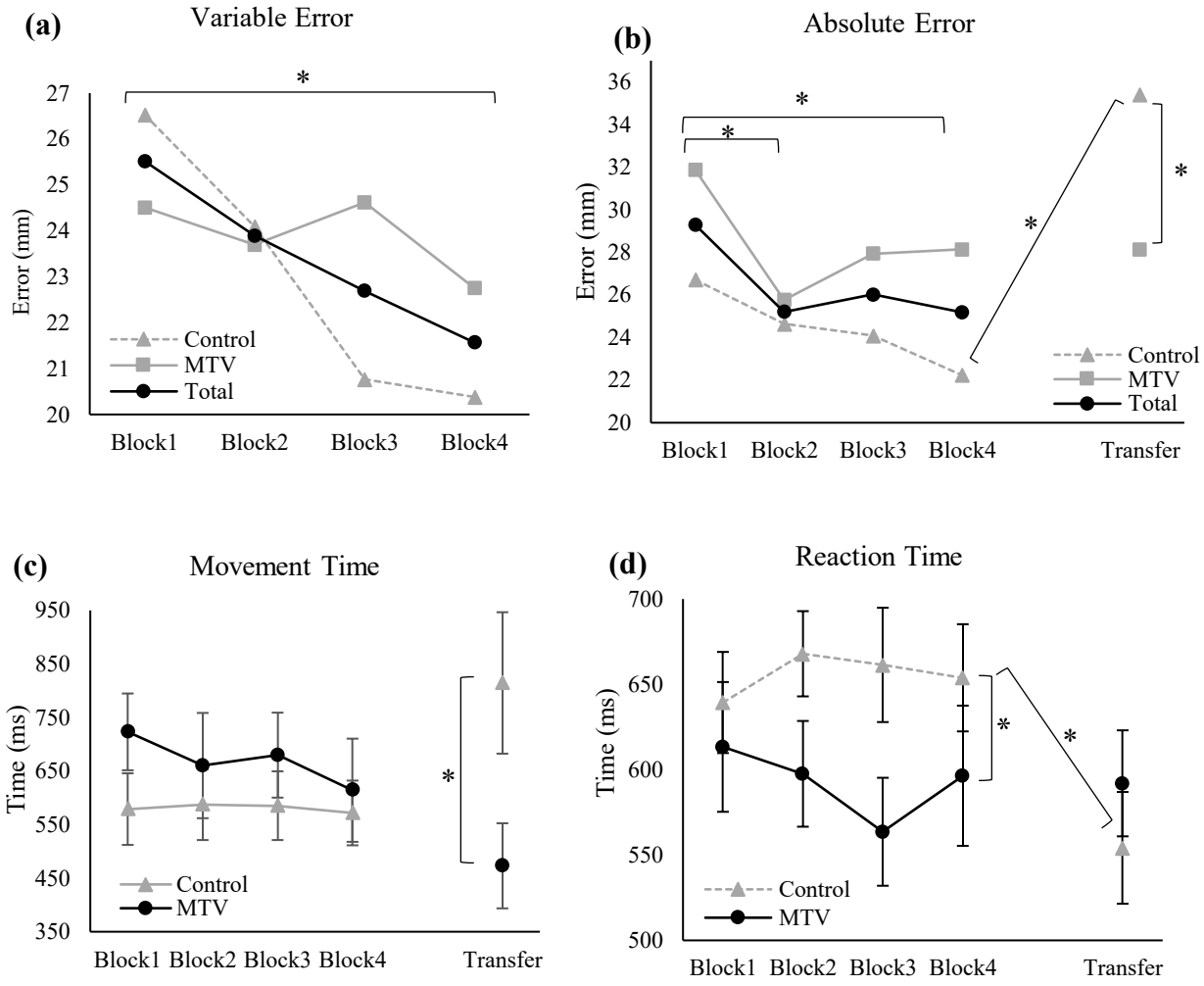

Figure 6-4 *Results of the spatial* ***(a & b)*** *and temporal* ***(c &d)*** *variables of the cursor movements; error bars represent standard error.*

6.3.5 Accuracy, change over blocks

For CE, the interaction was not significant, Block by Group, F (3,54) =2.059, p=0.117, partial eta square=0.103. For VE, there was a significant main effect for the block number, F (3,54) =2.991, p=0.039, partial eta square=0.143; Tukey's HSD post hoc test revealed a significant difference between VE of blocks 1 and 4 only; with both groups having significantly less endpoint variability after 4 blocks of practice (Block1: M=25.5±6.2; Block4: M=21.6±3.9; Figure 6-4a). Analysis of AE showed a significant main effect for block, F (3,54) =3.273, p=0.028, partial eta

square=0.154. Tukey's HSD test revealed significant differences between the first and second, and first and fourth blocks of trials; that is, when compared to the first block, participants were more accurate after block2 (M=25.2±5.3) and block4 (M=25.2± 6.9) (M=29.3±6.5, Figure 6-4b).

6.3.6 Temporal outcomes changes, over blocks

MT did not change significantly (Figure 6-4c). For RT there was a significant interaction between group and block of trials, F (3,54) =2.830, p=0.047, partial eta square=0.136 (Figure 6-4d). Tukey's HSD test showed that while the RT for the two groups were not significantly different at the first block (MTV group: M=613.3±120.2; Control group: M=639.4±93.7), the MTV group showed significantly shorter RT (MTV group: M=596.4±129.9) compared to the control group (Control group: M=653.8±99.3) at block4.

6.3.6.1 Accuracy and temporal outcomes in different movement directions

For all of the outcomes related to the accuracy of the aiming task (AE, VE, CE), there was no main effect or interaction for the factors of direction of the movement (towards flexion or extension) and group. For MT, there was a significant interaction between group and direction of movement, F (1,18) =5.464, p=0.031, partial eta square=0.223. Post-hoc comparisons using Tukey's HSD test indicated that when comparing MT between movement directions, for the MTV group only, MT was significantly longer for wrist extension (M=798.6±374.8) when compared to wrist flexion (M=547.9±202.6). Moreover, MTs for movements towards extension were significantly longer for the MTV group (M=798.6±374.8) when compared to the control group (M=531.9±156.6); the MT for the two groups was not significantly different for flexion movements. For RT, there was a significant main effect for movement direction, F (1,18) =6.702, p=0.019, partial eta square=0.271. Tukey's post-hoc test revealed that RT was significantly longer for wrist extension (M=630.2 ±91.5) than wrist flexion (M=611.7±111.7).

6.3.7 Comparisons of transfer block VS performance blocks

In order to compare performance during the transfer versus the performance block, the results of block 4 was compared to the transfer block. For the spatial parameter of CE, there was no significant main effects for group or block of trials. For AE, there was a significant group by block interaction, F (1,18) =11.019, p=0.004, partial eta square=0.380, and a significant main

effect for block, F (1,18) =10.980, p=0.004, partial eta square=0.379. Tukey's HSD post-hoc test indicated that when the control group received vibration for their transfer block, they had significantly larger errors (M=35.4 ±10.1) versus their AE at block4 (M=22.2±5.4). This was not the case for the MTV group. Th AE of the MTV group did not change when they did not receive vibration during their transfer block. Moreover, the between group comparisons showed that the control group had significantly higher errors (M=35.4±10.1) compared to the MTV group (M=28.1±8.1) at the transfer block, while the two groups were not different in the magnitude of AE during the last block of trials in their respective conditions (block4).

For temporal parameters there was a significant group by block interaction, F(1,18)=6.205, p=0.023, partial eta square=0.256 (Figure 6-4c, left), for MT. Post-hoc tests indicated that although the two groups were not different in their MT at block 4 , when vibration was added for the control group and removed for the MTV group, MT decreased for the MTV group and increased for the control group, leading to the significant group difference at the transfer block (mean difference=340ms). For RT, there was a significant main effect for block, F (1,18) =15.462, p=0.001, partial eta square=0.462 (Figure 6-4d, right), which was superseded by a group by block interaction, F (1,18) =12.939, p=0.002, partial eta square=0.418. Tukey's HSD post-hoc test showed that the control group had significantly shorter RTs in the transfer block compared to block 4 (mean difference=100ms), whereas the RT of the MTV group did not change significantly between block4 and the transfer block (mean difference=4.4ms). Moreover, for the between group comparisons, the control group had significantly longer RT compared to the MTV group's RT during block 4 (mean difference=57ms), but the difference of RT for the two groups was not significantly different during the transfer block (mean difference=38ms).

6.4 Discussion

The current study assessed the effects of dual MTV on movement performance by comparing spatial and temporal movement variables of participants who performed the task with MTV versus without MTV. We predicted the vibration group would exhibit larger errors compared to the control group early in practice. However, there were no significant difference between the two groups at any timepoint in terms of errors. Unlike the expectation of more similarities between movement parameters after more practice, RT became significantly shorter for the MTV group compared to the control group at block 4. On the other hand, the conscious illusory sensation

results (i.e., Responses to the psychological questions) demonstrated that there was adaptation to the dual MTV. That is, with dual MTV participants reported less than half of the illusion that they perceived at baseline (i.e., adaptation to the sensory changes). The objective measurement of illusory movement sensation (i.e., polar plot test) also showed a trend toward less illusory movement sensation after 2 blocks of having MTV on, however these changes (adaptations) were not statistically significant, $F(2,32) = 2.54$, $p = 0.11$, partial eta square $= 0.14$.

6.4.1 Perceptual adaptation to MTV

The subjective illusion assessments showed that most participants felt vibration in the expected direction. It is established already that vibration of a muscle-tendon leads to illusory movement sensation in the same direction as if the vibrated muscle was stretched (Goodwin et al., 1972). In the present study there was an illusory sensation of wrist movement towards extension when MTV was applied on the wrist flexors and vice versa. However, some participants did not feel any illusion when vibration was applied over the wrist extensors or flexors. Lack of responsiveness to illusory movement sensation was also seen in other studies and its cause is not clear (Fuentes et al., 2012; Roll et al., 2009). In this study, participants were included regardless of their perceived illusory sensation assessments so that the results would not be biased to participants who had higher levels of conscious awareness or sensitivity to muscle spindle stimulation.

Although all participants received dual vibration on their wrist antagonists with equal intensity and frequency at baseline, most participants felt movement toward both directions alternately (n=7). This finding may be because of participants' lack of familiarity with the illusory movement sensation and reporting the tactile sensation instead (e.g., considering the mechanical displacement of the motors as the illusory movement). After 2 blocks of practice only one participant (out of 4) in the MTV group reported this alternating feeling. Moreover, the results of the psychological questionnaire showed a reduction in the scores related to the feeling of illusion after more time with the MTV on, which can be interpreted as the participants adaptation to the sensory changes caused by MTV.

For the MTV group, when dual MTV was applied, the sum of scores for the three psychological questions was reduced from 16 points at baseline to 7.5 at block 4. The between the group comparison of the baseline polar plot results and questionnaire scores showed that the MTV

group was biased towards reporting higher scores for an illusion, but this difference was not statistically significant. According to the results of both the psychological questions and the polar plot test and similar to the findings of previous studies (Fuentes et al., 2012; Izumizaki et al., 2010) participants felt stronger illusory movement sensation towards flexion with extensor vibration than illusory extension with flexor vibration. Even for dual MTV participants reported feeling an illusion towards flexion at baseline (also see Bellan et al., 2016, for stronger illusory sensation towards the midline/flexion in different joints). One explanation for this finding could be that the natural resting posture of the wrist joint is in some degree of flexion and that can cause a tendency towards reporting more illusory flexion of the wrist.

The tendency for a stronger perceptual illusion towards flexion is also consistent with the positioning of a neutral wrist position as assessed by the motion capture system (Figure 6-3c). Although not statistically significant, descriptive statistics from the motion capture system data showed that as the blocks of aiming task were performed, the vibration group moved their hand toward extension and the control group towards flexion. The shift of actual wrist position towards extension in the MTV group may be due to the stronger illusion towards flexion that the participants attempted to overcorrect, leading to their wrist being positioned in slight extension instead of neutral.

6.4.2 Effect of MTV on movement planning/execution

There are studies that show proprioception is an important source of feedback throughout aiming movements. In order to investigate the role of visual and proprioception in different phases of upper limb aiming movements studies have used different methods to perturb the sensory systems. A few example of perturbations include using tendon vibration aftereffects (Goodman & Tremblay, 2018), (visual) prismatic shift in the hand's start position (Rossetti et al., 1995), and displacing the hand by delivering bursts using an air compressor in the absence of vision of the limb (Grierson et al., 2009). In the current study vision of the effector (i.e., the cursor) and upper limb was obstructed, so the sensory input available online was proprioception and tactile sensory inputs.

6.4.3 MTV and temporal variables

Changes in RT in the current study indicate an increase in efficiency of movement planning (Hansen et al., 2005). One explanation for the RT results could be that the MTV enhanced attention to the proprioceptive input that in turn led to more efficient movement initiation. For instance, Spence et al. investigated the effect of shifting tactile, auditory, and visual cue modalities on RT (Spence et al., 2001). The results provided evidence that the RT for an expected sensory modality was shorter than when the participants did not expect a modality or were not informed about the available modality. Moreover, shifting attention from visual and auditory modalities to the tactile modality led to the largest increase in RT. In other words, humans respond more quickly when they can prepare for which modality they will receive the information from. In our study, the MTV group received a somatosensory stimulation (tactile/vibration) and were expected to perform a task using a sensory modality within the somatosensory modality (i.e., proprioception). That is, the input modality was congruent with the sensory modality used for the task. Hence, the shorter RT in the MTV group compared to the control group could be the result of the MTV group's consistent attention towards somatosensory related modalities as a result of MTV application.

Overall, the temporal parameters of the movement towards extension seemed to be more affected by MTV than flexion. In the MTV group, MT was significantly longer for wrist extension compared to flexion whereas for the control group MT was not different for different movement directions. The higher tendency for the illusory movement sensation towards flexion may explain this finding. It seemed that although the same vibration was applied on both antagonist groups, the extensor muscle groups were more affected by the vibration and this augmented proprioceptive input may have led to more online corrections toward extension than flexion. That latter explanation is consistent with why the MTV group had longer MTs for their extension movements.

There are a few possible explanations for why MTV improved performance of the goal directed proprioceptive aiming task used in the current study by decreasing RT while maintaining spatial accuracy. MTV is thought to lead to covert attention to the proprioception sensory inputs. MTV has also been shown to increase excitability of the motor related cortex and corticospinal pathways as measured by H-reflex (Bock et al., 2007), and muscular spasticity assessments (Mortaza et al., 2019). Along with the behavioral changes with MTV, studies on the CNS showed changes in cortical and corticospinal excitability. Several studies have used transcranial magnetic stimulation (TMS) to explore how MTV, as a somatosensory stimulation, affects the excitability

of the motor cortex. These studies focused on cortical level changes in healthy individuals (Forner-Cordero et al., 2008; Marconi et al., 2008; Rosenkranz et al., 2003) and in individuals with stroke (Marconi et al., 2011). The results of these studies indicate changes in excitability of the motor areas related to the vibrated muscles, as well as patterns of intra-cortical inhibition and facilitation. An increase in map volume of the vibrated muscle and its antagonist on the motor cortex measured using TMS (Marconi et al., 2011) have also been reported. In order to elucidate the contributions of the above mechanisms future experiments will investigate the effect of MTV on the changes in the somatosensory system.

6.4.4 MTV and spatial variables

Regardless of group assignment, with practice participants improved their movement accuracy. While CE results showed that there was no consistent bias towards overshooting or undershooting the targets, the results of the spatial parameters showed that endpoint variability was reduced from block 1 to 4. Participants were not only more precise in hitting the targets by the end of their practice, but that they were more accurate in their aiming (Schmidt et al., 2018). Further, since the two groups were not different in terms of improvements in their accuracy and precision after 4 blocks, we propose that MTV had no adverse effect of on this upper limb task. These results are in line with the finding of the study by Gonzales and Goble that showed proprioception adaptation happened within about 10 minutes of biceps-triceps vibration as measured by an elbow angle matching task (Gonzales & Goble, 2014). Specifically, their results showed that the amplitude of the undershoot errors (constant error) for the matching task decreased at the later trials when compared to the early trials. Also, matching variability (variable error) did not increase significantly during biceps-triceps vibration. On the other hand, in a methodological study Bock et al. (Bock et al., 2007) suggested that the equal vibration stimulation over antagonist muscle groups will degrade proprioception. Bock et al. assessed this hypothesis using three tasks: angle matching, force production, and haptic shape perception. One explanation for the different findings of the current study and Bock et al.'s methodological study (Bock et al., 2007) could be that they used tasks that were passive or less dependent on active movement. There was also not enough time for participants to adapt to the added sensory input of vibration in the latter study. These differences could explain why the current study did not find any adverse effects of dual MTV on proprioceptive perception. By applying MTV during voluntary movement, as in the

present protocol, it is possible to understand the effects of augmented sensory input in a functional setting and enhance the ecological validity of the present findings.

6.4.5 Better learning with MTV

The largest group difference was in spatial accuracy during the transfer tasks. The MTV group was able to maintain all the performance improvements they achieved in endpoint accuracy (mean AE different between block 4 and transfer=0.0mm) when vibration was removed during the transfer block. In contrast, the AE of the control group increased by a mean difference of 13mm from block 4 (without MTV) to the transfer block (with MTV). Although the result of the control group is in line with the specificity of learning effect, the results of the transfer block for the MTV group is not. That is, similar to the control group the performance of participants of the MTV group was expected to worsen when the vibration was removed during transfer. Moreover, similar to the results of end point accuracy, during the transfer block, MT and RT did not change for the MTV group when vibration was removed. However, when the control group received vibration, their RT became significantly longer.

The results of the MTV group are contradictory to the specificity of learning effect. That is, motor learning is specific to the source of sensory information provided during practice (Proteau et al., 1992). In the case of performing a new motor task, the CNS identifies the sources of afferent information available to the task and uses them to form a set of motor commands (Proteau et al., 1992). In the current study, participants of the MTV group had full attention to using their proprioception in order to perform the aiming task, so when they performed the no-vibration transfer block, they could still focus on the proprioceptive information from the practice blocks to perform in the transfer condition. Although the control group also used proprioceptive input to learn the task, they did not face the modified version of the proprioceptive information during practice and thus likely did not have enough practice without the vibration to overcome the change of afferent input intensity in the transfer block.

Another explanation for better performance of the MTV group during the transfer block (smaller AE) may be a masking effect of vibration. Masking of the target stimulation happens when a non-target stimulation is applied simultaneous to the target stimuli. In such situations, the ability of the nervous system to detect and interpret the target stimulation may be inhibited or deteriorate (Craig, 1995). In the current study applying MTV may have masked proprioception sensory inputs

from the wrist muscle spindles by saturating the CNS and reduced its ability to detect the task relevant signals. This masking may have increased the challenge of the acquisition context which led to superior performance of the MTV group during the transfer block (for contextual interference and Challenge point framework see Guadagnoli & Lee, 2004, and Shea & Morgan, 1979). This interpretation agrees with the findings of a vibrotactile sensory letter learning study by Passmore et al. (Passmore et al., 2014). The authors induced radiating paresthesia as the interfering stimulus during acquisition, retention, and transfer of a Morse code vibrotactile letter identification task. Their results showed that participants who learned the task when paresthesia was induced performed better than the non-paresthesia control group at transfer, which may indicate facilitated learning as a result of a challenging learning context.

One limitation of the current study was the level of difficulty of the aiming task. The task included six different target locations that were presented in a random order. The multiple target positions may have been too hard for participants to acquire in the allotted practice. Future work will investigate both cortical excitability and behavioral results to achieve a comprehensive understanding of the effects of dual MTV on movement control.

6.5 Conclusion

The findings of the current study shed light on the effects of dual MTV on the performance of a goal-directed aiming task. We did not find any adverse effects of applying MTV at the wrist during performance of target aiming task. The results of the perceptual assessments showed the potential of the somatosensory system to adapt to the sensory changes. With respect to motor performance, the perceptual changes (i.e., illusory sensation) caused by MTV regarding the hand position were corrected when MTV was applied for a relatively short period of time (<100 trials). Considering the benefits of MTV in rehabilitation for proprioception deficiencies and the lack of adverse effects during a goal-directed aiming task, a clinical application of the findings of the current study could be to use MTV in a wearable rehabilitation device to improve attention during functional movements.

6.6 Declarations

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Ethics approval

This study was carried out in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki. Approval by the University of Manitoba (Education and Nursing) research ethics board was granted (approval number: E2019:013).

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CHAPTER 7

GENERAL CONCLUSION

7.1 Aims of Thesis and Summary of Key Findings

The goal of the current thesis was to understand the effect of modifications in proprioceptive inputs on the accuracy and efficiency of motor planning and execution, including assessing the adaptability of the sensorimotor system to such sensory modifications. These findings were intended to be used for designing a medical device that uses muscle-tendon vibration to stimulate muscle spindles with the expectation that this augmented stimulation will cause neuroplastic changes in the sensory and motor circuitries in the central nervous system (Forner-Cordero et al., 2008; Marconi et al., 2008; Rosenkranz et al., 2003). The ultimate goal being the lost motor performance will be restored through performing motor tasks while wearing the device (Mortaza et al., 2019). The modifications in the proprioception inputs were acquired by inducing paresthesia (Glazebrook et al., 2020; Passmore et al., 2014; Passmore et al., 2020) in the first two studies where the role of proprioception versus different components of visual sensory feedback (i.e., vision of the limb, and target location) was investigated. In the first study, included in chapter 2, induced paresthesia was combined with removing target vision to induce a preplanned movement while performing a goal-directed aiming task (Elliott, 1988). The finding of study one was intended to clarify the role of proprioception in a preplanned movement control process. The findings of study1 showed that movements performed in the presence of induced paresthesia took longer to execute, but not any longer to plan or initiate. As expected, visual input was the dominant source of information (Ernst & Banks, 2002; Ernst & Bülthoff, 2004; Rock & Victor, 1964) and when vision of the target was available participants' accuracy and motor control strategies did not change as a result of induced paresthesia. When vision of the target was not available, paresthesia adversely affected accuracy and efficiency of the task performance. We found participants learned to adapt to the changes caused by induced paresthesia with more practice by preplanning the movement, performing fewer online corrections, as well as decreasing their initial movement impulse, to compensate for the increased neuromuscular noise. We suggested that removing vision of the target led to memory guided movement control (Elliott, 1988), so participants relied on their perception of the target location (Heath, 2005) which could have been distorted or biased as a result of induced paresthesia by median nerve stimulation (Ghilardi et al., 1995; Haggard et al., 2000; Jones et al., 2010).

In the second study a similar goal-directed aiming task was used, but this time the visual manipulation included occluding the visual input to understand if participants' reliance on visual

feedback of their limb specifically increases in the presence of modified proprioception input. We found that the combination of paresthesia and no vision of the limb led to a significant movement bias towards the body midline. This finding shows that the contribution of proprioceptive input for movement accuracy is indeed larger in the absence of visual feedback of the limb. The temporal outcome measures showed that with intact sensory input participants had the longest MT, with most of the time spent for limb-target regulation. However, when paresthesia was induced participants performed a more pre-planned movement, even with full vision available. Visual feedback of the moving limb had a significant role on endpoint accuracy and variability, however paresthesia, or lack of intact proprioceptive input, induced a pre-planned movement strategy for a goal-directed reaching movement, even when full visual feedback was available. Together the results of the two fundamental studies (studies 1 and 2) provide further evidence on the importance of proprioceptive input for the planning and online control of goal-directed movements (Bagesteiro et al., 2005; Goodman & Tremblay, 2018), even in the presence of visual feedback.

Study 3 (Mortaza et al., 2019), a literature review with meta-analysis (chapter 4), explored the available clinical evidence for the effectiveness of muscle-tendon vibration as a method of rehabilitation using somatosensory stimulation/modification for individuals post-stroke. Meta-analysis of the results of 8 included clinical trials showed that the use of muscle-tendon vibration in individuals with subacute and chronic stroke was not associated with significant improvement in functional movements of the upper limb and did not reduce spasticity. This finding was according to specific standard clinical assessment methods used in these studies for evaluating the performance of the upper limb. The results also stressed the lack of sufficient clinical evidence on the efficacy of muscle tendon vibration for upper limb rehabilitation post-stroke. However, results of the secondary outcome of movement time to complete a reaching task showed significantly faster movements for the group that received the muscle-tenson vibration treatment (Casale et al., 2014; Tavernese et al., 2013). We used the findings of this literature review for determining the parameters of an effective vibration protocol as well as the outcomes measure that are sensitive enough to detect changes as result of muscle -tendon vibration in the next two studies.

In study 4 (Mortaza & Glazebrook, 2019)(chapter 5) a practical method was established to measure the characteristics of the muscle tendon vibration using affordable accelerometers. This method was used in the last study (study 5), which was a behavioral experiment presented in Chapters 6, that aimed to investigate the effects of applying MTV on performance of a functional

goal-directed aiming task over a series of practice trials. A secondary objective of this study was to determine if there is a correlation between the conscious perception of any illusory movement caused by the MTV and associated changes in movement performance. The findings of this behavioral study showed no adverse effects of applying MTV at the wrist during performance of an upper limb aiming movement. The results of the perceptual assessments showed the adaptability of the somatosensory system to the perception of sensory changes along with the motor performance: the perceptual changes (i.e., illusory sensation) caused by MTV regarding the hand position were corrected when MTV was applied for a relatively short period of time (less than 20 minutes).

7.2 Future Directions

Future research will investigate the sensory motor excitability, using somatosensory evoked potentials (SEPs), to explore the effect of dual MTV versus MTV over one muscle group on the excitably of the somatosensory cortex, associated pathways, and the potential effects on related motor control processes (Appendix 1). The results of the SEPs study combined with the behavioral results will contribute to a comprehensive understanding of the effects of dual MTV on movement control. Given the proof-of-concept study on the healthy neurotypical population in study 5 did not show any adverse effect of applying MTV during a functional upper limb task, future work will focus on clinical trials on major populations with proprioception deficiencies such as individuals who are post-stroke and older adults.

In study 5 we included subjective conscious perceptual measurements of illusory movement sensation to validate that the applied protocol of muscle-tendon vibration did in fact stimulate the targeted afferent system. Future work should consider including H-reflex assessment with and without muscle-tendon vibration as an objective measurement method to compliment the conscious perceptual measurements. The addition of the H-reflex assessment will further validate that our proposed wearable muscle-tendon vibration device is effectively stimulating the proprioceptive pathways. Moreover, we suggested in study 5 that the vibration may also bring additional attention to proprioceptive input and thus may contribute to more efficient performance of a goal-directed movement with muscle-tendon vibration. Thus, there is a need for more research on the effects of muscle-tendon vibration on different aspects of attention, physiological reflex pathways, along with its effects on the motor control performance and learning.

7.3 Limitations

One limitation of the current dissertation was the choice of the primary axis of the movement for the first two fundamental studies. As observed in the results of both studies, median nerve stimulation caused endpoint bias in the mediolateral direction. A task with a mediolateral direction as the primary movement would likely be more sensitive to changes in motor performance as a result of induced paresthesia caused by median nerve stimulation. In the first two studies mono-filament pressure testing was utilized to assess gross sensory pressure changes as a result of induced paresthesia. However, a measure of sensory acuity, such as 2-point discrimination test was not included. Future studies should also include illusory limb location assessment as a result of the induced paresthesia along with a measurement of sensory acuity. This assessment is expected to help with better interpretation of the results of the movement accuracy outcomes as well as assessment of the intensity of the induced paresthesia. A limitation of study 5 was the level of difficulty of the chosen aiming task. The task included in the MTV behavioral study included six different target locations that were presented in a random order. The random presentation of target location made it difficult for the performance of each trial to benefit from the feedback from the preceding trial. The task may have been too hard for participants to learn and not sensitive enough to detect group differences. Future work will use fewer target choices and present the same target for a specified number of trials.

7.4 Theoretical and Clinical Implications

The results of the present thesis contribute to developing our understanding of how humans adapt their motor control strategies when available somatosensory input is disrupted. The theoretical contributions of this thesis are three-fold. First, we found that induced paresthesia adversely affected accuracy and efficiency of motor performance during a memory guided pre-planned goal-directed movement (Elliott, 1988), (study 1). Second, induced paresthesia in the presence of full vision did not affect movement accuracy. However, induced paresthesia did affect the movement strategy with respect to fewer online corrections and a more pre-planned movement, which signifies the role of proprioception for the online correction of reaching movements (Bagesteiro et al., 2005; Goodman & Tremblay, 2018) (study 2). Third, by comparing the performance on early versus late trials we found evidence that participants learned to adapt to the

change in their proprioceptive input by changing their movement strategy (e.g., preplanning, decreased initial movement impulse, study 1 and study 2). This fundamental research represents the first step towards extending this line of work to clinical populations who experience disrupted somatosensory feedback. In particular, how individuals are able to adapt their movement strategies to account for the altered proprioceptive input. These findings may also provide information for therapists regarding the types of augmented and intrinsic feedback that may help individuals learn to perform accurate and efficient movements when somatosensory feedback is disrupted.

The two major contributions to the field of neurorehabilitation of the systematic review with meta-analysis are: i) the need for larger, higher quality clinical trials on specific patient populations (e.g., stroke and older adults), and ii) to consider the clinical relevance of performance-based outcome measures that focus on time to complete a functional movement (e.g., RT and MT) such as a goal-directed aiming task (Mortaza et al., 2019) (study 3). This current thesis also provides the first report on the design of a novel wearable rehabilitation device. A methodology study on the measurement of the vibration frequency was conducted in order to assess a feasible method to measure and monitor for the most effective vibration characteristics for stimulating the muscle spindles (Mortaza & Glazebrook, 2019)(study 4). The proof-of-concept study on the effects of MTV on the performance of a goal-directed aiming task in neurotypical healthy adults (Mortaza & Glazebrook, 2020)(study 5) showed no adverse effects of muscle-tendon vibration on performance of upper limb aiming movements. Similar to the findings of study1 and study 2, results of this study also supported the potential of the somatosensory system to adapt to vibrotactile input used to manipulate (or augment) intrinsic proprioceptive input through the associated changes in perception and motor performance. Hence, a clinical application of the findings of study 5 will be using muscle-tendon vibration in a wearable rehabilitation device to improve performance during functional movements.

In summary, the findings of the current thesis inform future work that will examine the effects of a novel vibration device on the neurophysiologic and behavioral performance of individuals with chronic stroke and older adults. Finally, the wearable muscle-tendon vibration device proposed in the current thesis is a low-tech, inexpensive, and non-invasive rehabilitation solution for stimulating the sensorimotor pathways and cortices. It may be beneficial to be used as complementary treatment for individuals with motor deficits as a result of proprioception loss.

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APPENDICES

Appendix 1 – Future research study proposal

CHANGES IN THE SOMATOSENSORY CORTEX EXCITABILITY AFTER DUAL MUSCLLE TENDON VIBRATION

Introduction

Short-term changes in the afferent inputs such as electrical (Forner-Cordero et al., 2008; Léonard et al., 2013; Marconi et al., 2008; Ridding et al., 2001; Rocchi et al., 2017; Rosenkranz et al., 2003) and vibration stimulation have shown to cause neuroplastic changes in the human sensory and motor cortices (Naito & Ehrsson, 2001; Naito et al., 1999). Vibration over the muscle tendons can selectively stimulate the muscle spindles and cause sensation of movement (Roll & Gilhodes, 1995; Roll & Vedel, 1982) perceived as the vibrated muscle being stretched (Goodwin et al., 1972). Several studies have used transcranial magnetic stimulation (TMS) to explore how muscle tendon vibration (MTV), as a somatosensory stimulation, affects the excitability of the motor cortex. These studies focused on cortical level changes in healthy individuals (Forner-Cordero et al., 2008; Marconi et al., 2008; Rosenkranz et al., 2003) and in individuals with stroke (Marconi et al., 2011). The results of these studies indicated changes in excitability of the motor areas related to the vibrated muscle as well as patterns of intra-cortical inhibition and facilitation. Marconi et al. showed that MTV in individuals with stroke increased map volume of the vibrated muscle and its antagonist on the motor cortex as measured by TMS (Marconi et al., 2011). Motor cortical excitability changes in individuals with stroke was also accompanied by reduced spasticity and improved functional movement. Moreover, results of several clinical trials suggest that MTV improves motor performance of the upper limb (Mortaza et al., 2019). In summary, the above findings suggest somatosensory stimulation such as MTV, increases the excitability of the relevant cortical and subcortical areas which will eventually contributed to improved motor performance in individuals with somatosensory deficiencies. So, MTV could be included as a complementary treatment to the rehabilitation programs in such individuals.

Roll and Gilhodes showed that the same vibration frequency over two antagonistic muscles groups (dual MTV) does not induce kinesthetic illusions(Roll & Gilhodes, 1995). Unlike MTV on one muscle group in a joint (single MTV), there are only a few studies on the excitability of the cortical and subcortical structures when antagonist muscle groups in a joint are vibrating

equally and simultaneously (Bock et al., 2007; Romaiguère et al., 2003). An fMRI study showed that although the illusion was not felt with dual vibration, the somatosensory areas of the cortex were still activated with dual MTV with similar vibration frequencies, however the motor areas were not active when the illusion was not perceived (Romaiguère et al., 2003). Thus, there is not enough evidence on the effects of dual MTV on cortical excitability. Also, there are no studies with the focus on the response of the somatosensory system, including the cortical, subcortical and corticospinal pathways to MTV.

Somatosensory evoked potentials or SEPs is a technique used to assess the neuroplastic changes and function of the dorsal column- medial lemniscus system. This system is a pathway that conveys sensory signals related to proprioception (Cruccu et al., 2008). The upper limb SEPs is usually acquired by 0.1-0.2 ms duration square wave pulse electrical stimulation of the median nerve. To record the electrical activity of the somatosensory pathway and cortex, surface electrodes are attached along the median nerve and spinal cord track as well as over the somatosensory cortex (S1) contralateral to the stimulation side, which would be C3' or C4' according to the 10-20 international system of electroencephalogram (EEG) electrode placement. SEPs signals include peaks and troughs that are named according to their direction and latencies relative to the median nerve stimulation (Nuwer et al., 1994). Latency and amplitude of these peaks respectively indicate the anatomical location of the somatosensory system that is affected by the stimulation and the amplitude of the peaks indicate the strength of the afferent signal. For example N20 is a negative SEPs peak that appears at about 20ms post-stimulation, which is thought to indicate the earliest processing of afferents in S1 (Passmore et al., 2014). SEPs measurement has shown to be an appropriate method to measure the immediate changes in the sensory pathways and cortex (Angel et al., 1984). Several studies have shown that the amplitude of somatosensory evoked potentials are negatively correlated with passive and active joint movement (Angel et al., 1984; Coquery, 1978; Rushton et al., 1981) as well as vibration, when performed during SEPs assessment (Cohen & Starr, 1985; Manzano et al., 1998). One possible explanation for the observed correlations could be due to "gating" phenomenon. That is, the pathways involved with the somatosensory input or motor task are pre-occupied (with the somatosensory input or motor task) and are unable to react to the median nerve stimulation, or the activated motor cortical areas that are related to a concurrent movement task, supress the cortical neurons related to the response to SEPs stimulation. (Cohen & Starr, 1987; Rushton et

al., 1981). SEPs assessment after spinal manipulation, repetitive task performance and learning have all shown increased SEPs amplitudes, indicating neuroplastic changes (Andrew et al., 2015; Andrew et al., 2014). Hence, it seems that SEPs is a relevant measurement of the plastic changes as a result of somatosensory stimulation. In the current study SEPs measurements will be used to explore the effects of applying MTV on the excitability of the somatosensory cortex and related structures.

As mentioned above, it has been shown that single MTV increases excitability of both the somatosensory and motor cortex when accompanied by an illusory movement sensation. Dual MTV does not cause any illusory movement sensation; however, it is not established if this lack of sensory perception is accompanied by a lack of activity in the somatosensory cortex. So, the purpose of the current study is to investigate the impact of applying MTV on SEPs and specifically to compare the effects with dual MTV versus single MTV. The secondary objectives are: i) to study the effect of the length of MTV application on SEPs changes (i.e., 10 minutes versus 20 minutes) and ii) to investigate if there is a correlation between the perception of illusory movement sensation caused by MTV and changes in the SEPs measurements. Based on the results of the previous studies on the changes in the excitability of the somatosensory regions of the cortex in response to single MTV (Naito & Ehrsson, 2001) versus dual MTV (Romaiguère et al., 2003), I predict an increase in SEPs peak amplitudes in both MTV protocols (dual and single). The changes are anticipated to be greater when one muscle group is vibrated. We do not expect SEPs gating since the measures will be performed when the vibration is removed.

Material and Methods

Participants

The required sample size was calculated using G*Power 3.1. An a priori power analysis was conducted with alpha set at 0.05 and power set at 80%. The number of groups was set as 2, number of measurements set at 4, and the correlation among repeated measures was chosen as an expected moderate value of 0.5. Since there were no comparable studies to the current one medium effect size f of 0.25 was used for calculation and a total sample size of 24 was suggested.

Twenty-four typically developing adults (12 participants for each of the two experimental condition) between18-35 years-old with no known neurological conditions (including concussion with unresolved symptoms within the past six month) will participate in this experiment. They

will have normal or corrected-to-normal vision and normal hearing. Participants will be excluded if they have had a recent (within the past six months) injury to their upper limb.

Illusory Movement Perception Assessment

To measure the degree of the illusory movement sensation the participants will sit at a table with their forearm placed over a block, so that their hand will not touch the table. A monitor will be placed on a shelf over the participants' hand, parallel to the table. This set up will obstruct the vision of the testing limb as well. The monitor will display a polar plot with 37 radial lines (see Figure 1). The interval between every two lines will be five degrees. Each line will be marked with one or two unique letter(s), allowing the participants to report a maximum range of 90 degrees for each of the wrist extension and flexion movements. The first five degrees on the left will randomly alternate between A, B, and C in order to encourage attention to the perception task. The vibration motors will be turned on according to the test condition determined by the group assignment. The wrist will be aligned with the zero line on the polar plot. Before the vibration switches on, the participants will verbally report the letter that corresponds to their perceived current wrist angle. The duration of the vibratory stimulus for the first assessment will be 30 seconds and was chosen based on previous work indicating that dual MTV increases position uncertainty and decays "proprioceptive memory" after only 12 seconds of sustained vibratory stimulus and this uncertainty reaches higher levels after 20 seconds (Fuentes et al., 2012). Participants will see the polar plots three times. They will have four seconds to indicate their perceived hand location. The polar plot will disappear after four seconds, and the next trial begins. The main outcome measure for the effects of vibration on position sense will be the angular difference between wrist position range reported at the end of each 15-minute period of vibration/rest and the reported baseline position. The mean of the reported degrees of wrist flexion or extension (i.e., the degrees associated with the reported letter) will be obtained and normalized by the perceived wrist location before vibration/rest duration was applied. This normalized score will be used as the outcome measure for the perceived wrist flexion/extension. Similar to the method used by Steyvers et al. (Steyvers et al., 2003), after each position test the participants will be asked three questions to quantify the continuance, vividness and strength of the vibrations (see Table 1) on a scale from 0 to 10.

Table 1 Question regarding the psychological experience of vibration; score 0 -10; 0 if no illusion was felt. Adapted from: Steyvers, et al., 2003.

Q1: Continuance: How long was the illusory movement was felt during the vibration period? (Score 10 if the illusion was perceived during the whole block)
Q2: Vividness: Was the illusory movement sensation as if the wrist was actually moving [ ] away or toward [ ] your midline? (Score 10 if the illusion was perceived as if the wrist was actually moving)
Q3: Strength: What was the amplitude of the wrist movement that you felt toward [ ] or [ ] away from your midline? (Score 10 if he wrist was perceived to be maximally flexed or extended)

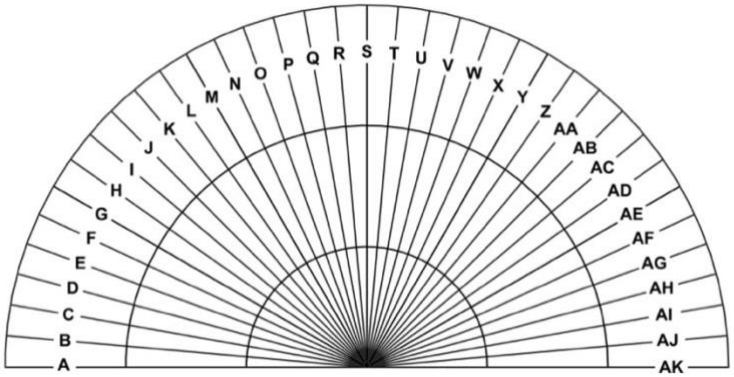

Figure 1 Polar plot for illusory movement sensation assessment.

Somatosensory Evoked Potential (SEP) assessments

In the current study, SEPs will be elicited and recorded using a Digitimer DS7AH constant current stimulator (Digitimer Ltd, UK) along with a CED 1902 amplifier electroencephalography system (Cambridge Electronic Design, UK) in order to measure the changes in the excitability of the somatosensory cortex as a result of vibration. The SEPs protocol and peak measurement method that will be used in the current study is in accordance to the International Federation of Clinical Neurophysiology recommended standards (Nuwer et al., 1994). SEPs stimuli will consist of electrical square pulses with 0.2 millisecond duration delivered at frequencies of 5 Hz through Ag/AgCl conductive adhesive surface electrodes placed over the median nerve on the skin 2–3 cm proximal to the distal crease of the wrist. The stimulus

intensity will be increased until motor threshold is attained in abductor pollicis brevis. Following data collection, SEPs peak amplitudes will be measured from the averaged 1500 sweeps of the waveforms. To record SEP signals, recording electrodes will be placed (Figure 3) on the ipsilateral Erb's point and over the C5 spinous process (both referenced to contralateral Erb's point), as well one scalp site, the Cc' (2 cm posterior to contralateral central C3/4) including the cephalic (with the forehead reference site, Fz) and non-cephalic channels (with the contralateral Erb's point reference site). The two cephalic site electrodes (Cc' and Fz) will be two millimeters gold cup EEG electrodes. Ag/AgCl conductive adhesive surface electrodes will be used for recording the signals from Erb's point and C5 locations. The SEPs signal will be amplified (gain 10,000) and filtered (0.2–3000 Hz) (Nuwer et al., 1994; Rossini et al., 1981).

The amplitudes and latencies of the SEPs components, including the peripheral N9, the spinal N13, the far-field N18 (P14–N18 complex), the parietal N20 (P14–N20 complex) and P25 (N20–P25 complex) will be visually identified and Signal software (Cambridge Electronic Design, UK) will be used to measure the peaks and their latencies. Latencies for SEP components represent the anatomical location of the activity of the nervous system and the peak-to-peak measures represent the amplitude of afferent volley and response of the cortical and subcortical structures to an external stimulus (Passmore et al., 2014).

Experimental procedure

The test protocol includes two conditions and participants can choose to participate in either or both sessions (at least one week apart). Each session will include one of the following vibration conditions: i) with two vibration motors on, located on the wrist flexors and extensors (dual MTV); ii) with only one vibration motor on, located on the wrist flexors (single MTV). The participants will be seated with their dominant arm on a table with the elbow extended and wrist in a neutral supination/pronation position. During vibration, vision of the upper limbs will be obstructed, and subjects will be instructed to relax their forearm muscles.

The flow of the experimental procedure is illustrated in figure 2. All participants will start the experiments with two baseline SEPs assessments with 10 minutes of rest interval. The comparison of two baseline measurements will rule out the possibility that any observed changes in the SEPs peaks as a result of TMV are by chance. Then, they will perform three orientation trials for the Polar-plot task before performing the baseline polar-plot assessment without

vibration. This baseline without vibration is included to calculate the possible bias that the participants may have for reporting their wrist position without the vibration; the results of the future trials will be corrected for the baseline bias. The baseline illusion assessment with vibration will be performed in three vibration conditions: i) vibration on wrist flexors, ii) vibration on extensors, and iii) vibration on both muscle groups. This assessment includes five polar-plot trials and the psychological questions for each vibration condition. Each experimental condition will begin with 30 seconds of the assigned vibration condition. The order of the conditions will be randomized and there will be at least one-minute rest without vibration to washout the vibration aftereffects for each condition. This baseline measurement will assess the capacity of the participant for perceiving the illusory movement and also controls for an equal amount of vibration stimulation for the dual vibration condition. After at least one-minute rest, the participants will receive one of the vibration conditions, which will be selected randomly, for two sets of 10 minutes. After each set of vibration, SEPs assessment will be performed (overall four assessments for each session). The assessment of the illusory movement sensation caused by the vibration will be performed at the beginning of the first vibration period and at the end of the first and second vibration periods. Vibration will be off for at least three minutes at the end of the first 10 minutes of vibration. Three minutes was chosen to allow enough time for the vibration aftereffects to wash out (Seizova-Cajic et al., 2007) for SEPs assessment. After SEPs assessment, the vibration will be turned on again for the second illusory movement sensation assessment and the following round of vibration. A summary of the experimental procedure is illustrated in figure 2 below.

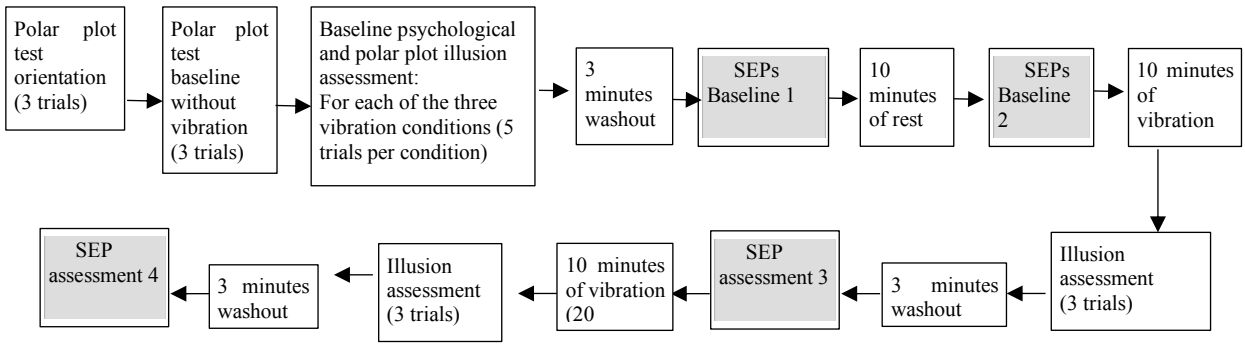

Figure 2 Illustration of the experimental procedure.

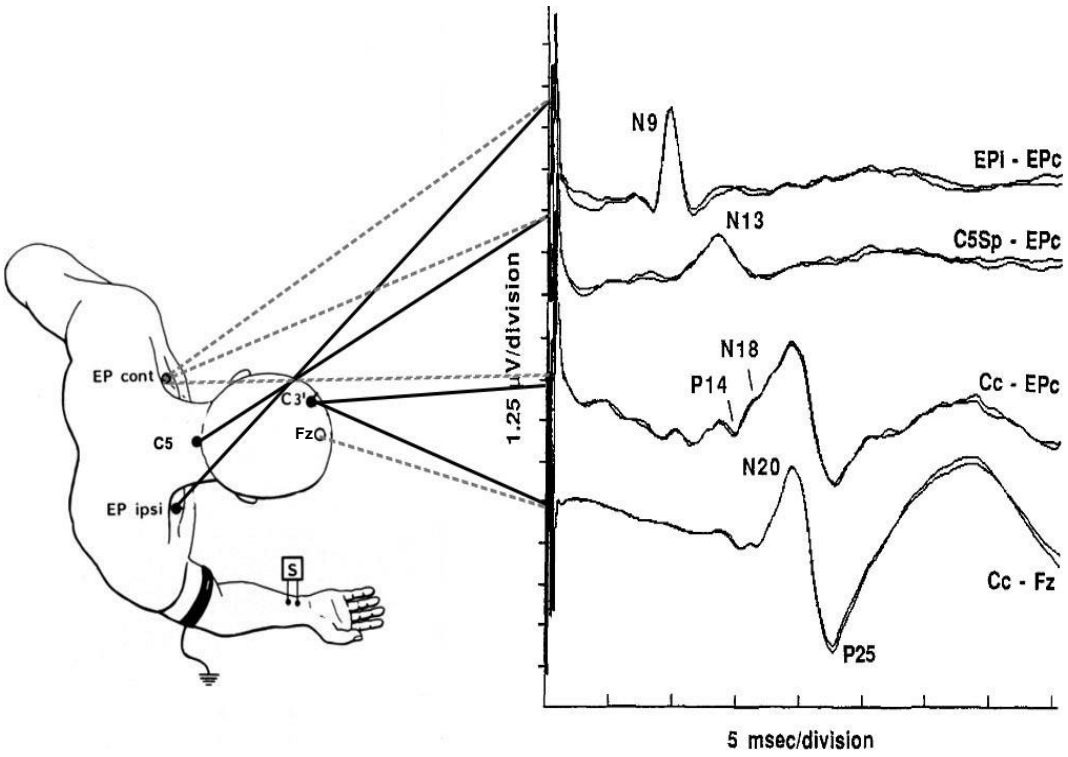

Figure 3 Somatosensory evoked potentials recording-reference electrode set-up; figure adapted from: Li, C., Houlden, D. A., & Rowed, D. W. (1990). Somatosensory evoked potentials and neurological grades as predictors of outcome in acute spinal cord injury. Journal of neurosurgery, 72(4), 600-609; and: Nuwer, M. R., Aminoff, M., Desmedt, J., et. al., (1994). IFCN recommended standards for short latency somatosensory evoked potentials. Report of an IFCN committee. International Federation of Clinical Neurophysiology. Electroencephalogr Clin Neurophysiol, 91(1), 6-11.

Data Analysis

To compare independent variables at different time points (baseline 1, baseline 2, after 10 minutes, and after 20 minutes of vibration) and between two vibration conditions (dual MTV, single MTV), a 2 Conditions × 4 Timepoints mixed-design ANOVAs will be performed. The dependent variables for SEP measurements include latency and peak-to-peak amplitude of each SEP component (N9, N13, N18, N20, and P25 peaks), acquired from the average waveform of 1500 sweeps. The variables for illusion assessment include scores for degrees of illusory movement sensation, and continuance vividness and strength of the vibrations. In case of any significant effect from the ANOVA tests, post-hoc comparisons will be done using the Tukey HSD test with alpha set at 0.05.

Finally, to analyze if there is a correlation between the perception of illusory movement sensation caused by MTV and changes in the SEP measurements, a two-way ANCOVA will be performed with Conditions (two groups: with dual MTV or single MTV), and Timepoints (baseline 1, baseline 2 , after 10 minutes, and after 20 minutes of vibration) as the independent variables, each of the above SEPs elements as the dependent variable, and the polar plot test score at the baseline with the vibration on extensors muscles as the covariate. Extensor muscles are chosen since they have shown to be prone to more illusion than the extensors (Fuentes at. Al, 2012).

The Kolmogorov-Smirnov test will be used to test the normality assumption required by statistical tests included in this proposed study (mixed-design ANOVA, two-way ANCOVA). In case of violation of the normality assumption, non-parametric analyses will be used.

Pilot Data and Summary

Figure 4 illustrates a sample of the SEPs pilot test results. The depicted waveform is the average of 1500 sweeps that have been recorded and analyzed with target SEP peaks marked. The experimental work for the current study could not conclude since restrictions related to the COVID pandemic did not allow testing that required close contact with human participants.

Findings of the SEPs assessment will reveal the extent and source of possible changes in the somatosensory pathways through measurement of amplitude and latency of SEPs peaks caused by dual versus single MTV. Based on the results of the previous studies on the changes in the excitability of the somatosensory regions of the cortex in response to single MTV (Naito & Ehrsson, 2001) versus dual MTV (Romaiguère et al., 2003), we anticipate an increase in SEPs peak amplitudes in both MTV conditions (duals and single), but these changes are expected to be higher when the vibration is causing more illusory movement sensation. I anticipate that changes will correspond with the perception of illusion as measured by the polar plot tests and the psychological questions. In other words, greater changes are expected for single MTV versus dual MTV.

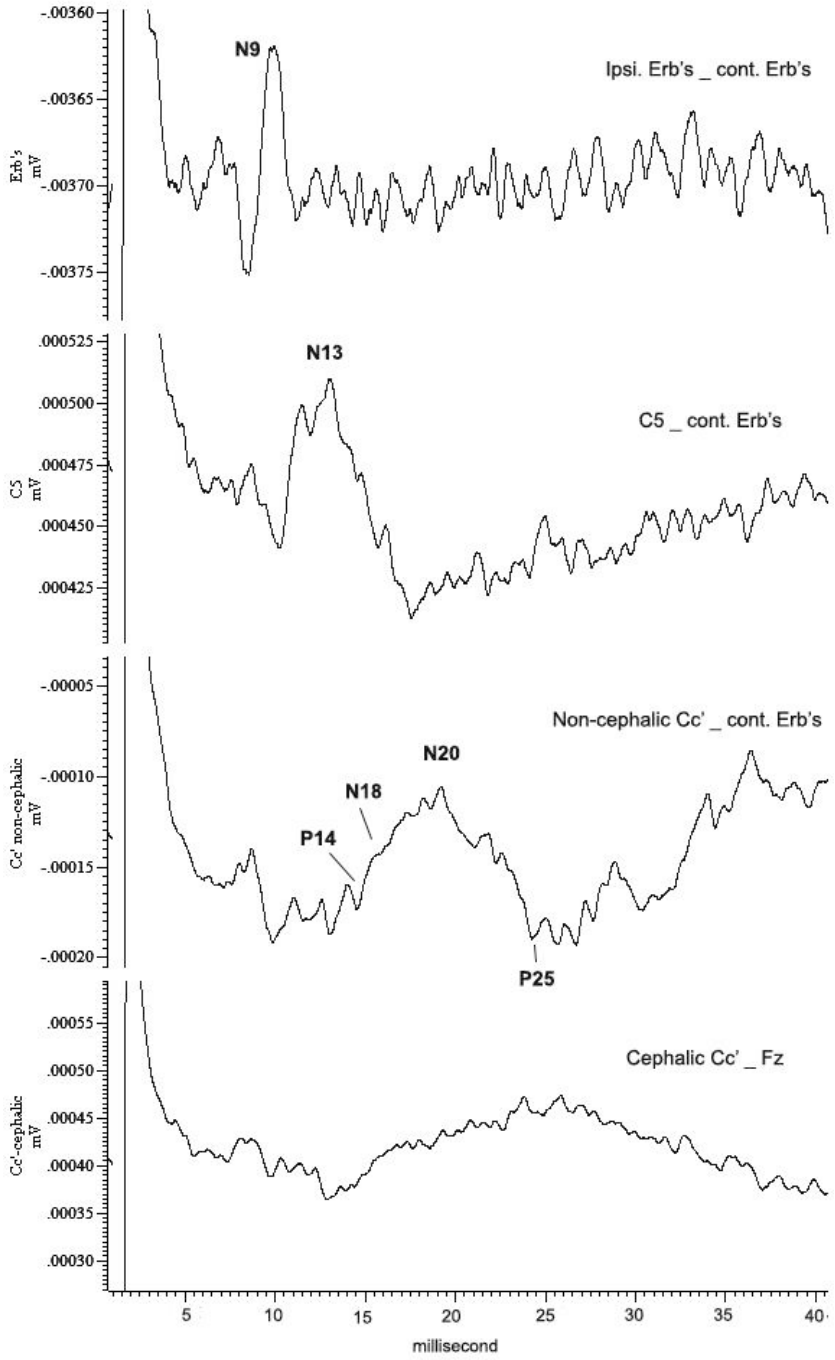

Figure 4 Results of pilot test presented as an average waveform of 1500 sweeps for four recording EEG channels.

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Appendix 2 - Scales/measures used for assessing the primary and secondary outcome measures

	Scale/measure	**Description**
Primary outcome	Wolf Motor Function Test (WMFT)	This test involves timed joint-segment movements, and tasks and timed integrative functional movements to evaluate upper extremity performance. (Wolf et al., 2001) Besides the timed tasks, the WMFT has a functional ability section that rates performance using a 6-point ordinal scale (0-5), with a maximum score of 85. WMFT is one of the most used outcome measures in studies on upper limb rehabilitation after stroke. (Morris, Uswatte, Crago, Cook, & Taub, 2001)
	Jebsen-Taylor Hand function Test (JTT)	This test includes seven manipulative tasks and measures how much time was spent on each task in seconds. (Jebsen, Taylor, Trieschmann, Trotter, & Howard, 1969)
	Motor Status Score (MSS)	This test is the Expanded Fugl-Meyer motor assessment for upper Extremity). Performance is measured on 40 tasks with a 6-point ordinal scale for shoulder/elbow (0, –1, 1,+1, –2, 2; maximum score 40) and 3-point ordinal scale for wrist/hand/fingers (0,1, 2; maximum score 42); total maximum score of 82.(Ferraro et al., 2002)
	Box and block test (BBT)	This test is a test of gross manual dexterity and upper limb function and is scored by counting the number of blocks carried over a partition during one minute. (Mathiowetz, Volland, Kashman, & Weber, 1985)
Secondary outcome	Movement time	movement execution time that is: $T_{start} - T_{end}$ of an upper limb reaching task. (Tavernese et al., 2013)
	Modifies Ashworth Scale (MAS)	MAS is a primary tool to assess the amount of spasticity in different muscles groups with scores ranging from 0-4. (Bohannon & Smith, 1987)

Appendix 3- Medline search strategy

1. cerebrovascular disorders/ or exp basal ganglia cerebrovascular disease/ or exp brain ischemia/ or exp carotid artery diseases/ or exp intracranial arterial diseases/ or exp "intracranial embolism and thrombosis"/ or exp intracranial hemorrhages/ or exp stroke/ or exp brain infarction/ or exp vertebral artery dissection/
2. stroke.tw,kf.
3. (("cerebral vascular" or cerebrovascular or moyamoya) adj2 (disorder* or accident* or disease* or attack*)).tw,kf.
4. ((cerebral or brain) adj5 (infarction* or ischemi* or h?emorrhage* or angiopath*)).tw,kf.
5. ("carotid arter*" adj2 (disease* or injur* or thrombos* or stenosis or fistula* or dissection*)).tw,kf.
6. (intercranial adj5 ("artery disease*" or embolism* or thrombos* or h?emorrhage* or aneurysm* or arteriosclerosis)).tw,kf.
7. "vertebral artery dissection".tw,kf.
8. (("basal ganglia" or putaminal) adj2 h?emorrhage*).tw,kf.
9. "Vertebrobasilar Insufficiency".tw,kf.
10. ((lateral medullary or subclavian) adj3 syndrome).tw,kf.
11. "vascular dementia".tw,kf.
12. ((subcortical or binswanger* or arteriosclerotic) adj3 (dementia* or encephalopath* or disease* or leukoencephalopath*)).tw,kf.
13. or/1-12
14. vibration/
15. (vibrat* or vibrot*).tw,kf.
16. oscillat*.tw,kf.
17. (pulsing or pulsat*).tw,kf.
18. (tapping or tapped).tw,kf.
19. or/14-18
20. 13 and 19
21. randomized controlled trial.pt.
22. controlled clinical trial.pt.
23. clinical trials as topic.sh.
24. (randomi#ed or randomly or RCT$1 or placebo*).tw.
25. ((singl* or doubl* or trebl* or tripl*) adj (mask* or blind* or dumm*)).tw.
26. trial.ti.
27. cross-over studies/
28. (crossover or "cross over").tw,kf.
29. or/21-28
30. 20 and 29
31. Animals/ not (Animals/ and Humans/)
32. 30 not 31
33. (letter not (letter and randomized controlled trial)).pt.
34. (comment or editorial or interview or news).pt.
35. or/33-34
36. 32 not

Appendix 4- Supplementary File 1

Excluded studies, and reason for the exclusion.

Study	Reasons for exclusion
Ageranioti SA, Hayes KC. Effects of vibration on hypertonia and hyperreflexia in the wrist joint of patients with spastic hemiparesis. *Physiotherapy Canada.* 1990;42(1):24-33.	No data on the outcomes included in the current systematic review
Sim S-M, Oh D-W, Chon S-c. Immediate effects of somatosensory stimulation on hand function in patients with poststroke hemiparesis: a randomized cross-over trial. *International journal of rehabilitation research.* 2015;38(4):306-312.	Cross-over trials with no pre/post-treatment data available before the groups are crossed-over to the control/treatment conditions
Conrad MO, Scheidt RA, Schmit BD. Effects of wrist tendon vibration on targeted upper-arm movements in poststroke hemiparesis. *Neurorehabilitation and Neural Repair.* 2011;25(1):61-70.	No data on the outcomes included in the current systematic review
Paoloni M, Tavernese E, Fini M, et al. Segmental muscle vibration modifies muscle activation during reaching in chronic stroke: A pilot study. *NeuroRehabilitation.* 2014;35(3):405-414.	No data on the outcomes included in the current systematic review

Appendix 5- Supplementary File 2

Quality assessment of selected randomized controlled trials using Physiotherapy Evidence Database (PEDro) scale: higher score implies higher quality

Study	Eligibility Criteria	Random Allocation	Concealed Allocation	Baseline Comparability	Blind Subjects	Blind Therapists	Blind Assessors	Adequate Follow-Up (Drop-out rate)	Intention-to-Treat Analysis	Between-Group Comparisons	Point Estimates and Variability	PEDro Score
Caliandro et al. 2012	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	10
Tavernese et al. 2013	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes	9
Casale et al. 2014	Yes	Yes	No	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	9
Marconi et al. 2011	No	Yes	No	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	8
Costantino et al. 2017	Yes	Yes	No	Yes	Yes	No	No	Yes	Yes	Yes	Yes	8
Celleti et al. 2017	Yes	Yes	Yes	Yes	No	No	Yes	No	Yes	No	Yes	7
Choi 2017	No	Yes	No	Yes	No	No	No	No	Yes	No	Yes	4
Liu et al. 2011	No	Yes	No	No	No	No	Yes	No	No	Yes	Yes	4

Appendix 6 - MATLAB scripts

Script used to acquire vibration Peak-to-Peak and frequency from the acceleration

```
% place the raw data file in the working folder
clearvars -except q % name the main accelerometer data file "q"
vol=q.values(:,7); %exporting the frame data out of the struct
pow_vol = abs(vol_fft);    % power analysis of the voltage data

%below is the frequency content analysis for vibration:

fs=10000; % sampling frequency
n = length(vol);  % number of samples
f = (0:n-1)*(fs/n);     % frequency range
vol_fft = fft(vol(:,:)); % vol: raw voltage data
pow_vol = abs(vol_fft);    % pow: power

% Calibration for 16G accelerometer: using the 16.35 coefficient to convert voltage
output to acceleration data in g and 160.4252 to m/s^2 %
coef = 160.4252;
acc = vol.*coef;
acc = acc - mean(acc);
dt = 9.999999747378752e-05; % time step for data collection during experiment
time = 0:dt:(length(acc) - 1) * dt;%zeros(1,t);

vel = cumtrapz(time,acc); % integrating acceleration data to get velocity
vel_fft = fft(vel(:,:));
n = length(vel);          % number of samples
f = (0:n-1)*(fs/n);     % frequency range
pow_vel = abs(vel_fft);

%filter (Butterworth bandpass) the velocity data
order=2;
high_cutoff=150; % for vibration set the high at 150. These cut offs are based on a long
recording to figure out noise content
low_cutoff=50;
[b1,a1]=butter(order,[low_cutoff,high_cutoff]/(fs/2),'bandpass');
vel_filt=filtfilt(b1,a1,vel); %filtered signal; dualpass

% integrating velocity data to get dicplacement

displace = cumtrapz(time, vel);
displace_filt = cumtrapz(time, vel_filt);
plot(displace_filt - mean(displace_filt))
```

```
displace = cumtrapz(time,vel_filt); %displacement in mm
displace_fft = fft(displace(:,:));
n = length(displace);          % number of samples
f = (0:n-1)*(fs/n);     % frequency range
pow_displace = abs(displace_fft);

figure  %plot frequecny content for vel,vol,disp
subplot(3,1,1);

%plot frequency content for voltage
plot(f(2:length(vol)),pow_vol(2:length(pow_vol)));
xlabel('Frequency_vol')
ylabel('pow_vol')
vol_freq = find(vol_fft(2:length(vol_fft)) == max(vol_fft(2:length(vol_fft))));
disp('peak freq for vol is: ')
VVVV=f(vol_freq);
disp(string(VVVV(1:1)))
subplot(3,1,2);
% plot frequency content for velocity
plot(f(2:length(vel)),pow_vel(2:length(pow_vel)));
xlabel('Frequency_vel')
ylabel('pow_vel')
vel_freq = find(vel_fft(2:length(vel_fft)) == max(vel_fft(2:length(vel_fft))));
disp('peak freq for vel is: ')
f(vel_freq)

subplot(3,1,3);
% plot frequency content for displacement
plot(f(2:length(displace)),pow_displace(2:length(pow_displace)));
xlabel('Frequency_disp')
ylabel('pow_displace')
displace_freq = find(pow_displace(2:length(pow_displace)) ==
max(pow_displace(2:length(pow_displace))));
disp('peak freq for displace is: ')
f(displace_freq)
%%%%%%%calculate peak-peak displacement

pks_z = findpeaks(displace);
pks_z = pks_z(pks_z > 0);
downs_z = -1 * findpeaks(-1 * displace);
downs_z = downs_z(downs_z < 0);

len = min([length(pks_z), length(downs_z)]);
pks_z = pks_z(1:len);
downs_z = downs_z(1:len);
```

```
pk_to_pk_z = pks_z - downs_z;
pk_to_pk_avg_z = mean(pk_to_pk_z)*1000; % P-P displacement value in mm


disp('avg z peak to peak in mm is = ')
disp(string(pk_to_pk_avg_z))

%%%%%%%% finding the peaks for velocity
pks_vel = findpeaks(vel_filt);
pks_vel = pks_vel(pks_vel > 0);
downs_vel = -1 * findpeaks(-1 * vel_filt);
downs_vel = downs_vel(downs_vel < 0);
pks_vel_ave=mean(pks_vel);
downs_vel_ave=mean(downs_vel);


%%%%%% display peak to peak values for velocity
disp('avg upward velocity peak is = ')
disp(string(pks_vel_ave))

disp('avg down velocity peak is = ')
disp(string(downs_vel_ave))

%%%%%%%% finding the peaks for acceleration graph
pks_acc = findpeaks(acc);
pks_acc = pks_acc(pks_acc > 0);
downs_acc= -1 * findpeaks(-1 * acc);
downs_acc = downs_acc(downs_acc < 0);
pks_acc_ave=mean(pks_acc);
downs_acc_ave=mean(downs_acc);

%%%%%% display  peak values for acceleration
disp('avg upward acceleration peak is = ')
disp(string(pks_acc_ave))

disp('avg down acceleration peak is = ')
disp(string(downs_acc_ave))
```

Script used to acquire vibration Peak-to-Peak and frequency from Optotrak data:

```
NDI_Z=NDI(:,4); %loading the Z-axis data from raw Optotrak displacement data

NDI_Y=NDI(:,3);

NDI_X=NDI(:,2);
```

```
%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%calculate FFTs
X = fft(NDI_X);
Y=fft(NDI_Y);
Z= fft(NDI_Z);%select z axis
n = length(NDI);          % number of samples
f = (0:n-1)*(fs/n);     % frequency range
pow_X = abs(X);    % pow of the DFT
pow_Y = abs(Y);
pow_Z = abs(Z);
figure  %plot frequecny content for X,Y,Z axis
subplot(3,1,1);
plot(f(2:length(NDI)),pow_X(2:length(pow_X)))
xlabel('Frequency_X')
ylabel('pow_X')
subplot(3,1,2);
plot(f(2:length(NDI)),pow_Y(2:length(pow_Y)))
xlabel('Frequency_Y')
ylabel('pow_Y')
subplot(3,1,3);
plot(f(2:length(NDI)),pow_Z(2:length(pow_Z)))
xlabel('Frequency_Z')
ylabel('pow_Z')
figure %%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%% simple X vs. F
graphs
hold on
subplot(3,1,1);
plot(NDI(:,1), NDI_X)
xlabel('F')
ylabel('X')
subplot(3,1,2);
plot(NDI(:,1), NDI_Y)
xlabel('F')
ylabel('Y')
subplot(3,1,3);
plot(NDI(:,1), NDI_Z)
xlabel('F')
ylabel('Z')
% display significant frequency for X axis
MX=max(pow_X(40:(length(pow_X)-40)));
MMX=find(pow_X== MX);
MMMX=f(MMX);
disp('max frequency for X=')
disp(string(MMMX(1:1)))
% display significant frequency for Y axis
MY=max(pow_Y(40:(length(pow_Y)-40)));
MMY=find(pow_Y== MY);
MMMY=f(MMY);
disp('max frequency for Y=')
disp(string(MMMY(1:1)))
% display significant frequency for Z axis
```

```
MZ=max(pow_Z(40:(length(pow_Z)-40)));
MMZ=find(pow_Z== MZ);
MMMZ=f(MMZ);
disp('max frequency for Z=')
disp(string(MMMZ(1:1)))
finding peak to peak amplitude
% x axis
pks_x = findpeaks(NDI_X);
downs_x = -1 * findpeaks(-1 * NDI_X);

len = min([length(pks_x), length(downs_x)]);
pks_x = pks_x(1:len);
downs_x = downs_x(1:len);

pk_to_pk_x = pks_x - downs_x;
pk_to_pk_avg_x = mean(pk_to_pk_x);


disp('avg x peak to peak is = ')
disp(string(pk_to_pk_avg_x))
% y axis
pks_y = findpeaks(NDI_Y);
downs_y = -1 * findpeaks(-1 * NDI_Y);

len = min([length(pks_y), length(downs_y)]);
pks_y = pks_y(1:len);
downs_y = downs_y(1:len);
pk_to_pk_y = pks_y - downs_y;
pk_to_pk_avg_y = mean(pk_to_pk_y);


disp('avg y peak to peak is = ')
disp(string(pk_to_pk_avg_y))
% z axis
pks_z = findpeaks(NDI_Z);
downs_z = -1 * findpeaks(-1 * NDI_Z);

len = min([length(pks_z), length(downs_z)]);
pks_z = pks_z(1:len);
downs_z = downs_z(1:len);

pk_to_pk_z = pks_z - downs_z;
pk_to_pk_avg_z = mean(pk_to_pk_z);


disp('avg z peak to peak is = ')
disp(string(pk_to_pk_avg_z))

%%%%%%%%%%%%%%%%%%2nd marker

%%%%%calculating the displacement and velocity from the Optotrak data.
```

```
Displace_Z=NDI_Z * 1e-3; %displacement in meter
% t=NDI(:,1) time
% sf=900; %sampling freq
dt = 1/fs; % time step for data collection during experiment
t= 0:dt:(length(Displace_Z) - 1) * dt;%zeros(1,t);

velocity_Z = diff(Displace_Z) / dt; % in m/s
acceleration_Z = diff(velocity_Z) / dt; % in m/s^2

%%%%%for X axis
Displace_X=NDI_X * 1e-3; %displacement in meter
% t=NDI(:,1) time
% sf=900; %sampling freq
dt = 1/fs; % time step for data collection during experiment
t= 0:dt:(length(Displace_X) - 1) * dt;%zeros(1,t);

velocity_X = diff(Displace_X) / dt; % in m/s
acceleration_X = diff(velocity_X) / dt; % in m/s^2

%%%%%%%% finding the peaks for acceleration graph and peak_to_peak amplitue
pks_acc_Z = findpeaks(acceleration_Z);
downs_acc_Z = -1 * findpeaks(-1 * acceleration_Z);
pks_acc_ave_Z=mean(pks_acc_Z);
downs_acc_ave_Z=mean(downs_acc_Z);
%%%%%for X axis
pks_acc_X = findpeaks(acceleration_X);
downs_acc_X = -1 * findpeaks(-1 * acceleration_X);
pks_acc_ave_X=mean(pks_acc_X);
downs_acc_ave_X=mean(downs_acc_X);

% len = min([length(pks_acc), length(downs_acc)]);
% pks_acc = pks_acc(1:len);
% downs_acc = downs_acc(1:len);
% pk_to_pk_acc = pks_acc - downs_acc;
% pk_to_pk_avg_acc = mean(pk_to_pk_acc);

%%%%%% display negative and positive peak values for acceleration
disp('avg upward Z acceleration peak is = ')
disp(string(pks_acc_ave_Z))

disp('avg down Z acceleration peak is = ')
disp(string(downs_acc_ave_Z))

disp('avg upward X acceleration peak is = ')
disp(string(pks_acc_ave_X))

disp('avg down X acceleration peak is = ')
disp(string(downs_acc_ave_X))

%%%%%%%% finding the peaks for velocity graph and peak_to_peak amplitude
```

```
pks_vel_Z = findpeaks(velocity_Z);
downs_vel_Z = -1 * findpeaks(-1 * velocity_Z);
pks_vel_ave_Z=mean(pks_vel_Z);
downs_vel_ave_Z=mean(downs_vel_Z);

%%%%%for X

pks_vel_X = findpeaks(velocity_X);
downs_vel_X = -1 * findpeaks(-1 * velocity_X);
pks_vel_ave_X=mean(pks_vel_X);
downs_vel_ave_X=mean(downs_vel_X);

% len = min([length(pks_vel), length(downs_vel)]);
% pks_vel = pks_vel(1:len);
% downs_vel = downs_vel(1:len);
% pk_to_pk_vel = pks_vel - downs_vel;
% pk_to_pk_avg_vel = mean(pk_to_pk_vel);

%%%%%% display peak to peak values for velocity
disp('avg upward Z velocity peak is = ')
disp(string(pks_vel_ave_Z))

disp('avg down Z velocity peak is = ')
disp(string(downs_vel_ave_Z))

disp('avg upward X velocity peak is = ')
disp(string(pks_vel_ave_X))

disp('avg down X velocity peak is = ')
disp(string(downs_vel_ave_X))
```

Appendix 7- Ethics approval letter for studies 1& 2

UNIVERSITY OF MANITOBA | Research Ethics and Compliance
Office of the Vice-President (Research and International)

Human Ethics
208-194 Dafoe Road
Winnipeg, MB
Canada R3T 2N2
Phone +204-474-7122
Fax +204-269-7173

RENEWAL APPROVAL

May 28, 2013

MMSF

TO: **Cheryl Glazebrook**
Principal Investigator

FROM: **Stan Straw, Chair**
Education/Nursing R[redacted] (ENREB)

Re: **Protocol #E2012:05[redacted]**
"Optimizing Movement Performance with Altered Sensation: An Examination of Multisensory Inputs"

Please be advised that your above-referenced protocol has received approval for renewal by the **Education/Nursing Research Ethics Board**. This approval is valid for one year only.

Any significant changes of the protocol and/or informed consent form should be reported to the Human Ethics Secretariat in advance of implementation of such changes.

Appendix 8 - Ethics approval letter for study 5

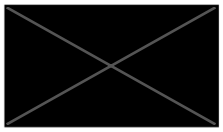
UNIVERSITY OF MANITOBA | Research Ethics and Compliance

Human Ethics
208-194 Dafoe Road
Winnipeg, MB
Canada R3T 2N2
Phone +204-474-7122
Email: humanethics@umanitoba.ca

PROTOCOL APPROVAL

TO: **Niyousha Motaza** **(Advisor: Cheryl Glazebrook)**
Principal Investigator

FROM: **Joseph Gordon, Chair**
Education/Nursing Research Ethics Board (ENREB)



Re: **Protocol #E2019:013 (HS22650)**
Effects of Upper Limb Tendon Vibration: A Neurophysiological and Behavioral Study

Effective: May 6, 2019 **Expiry:** May 6, 2020

Education/Nursing Research Ethics Board (ENREB) has reviewed and approved the above research. ENREB is constituted and operates in accordance with the current *Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans.*

This approval is subject to the following conditions:

1. Approval is granted for the research and purposes described in the application only.
2. Any modification to the research or research materials must be submitted to ENREB for approval before implementation.
3. Any deviations to the research or adverse events must be submitted to ENREB as soon as possible.
4. This approval is valid for one year only and a Renewal Request must be submitted and approved by the above expiry date.
5. A Study Closure form must be submitted to ENREB when the research is complete or terminated.
6. The University of Manitoba may request to review research documentation from this project to demonstrate compliance with this approved protocol and the University of Manitoba *Ethics of Research Involving Humans*.

Funded Protocols:
- **Please mail/e-mail a copy of this Approval, identifying the related UM Project Number, to the Research Grants Officer in ORS.**

Appendix 9 – Consent form for study 1

UNIVERSITY OF MANITOBA

FACULTY OF KINESIOLOGY AND RECREATION MANAGEMENT

319 Max Bell Centre
University of Manitoba
Winnipeg, MB R3T 2N2
Telephone (204) 474-8773
glazebro@cc.umanitoba.ca

INFORMED CONSENT FORM:

Optimizing movement performance with altered sensation: an examination of multisensory inputs

PRINICIPLE INVESTIGATOR: Dr. Cheryl Glazebrook
University of Manitoba
(204) 474-8773

INVESTIGATORS: Kayla Duna, Leah Harpelle, Alyson Gysel
Faculty of Kinesiology and Recreation Management
University of Manitoba
(204) 480-1487

Dr. Steven Passmore
School of Medical Rehabilitation
University of Manitoba
(204) 787-1899

SOURCE OF SUPPORT: Manitoba Medical Service Foundation Research Grant

This consent form, a copy of which will be left with you for your records and reference, is only part of the process of informed consent. It should give you the basic idea of what the research is about and what your participation will involve. If you would like more detail about something mentioned here, or information not included here, you should feel free to ask. Please take the time to read this carefully and to understand any accompanying information.

PURPOSE: We are interested in how disrupted sensory feedback influences how you reach to different objects.

DESCRIPTION: During the study, you will be asked to make a series of reaching movements to targets on a screen. An OPTOTRAK 3-D motion recording system will be used to record your finger and arm movements. For some trials we will attach surface electrodes to your forearm and use a machine called a *Constant Current Stimulator* to create a tingling feeling in your hand and arm. The tingling feeling will feel similar to when your hand or arm is "asleep". The experimenter will use an alcohol swab to clean the area on your forearm before the electrodes are attached. Prior to the experimental protocol the experimenter will examine your tactile sensation by lightly touching your hand and arm using lightweight nylon filaments. Sensory testing will be

repeated when your nerve is being stimulated. You will also be asked to fill out a brief demographics questionnaire that inquires about your age, gender, handedness, whether you wear glasses. The whole procedure will take less than one hour to complete.

RISKS AND BENEFITS: There are no evident risks inherent in the tasks you will perform but some of the tests may become repetitive. While this may be frustrating to you, there will always be an investigator with you to assist you and support you.

The surface electrode techniques can sometimes, but rarely, cause skin irritation from the alcohol swab or electrode gel. The electrical stimulation is not painful but you will experience a tingling sensation along the nerve in the forearm and fingers, or even a light twitch of the muscles in your hand as the nerves at the wrist sends electrical signals to make these muscles contract.

COSTS AND PAYMENTS: There are no fees or charges to participate in this study. A small honorarium will be provided.

CONFIDENTIALITY: Your information will be kept confidential. You will be referred to by a code number. All files containing identifying information will be stored in a locked cabinet separate from data with your code number. Only Kayla Duna, Leah Harpelle, Alyson Gysel, and Steven Passmore will have access to any lists that contain identifying information. Your coded raw data files will only be accessible by the investigators and will be destroyed 5 years after the completion of the study. All papers containing personal information will be shredded. All electronic files will be deleted. Any CDs or DVDs containing data will be physically destroyed. Dr. Glazebrook will delete and destroy all electronic data. All paper files will be deposited for confidential shredding in the Health, Leisure, and Human Performance Main Office (Max Bell 307) by Dr. Glazebrook.

VOLUNTARY CONSENT: If you do not wish to participate in the study, you are free to leave without consequence and we thank you for your consideration. Your signature on this form indicates that you have understood to your satisfaction the information regarding participation in the research project and agree to participate as a subject. In no way does this waive your legal rights nor release the researchers, sponsors, or involved institutions from their legal and professional responsibilities. You are free to withdraw from the study at any time, and /or refrain from answering any questions you prefer to omit, without prejudice or consequence. Your continued participation should be as informed as your initial consent, so you should feel free to ask for clarification or new information throughout your participation.

The University of Manitoba Research Ethics Board(s) and a representative(s) of the University of Manitoba Research Quality Management / Assurance office may also require access to your research records for safety and quality assurance purposes.

This research has been approved by the Education/Nursing REB. If you have any concerns or complaints about this project you may contact any of the above-named persons or the Human Ethics Coordinator (HEC) at 474-7122. A copy of this consent form has been given to you to keep for your records and reference.

If you would like to be contacted about other opportunities to participate in future studies please provide your preferred contact information on the line below. Your participation in any future studies will include an informed consent process like the present one. We will not share your information with anyone or use the information for any other purpose.

Preferred Contact Information: _____

If you would like to receive general summary of the results from this study when it is completed, please complete your email or mailing address below:

Email Address: _____

Mailing Address: _____

_____

_____

_____
Printed Name of Participant

_____ _____
Signature of Participant Date

_____
Printed Name of Investigator

_____ _____
Signature of Investigator Date

Appendix 10 – Consent form for study 2

UNIVERSITY OF MANITOBA

FACULTY OF KINESIOLOGY AND RECREATION MANAGEMENT

319 Max Bell Centre
University of Manitoba
Winnipeg, MB R3T 2N2
Telephone (204) 474-8773
glazebro@cc.umanitoba.ca

INFORMED CONSENT FORM:

Optimizing movement performance with altered sensation: an examination of multisensory inputs

PRINICIPAL INVESTIGATOR: Dr. Cheryl Glazebrook
University of Manitoba
(204) 474-8773

INVESTIGATORS: Kelsey Brown, Kayla Duna, Leah Harpelle, Alyson Gysel, Ran Zheng
Faculty of Kinesiology and Recreation Management
University of Manitoba
(204) 480-1487

Dr. Steven Passmore
School of Medical Rehabilitation
University of Manitoba
(204) 787-1899

SOURCE OF SUPPORT: Manitoba Medical Service Foundation Research Grant

This consent form, a copy of which will be left with you for your records and reference, is only part of the process of informed consent. It should give you the basic idea of what the research is about and what your participation will involve. If you would like more detail about something mentioned here, or information not included here, you should feel free to ask. Please take the time to read this carefully and to understand any accompanying information.

PURPOSE: We are interested in how disrupted sensory feedback influences how you reach to different objects.

DESCRIPTION: During the study, you will be asked to make a series of reaching movements to targets on a screen. An OPTOTRAK 3-D motion recording system will be used to record your finger and arm movements. For some trials we will attach surface electrodes to your forearm and use a machine called a *Constant Current Stimulator* to create a tingling feeling in your hand and arm. The tingling feeling will feel similar to when your hand or arm is "asleep". The experimenter will use an alcohol swab to clean the area on your forearm before the electrodes are attached. Prior to the experimental protocol the experimenter will examine your tactile sensation by lightly touching your hand and arm using lightweight nylon filaments. Sensory testing will be

repeated when your nerve is being stimulated. You will also be asked to fill out a brief demographics questionnaire that inquires about your age, gender, handedness, whether you wear glasses. The whole procedure will take less than one hour to complete on two separate days (total of 2 hours).

RISKS AND BENEFITS: There are no evident risks inherent in the tasks you will perform but some of the tests may become repetitive. While this may be frustrating to you, there will always be an investigator with you to assist you and support you.

The surface electrode techniques can sometimes, but rarely, cause skin irritation from the alcohol swab or electrode gel. The electrical stimulation is not painful but you will experience a tingling sensation along the nerve in the forearm and fingers, or even a light twitch of the muscles in your hand as the nerves at the wrist sends electrical signals to make these muscles contract.

COSTS AND PAYMENTS: There are no fees or charges to participate in this study. A small honorarium will be provided.

CONFIDENTIALITY: Your information will be kept confidential. You will be referred to by a code number. All files containing identifying information will be stored in a locked cabinet separate from data with your code number. Only Kayla Duna, Leah Harpelle, Alyson Gysel, and Steven Passmore will have access to any lists that contain identifying information. Your coded raw data files will only be accessible by the investigators and will be destroyed 5 years after the completion of the study. All papers containing personal information will be shredded. All electronic files will be deleted. Any CDs or DVDs containing data will be physically destroyed. Dr. Glazebrook will delete and destroy all electronic data. All paper files will be deposited for confidential shredding in the Health, Leisure, and Human Performance Main Office (Max Bell 307) by Dr. Glazebrook.

VOLUNTARY CONSENT: If you do not wish to participate in the study, you are free to leave without consequence and we thank you for your consideration. Your signature on this form indicates that you have understood to your satisfaction the information regarding participation in the research project and agree to participate as a subject. In no way does this waive your legal rights nor release the researchers, sponsors, or involved institutions from their legal and professional responsibilities. You are free to withdraw from the study at any time, and /or refrain from answering any questions you prefer to omit, without prejudice or consequence. Your continued participation should be as informed as your initial consent, so you should feel free to ask for clarification or new information throughout your participation.

The University of Manitoba Research Ethics Board(s) and a representative(s) of the University of Manitoba Research Quality Management / Assurance office may also require access to your research records for safety and quality assurance purposes.

This research has been approved by the Education/Nursing REB. If you have any concerns or complaints about this project you may contact any of the above-named persons or the Human Ethics Coordinator (HEC) at 474-7122. A copy of this consent form has been given to you to keep for your records and reference.

If you would like to be contacted about other opportunities to participate in future studies please provide your preferred contact information on the line below. Your participation in any future studies will include an informed consent process like the present one. We will not share your information with anyone or use the information for any other purpose.

Preferred Contact Information: _____

If you would like to receive general summary of the results from this study when it is completed, please complete your email or mailing address below:

Email Address: _____

Mailing Address: _____

_____

_____

_____
Printed Name of Participant

_____ _____
Signature of Participant Date

_____
Printed Name of Investigator

_____ _____
Signature of Investigator Date

Appendix 11 – Consent form for study 5

UNIVERSITY OF MANITOBA

FACULTY OF KINESIOLOGY AND RECREATION MANAGEMENT

108 Frank Kennedy Centre
University of Manitoba
Winnipeg, MB R3T 2N2
Telephone (204) 474-8773
cheryl.glazebrook@umanitoba.ca

INFORMED CONSENT
Experiment II:
Effects of Tendon Vibration on Somatosensory Evoked Potentials and Motor Execution and Learning

Principal Investigator: Niyousha Mortaza
Program of Applies Health Sciences
(204) 480-1487
Mortazan@myumanitoba.ca

Advisor: Dr. Cheryl Glazebrook
Faculty of Kinesiology & Recreation Management
University of Manitoba
(204) 474-8773
cheryl.glazebrook@umanitoba.ca

Co-investigator: Dr. Steven Passmore
Faculty of Kinesiology & Recreation Management
University of Manitoba
Office: 179 Frank Kennedy Centre
Steven.Passmore@umanitoba.ca

Student Research Assistants: Quinn Malone, Jessica Sutton, Stephanie Tomy, Carrie Peters, Byron Banuik, Anthonia Aina, Liam Gaudet-Thompson
Faculty of Kinesiology & Recreation Management
University of Manitoba

This consent form, a copy of which will be left with you for your records and reference, is only part of the process of informed consent. It should give you the basic idea of what the research is about and what your participation will involve. If you would like more detail about something mentioned here, or information not included here, you should feel free to ask. Please take the time to read this carefully and to understand any accompanying information.

PURPOSE: We are interested in learning the effects of applying vibration over the tendons of the upper limb muscles on motor control and learning, and changes in the nervous system.

DESCRIPTION: First, you will be asked to fill out a brief demographics questionnaire that inquiries about information such as your age, gender, handedness, whether or not your vision and hearing are corrected (glasses, contact lenses, hearing aids). Also, an OPTOTRAK 3-D motion recording system will be used to record upper limb movements. In order to measure the movements, we will attach infrared sensors on the upper limb using medical tape. Depending on the study group that you are assigned to, two tiny vibration motors may or may not be placed over the tendons of your upper limb during the experiment. You will be asked to make a series of movements to different tactile (Velcro) and/or visual (e.g. LED lights) targets During, before, and after the movement tasks, you will also be assessed and asked about perceiving any illusory movement sensation. Moreover, tactile sensation testing will also be done before and after the 30-minutes period. With set-up this experiment will take about 1.5-2 hours.

RISKS AND BENEFITS: There are no evident risks inherent in the above-mentioned experiment. The movement task may become repetitive and you may experience boredom and/or mild muscle fatigue in your arms. While this may be frustrating, the investigator with you will provide breaks throughout.

Your participation in this study will help us investigate the effects of applying vibration over the tendons of the upper limb on the motor control and learning, and changes in the nervous system. The findings from this study will be applied to the design of a new rehabilitation device for individuals who have deficiencies in sensing the position of their joints as a result of conditions such as stoke, diabetes, aging, etc.

COSTS AND PAYMENTS: There are no fees or charges to participate in this study. However, you will receive $15 per session as honorarium for your participation at the end of the session.

CONFIDENTIALITY: Your information will be kept confidential. Once you begin the study your name, information, and results will be referred to by a code number. All files containing identifying information will be stored in a locked cabinet separate from data with your code number. Your files will only be accessible by Niyousha Mortaza, Dr. Cheryl Glazebrook, and the research assistants listed. Any identifying information will be destroyed by Dr. Glazebrook approximately seven years after the completion of the study (approximately in the year 2026). All papers containing personal information will be shredded. All electronic files will be deleted. Only Niyousha Mortaza, Dr. Cheryl Glazebrook and the research assistants listed will have access to any lists that contain identifying information.

DEBRIEFING: Upon completion of the study the experimenter will describe the research questions being considered. If you would like to know the results of the study, please indicate 'yes' on the consent form where indicated and the student research assistant will contact you with a summary of the findings in approximately 4 months.

DISSEMINATION: The results of the study will be presented at academic conferences, invited presentations at academic and other community groups. The results will also be published in peer-reviewed academic journals and in the final report of Niyousha Mortaza's dissertation.

VOLUNTARY CONSENT: If you *do not wish to participate* in the study or wish to withdraw from the study, you are free to leave without consequence at any point in time and we thank you for your consideration. If you wish to have your data removed from the study, you may ask for it within two weeks from the date of your participation.

Your signature on this form indicates that you have understood to your satisfaction the information regarding participation in the research project and agree to participate as a subject. In no way does this waive your legal rights nor release the researchers, sponsors, or involved institutions from their legal and professional responsibilities. You are free to withdraw from the study at any time, and /or refrain from answering any questions you prefer to omit, without prejudice or consequence. Your continued participation should be as informed as your initial consent, so you should feel free to ask for clarification or new information throughout your participation. If you choose to withdraw from the study you will still receive compensation for the time you have participated. The University of Manitoba may look at your research records to see that the research is being done in a safe and proper way.

A copy of this consent form has been given to you to keep for your records and reference.

This research has been approved by the Education/Nursing Research Ethics Board. If you have any concerns or complaints about this project you may contact any of the above-named persons or the Human Ethics Coordinator (HEC) at 474-7122 or humanethics@umanitoba.ca.

INFORMED CONSENT

Research Study: The Effect of dual tendon vibration on Somatosensory evoked potentials and perception of illusory movement

Signature of Participant_____ Date _____

Researcher/ Delegate's Signature _____Date _____

SUMMARY OF FINDINGS: Would you like to be contacted by a student research assistant with a summary of the overall findings of this study? YES NO

If yes, please complete the following:

Name: _____

Phone Number: _____

Email Address: _____
