THE EFFECTS OF PERIODIC VS APERIODIC MUSCLE TENDON VIBRATION ON STRETCH REFLEX CIRCUITRY: THE ROLE OF INTENT TO RESPOND TO A PERTURBATION.

by

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The following individuals certify that they have read, and recommend to the Faculty of Graduate and Postdoctoral Studies for acceptance, a thesis entitled:

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Abstract

When a muscle is mechanically stretched, a stereotypical EMG response known as the stretch response occurs. The stretch response can be subdivided into a short and long latency response. The short latency response is analogous to the tendon tap reflex, while the long latency response involves both spinal cord circuits and transcortical pathways. The short latency response is typically only modulated by peripheral factors such as the size of the perturbation. The long latency response, in addition to being modulated by peripheral factors, can also be modulated based on the participants motor task. For example, if a participant is asked to respond to the stretch as fast as possible, the amplitude of the long latency response increases which would help the participant complete the task.

If you apply mechanical vibration to a muscle tendon, it can also result in activation of the sensory receptors involved in the stretch response. This activation can cause a multitude of effects within the central nervous system, however one main effect that is of particular interest in this thesis is it causes a suppression of the stretch response. However, a few key features remain unknown as followed; how the vibration frequency characteristics and how a participant's intent to respond to the perturbation effect this suppression. Therefore, the purpose of the current thesis was to investigate if the same effects are present when a periodic vs an aperiodic vibration was used, and whether asking a person to respond the perturbation as fast as possible could modulate this suppression.

The key findings from this thesis were that the suppression did not depend on the vibration characteristics, as both periodic and aperiodic vibration resulted in similar amounts of suppression. Additionally, it was found that a participants intent to respond did not modulate the

amount of suppression seen. The findings from this thesis provide a more detailed understanding of the stretch response circuitry and the response to tendon vibration.

Lay Summary

When we move our limbs in space, the nervous system must account for many different factors to complete the movement correctly. One of the key factors is the interaction between the sensory information from our limbs and the motor output from the central nervous system. When a muscle is stretched, the nervous system automatically attempts to correct for the stretch by increasing the muscular activation of that muscle. This correction can also be modulated based on the current motor task. For example, if a participant is asked to respond to the stretch, the amplitude of the response can increase. Mechanical vibration, which activated peripheral sensory organs, over a muscle tendon is known to suppress this stretch response. The purpose of the current thesis was to provide a more detailed understanding of tendon vibration and the central nervous system interactions during stretch responses.

Preface

The data from the current thesis was collected in the Perceptual-Motor Dynamics Laboratory at the University of British Columbia, Vancouver campus. The protocol in this thesis was approved by the University of British Columbia behavioural research ethics board (H17-00145).

The project was led by Gregg Eschelmuller with guidance from the supervisory committee composed of Dr. J Timothy Inglis, Dr. Romeo Chua, and Dr. Mark Carpenter. Gregg Eschelmuller was responsible for all data collection, data analysis, and preparation of the current thesis document.

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List of Abbreviations

EMG: Electromyography

PAD: Primary Afferent Depolarization

HD: Homosynaptic Depression

FCR: Flexor Carpi Radialis

ECR: Extensor Carpi Radialis

FCU: Flexor Carpi Ulnaris

GTO: Golgi Tendon Organ

DNI: Do Not Intervene

Comp: Compensate

ANOVA: Analysis of Variance

EPSP: Excitatory Post-Synaptic Potential

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Dedication

I dedicate this thesis to my friends and family.

Chapter 1: Introduction

Abrupt stretch to an active muscle produces characteristic muscle responses, known as the short latency response (R1), followed by the long latency response. The long latency response is commonly divided into two subcomponents R2 and R3. When a muscle is stretched the sensory receptors located within the muscle, known as muscle spindles, are also stretched. The muscle spindles receive sensory innervation from group Ia and group II afferent nerve fibres (Banks et al., 1982). The short latency response is thought to be primarily mediated by monosynaptic and short polysynaptic Ia afferent spinal pathways, analogous to the tendon tap reflex (Burke et al., 1984; Pierrot-Deseilligny & Burke, 2012). The long latency response is thought to involve more complex pathways, with involvement from long spinal cord and supraspinal pathways. Additionally, the long latency response can be significantly modulated based on the participant's task or instruction set. Specifically, the long latency response can be modulated in amplitude to aid in the completion of said task (Pruszynski & Scott, 2012). For example, if a participant is instructed to resist a perturbation to the joint, the long latency response demonstrates an increase in amplitude.

It has been well established that single frequency tendon or muscle vibration causes a distinct depression of the monosynaptic stretch reflex. That is, during tendon vibration, a subsequent activation of the Ia afferents results in a smaller α-motoneuron response, relative to no vibration conditions (De Gail et al., 1966; Gillies et al., 1969). However, studies have typically investigated this phenomenon using tendon vibration of a single frequency. Single frequency or periodic tendon vibration of a tendon or muscle additionally produces robust proprioceptive illusions at the joint the muscle acts on (Goodwin et al., 1972; Inglis et al., 1991; Inglis & Frank, 1990). Interestingly, when a noisy or aperiodic frequency vibration was delivered to the Achilles

tendon, there was no evidence to suggest a postural illusion was evoked (Mildren et al., 2017). As tendon vibration is known to be a strong stimulus for the muscle spindle afferents (Roll et al., 1989), the lack of postural response with aperiodic vibration would suggest that the nervous system processes periodic afferent volleys differently than randomly dispersed afferent volleys.

Therefore, the main purpose of the current thesis is to investigate the frequency dependence (periodic vs aperiodic) of afferent volleys on stretch reflex circuitry and how a participant's intent to respond to a perturbation may influence the effect of these afferent volleys.

1.1 The Monosynaptic Stretch Reflex

The monosynaptic stretch reflex circuit involves the muscle spindle, Ia afferent, and the α-motoneuron (Lloyd, 1943; Lundberg & Winsbury, 1960). This pathway is typically divided into its afferent arc (muscle spindle and Ia afferent) and the efferent arc (α-motoneuron and muscle fibres). The muscle spindle is a sensory receptor located within the skeletal muscle and is primarily sensitive to changes in muscle length. The Ia afferents transmit this information from the muscle spindle and have connections to α-motoneurons through both monosynaptic and polysynaptic pathways, as well as projecting to subcortical and cortical areas in the central nervous system (Pierrot-Deseilligny & Burke, 2012). Therefore, when a skeletal muscle is stretched, there is an increased firing of the Ia afferents, which in turn excite the α-motoneuron pool of the muscle in which the spindle resides (Jankowska, 2015). The two common methodologies for testing this pathway are the tendon tap reflex (T-Reflex) and the Hoffman reflex (H-reflex). The T-reflex can be induced via a strong percussion to a skeletal muscle tendon, which will evoke a large response from the muscle spindles. The H-reflex involves electrical stimulation over a nerve, which predominantly activates group I fibres, and therefore bypasses the muscle spindle. While both pathways test the Ia afferent-α-motoneuron synapse,

one key difference is that any changes in the muscle spindle would have no influence on the H-reflex, while it can dramatically change the tendon reflex. However, direct comparisons between these two techniques can be difficult due to differences in the temporal characteristics and dispersion of the evoked volleys (Burke, Gandevia, & McKeon, 1983).

1.2 The Muscle Spindle

The muscle spindle is a sensory receptor located within skeletal muscle that lies in parallel to the skeletal muscle fibres. Muscle spindles contain modified muscle fibres, which are known as intrafusal fibres, and they contain several nuclei each. The intrafusal muscle fibres can be divided into nuclear bag fibres (1-2 per spindle), in which the nuclei are clustered in the central region, and the nuclear chain fibres (3-5 per spindle), in which the nuclei are arranged serially in the central region of the muscle spindle (Ovalle & Smith, 1972). The bag fibres can be further subdivided into bag_1 (dynamic) and bag_2 (static) fibres, which have both morphological and functional differences (Thornell et al., 2015). A single muscle spindle usually contains two bag fibres, one of each type. One key difference between bag_1 and bag_2 is the innervation from the sensory afferent neurons. There are two types of sensory endings that innervate the muscle spindle; the primary endings, which spiral around the central region of the intrafusal fibres, and the secondary endings, which innervate either side of the central region (Banks et al., 1982). The primary endings give rise to large group Ia afferent nerve fibres, while the secondary endings give rise to the smaller group II afferent nerve fibres. The dynamic bag_1 fibres are innervated by the Ia afferent, but not the group II afferents, while the static bag_2 fibres received innervation from both the Ia and group II afferents. The intrafusal chain fibres are additionally innervated by both the Ia and group II afferent nerve fibres. Muscle spindles additionally have contractile components in the polar ends, which receive motor innervation via the γ-motoneuron system,

also known as the fusimotor system. Activation of γ-motoneurons induces a contraction in the intrafusal fibres of the muscle spindle resulting in an increase in their stiffness. Similar to the afferent innervation, the fusimotor system can be subdivided into dynamic and static systems. Activation of the dynamic fusimotor afferents will increase the dynamic sensitivity of the primary endings through contraction of the bag_1 fibres, while activation of the static fusimotor system will increase the static sensitivity of both the primary and secondary endings through contraction of the bag_2 and chain fibres (Banks, 1981; Banks et al., 1982; Boyd et al., 1977).

In a passive muscle spindle (no γ-motoneuron innervation), the primary (Ia afferents) and secondary (group II) endings show distinct responses to a stretch (Hunt, 1990). Specifically, the primary endings show both a dynamic as well as a static response to the stretch, while the secondary endings primarily display a static response. During a ramp and hold stretch for example, the muscle spindle primary endings will display a high frequency discharge at the onset of stretch and a subsequent high frequency discharge near the end of the ramp stretch. This is followed by a slow decrease in firing frequency ending in a sustained firing at the new static length. The initial frequencies the primary endings reach scales with the velocity of the stretch, while the sustained firing scales with the amplitude of the stretch. Through these mechanisms, the primary endings can signal both the velocity and amplitude of a given stretch to a muscle. The secondary endings on the other hand, display very little dynamic response to the stretch, but will display a strong static response. That is, the secondary endings code poorly for velocity of a stretch, but code strongly for the amplitude of a stretch. However, it has been shown that some secondary endings are able to show significant dynamic sensitivity (Hunt & Ottoson, 1975).

The above description of the primary and secondary endings applies for situations with no γ-motoneuron innervation. The result of γ-motoneuron innervation either increases the dynamic

sensitivity or the static sensitivity of the muscle spindles. However, it has been shown that the effect of γ-motoneuron innervation during ramp and hold stretches can be sub-categorized into 6 different categories, ranging from purely dynamic to purely static (Emonet-Dénand et al., 1977). Therefore, the nervous system has the ability to fine tune the responses of the muscle spindle, to become more sensitive to the velocity of the stretch (dynamic), the amplitude of the stretch (static), or a combination of both.

1.3 Modulation of the Stretch Reflex

The monosynaptic stretch reflex pathway can be primarily modulated at three different sites: the muscle spindle, the Ia-α-motoneuron synapse, and the α-motoneuron. The sensitivity of the muscle spindle can be modulated based on the level of γ-motoneuron input (see section 1.2 for details). Therefore, if there is a change in the level of γ-motoneuron activity to the muscle spindles, for a given stretch, there can be very different muscle spindle responses. In felines, there is direct evidence that the γ-motor system can be modulated based on the task (locomotion) independently from the α-motoneuron system (Murphy, Stein, & Taylor, 1984; Prochazka, Hulliger, Zangger, & Appenteng, 1985). In humans, due to the inability to record from γ-motoneurons directly, there is only indirect evidence for independent γ-motoneuron modulation. For example, in situations when there is postural threat to balance, it has been suggested that there is an increase in the dynamic sensitivity of the muscle spindles (Horslen et al., 2013, 2018). Additionally, recordings from single Ia afferents has demonstrated that when participants are asked to relax or pay attention to imposed ankle joint movements, during the pay attention condition there is significant modulation of the Ia afferent response to the imposed movements (Hospod et al., 2007; Ribot-Ciscar et al., 2009).

The Ia afferent-α-motoneuron synapse is another main site for modulation of the monosynaptic stretch reflex circuit. Multiple control mechanisms can modulate the transmission of information from the Ia afferent to α-motoneuron, and therefore can alter the gain of the reflex response. The Ia afferent-α-motoneuron synapse can be primarily modulated by changing the amount of neurotransmitter that is released at the Ia afferent terminals. There are two main mechanisms that have been shown to produce this effect: presynaptic inhibition and homosynaptic depression. Homosynaptic depression is a mechanism in which previous activation of the Ia afferent fibres results in the depression of a subsequent Ia afferent volley to the α-motoneuron (Hultborn et al., 2004). Analysis of the quantal release of neurotransmitter has suggested that the depression seen with repetitive firing of the Ia afferents is likely due to a decrease in the probability of neurotransmitter release at the synapse (Kuno, 1964). The other factor is presynaptic inhibition due to primary afferent depolarization. The mechanisms causing presynaptic inhibition were initially debated; however, now the mechanism generally accepted is that primary afferent depolarization (PAD) is due to an axo-axonal synapse at the primary afferent terminal (Rudomin, 1990). Specifically, the PAD interneurons synapse with the primary afferent terminals, resulting in activation of γ-aminobutyric acid (GABA) receptors, which lead to increases in the conductance of Cl^- ions (Rudomin & Schmidt, 1999). This Cl^- efflux depolarizes the afferent terminal, which is thought to result in a decrease in the amplitude of the action potential, and therefore decreased neurotransmitter release. The PAD interneurons receive inputs from multiple sources, from both the peripheral afferents (primarily group I), as well as supraspinal structures (Pierrot-Deseilligny & Burke, 2012). The supraspinal control of presynaptic inhibition is a mechanism in which the nervous system can effectively gate the

peripheral afferent input onto α-motoneuron pools, specifically the monosynaptic Ia input. In humans, it has been demonstrated that at the onset of voluntary movement there is a decrease in the amount of presynaptic inhibition on the Ia afferents synapses of the α- motoneurons of the contracting muscle (Flexor carpi radialis) (Aymard et al., 2001). Therefore, in normal physiological situations, the central nervous system can selectively control the gain of presynaptic inhibition depending on the motor task.

Lastly, the excitability of the α-motoneuron itself can be manipulated. The changes in excitability in the α-motoneuron can either come from peripheral afferent sources, or descending input from supraspinal structures. If there are any changes to α-motoneuron pool excitability, this could dramatically change the output of the α-motoneuron pool for a given input. Therefore, in studies investigating Ia afferent pathways, it is critical to control for background α-motoneuron pool activity. In humans, a way to control for this is for participants to maintain a background contraction that can be monitored, either via EMG or force output. In this way, it is possible to essentially set the α-motoneuron pool level and control this across trials or conditions. One exception to this is during fatigue; in this situation, EMG and force will not have the same relation as when the participant is not fatigued.

1.4 Muscle Responses to Mechanical Perturbations

Abrupt perturbation to an active muscle produces characteristic muscle responses, known as the short latency response, followed by the long latency response. The short latency response is thought to be primarily mediated by the monosynaptic and short polysynaptic Ia afferent spinal pathways, analogous to the tendon tap reflex (described in section 1.1). However, the long latency response is thought to involve more complex pathways, with involvement from long

spinal cord pathways, supraspinal structures, and transcortical loops. The short latency response typically refers to responses that occur between ~25-50ms, while the long latency response typically refers to responses that occur between 50-100ms, however these values will change depending on the muscle tested. These characteristic short and long latency responses were first shown in a study investigating the muscle response to a sudden extension of the elbow (Hammond, 1955). The short latency response can typically only be modulated based on peripheral factors, such as the amount of preload (background activation) or magnitude of the perturbation. As the level of background motor output increases, the size of the response increases, a phenomenon known as automatic gain compensation (Matthews, 1986). Additionally, as the size of the perturbation increases, and therefore the magnitude of the Ia afferent volley, the response also increases (Calancie & Bawa, 1985). The long latency response however is influenced by the factors mentioned above, while additionally being influenced by the task instruction or goal of the participant (Calancie & Bawa, 1985; Pruszynski et al., 2011). These two characteristics of the long latency response have been termed the load dependence, referring to the changes with increasing perturbation size, and the task dependence, referring to the changes with the task that the participant is attempting to perform.

One common paradigm that has been used to characterize the instruction dependence of the long latency response compares differences between a “do not intervene” and a “compensate” instruction set. In the “do not intervene” instruction set, participants are instructed to not voluntarily intervene with the perturbation, while in the “compensate” instruction set, participants are instructed to respond to the perturbation as fast as possible. The general premise is that as the task changes for the participant, the nervous system is able to modulate the amount of long latency EMG activity. In the “do not intervene/compensate” paradigm, the short latency

response is typically unaffected, while there is an increase in the amount of EMG activity during the long latency period during the compensate task (Calancie & Bawa, 1985; Crago et al., 1976). As the participants are trying the respond as fast as possible to this perturbation, this increase in EMG activity in the agonist muscle would be beneficial for the participant to complete the task. Additionally, if the participants are asked to "let go" when they receive a perturbation, they are able to suppress the EMG activity during the long latency period (Calancie & Bawa, 1985; Colebatch et al., 1979; Rothwell et al., 1980).

The short and long latency muscle responses have been further studied at the single motor unit level (Calancie & Bawa, 1985). One key finding from this study was that the probability of a single motor unit to respond in either the short or long latency period depended on if there was a tonic discharge or not. Specifically, when a single motor unit had a background discharge, it would respond predominantly during the short latency period, while if it did not have a background discharge, it would respond predominantly in the long latency period. Additionally, if a single motor unit responded during the short latency period, it was unlikely to also respond during the long latency period. This finding consolidated previous literature in non-human primates that suggested that different motor units preferentially responded to the short latency compared the long latency response (Bawa & Tatton, 1979). Calancie and Bawa, (1985) have suggested that the differences in results seen are because in the non-human primate, α-motoneurons were never studied in both tonic and phasic conditions. They have concluded that the tonic firing motor units are more likely to respond during the short latency period as they are already at or very close to threshold at the time of the Ia EPSPs, while units that are not tonically firing are not brought to threshold during the short latency period, but the temporal summation of the EPSPs in the long latency period is enough to generate a response.

Calancie and Bawa (1985) also investigated how the prior instruction to the participant may influence the responses of the α-motoneurons during the stretch response. The results described above were for the "do not intervene" condition, when the participant was asked not to intervene with the perturbation. Interestingly, in the condition where participants were asked to respond to the perturbation as fast as possible, unlike in the do not intervene condition, motor units that responded during the short latency period were also able to respond in the long latency period. The authors have used this finding to argue that the long latency response must have supraspinal input and cannot alone be described purely by spinal circuits. This could either mean that the Ia afferent information traverses a transcortical loop, or travels through a long spinal cord loop that receives supraspinal input. The mechanisms underlying the long latency response and its modulation have been extensively studied. As described above, a common paradigm to study modulation has been instructing participants to "resist" the perturbation (or compensate), which causes a characteristic increase in the long latency response amplitude. However, it has also been shown that modulation of the long latency response can account for orientation of the arm (Weiler et al., 2018), scale with the intended movement distance (Pruszynski et al., 2008), and has been demonstrated to display an internal model of the limb (Kurtzer et al., 2008)

1.5 Receptors Activated by Vibration

Tendon vibration has been shown to cause distinct proprioceptive illusions at a joint the vibrated muscle acts on (Goodwin et al., 1972; Inglis et al., 1991; Inglis & Frank, 1990). Specifically, it produces the illusion that the vibrated muscle is lengthening. Due to these illusions, the sensory receptors activated by tendon vibration became of interest to researchers looking to understand the sensory origins of proprioception. Using microneurography, the study of the response of single sensory receptors to vibration has been possible. The responses of

sensory receptors to tendon vibration have been studied extensively in both active and passive muscles. In a passive muscle, when the tendon is vibrated with frequencies between 20-220 Hz, both the muscle spindle primary endings and the secondary endings have been shown to respond strongly, with the primary typically being more sensitive to vibration compared secondary endings (Burke et al., 1976b) . If the muscle length did not change, the response of a receptor was consistent across trials and the duration of the vibration. Most spindle endings were able to be driven in a one-to-one ratio until a certain limiting discharge rate was reached, and then the afferents would drop to a subharmonic of the vibration frequency. The majority of muscle spindle primary endings were able to be driven in a one-to-one ratio above 50Hz, with some reaching discharge frequencies of 220 Hz. The secondary endings typically could not be driven one-to-one to as high frequencies as the primary endings, with 5/13 not being able to follow frequencies above 50 Hz. These authors have also been able to show that attentive state or reinforcement maneuvers were not able to modify background spindle discharge rates. Lastly, in the passive muscle three Golgi tendon organs were also able to respond, however two only responded at subharmonics, and the third responded at one-to-one or a subharmonic when the muscle was in a stretched state. Therefore, in a passive state, the muscle spindle endings respond robustly to tendon vibration, while the GTOs are not strongly responsive. The responses of muscle spindles have also been studied during voluntary contraction (Burke, Hagbarth, Löfstedt, & Wallin, 1976a). One key finding was that the responses of the muscle spindle endings was enhanced during a voluntary contraction, which has been attributed to α-γ motoneuron coactivation. Specifically, the γ-motoneuron activation was strong enough to counteract the unloading of the muscle spindle sensory region caused by the extrafusal fibres. It has been further shown that during a contraction, the Ib afferent fibres are strongly responsive to the

tendon vibration, and in some cases can be driven in a 1:1 ratio with the vibration cycle (Fallon & Macefield, 2007). Taken together, it is clear that tendon vibration generates responses in both the muscle spindles and the Golgi tendon organs that reside in that muscle.

1.6 Vibration Induced Suppression of the Monosynaptic Stretch Reflex

It has been clearly shown in multiple studies that tendon vibration induces a suppression of the monosynaptic stretch reflex. De Gail et al. (1966) demonstrated that when mechanically vibrating the tendon there is a clear depression of the tendon tap reflex in both the lower and upper limbs (De Gail et al., 1966). The authors found that increasing the frequency of vibration above 20 Hz did not cause a further depression, and in some participants this depression was even diminished. There were large variations in the time course of the depression seen, with some participants showing a depression to less than 5% of the control reflex within seconds of the onset, whereas in others, the maximal depression was not reached for minutes. This depression was additionally demonstrated using electrical stimulation (H-reflex). Using this technique, it was shown that the depression of the reflex started at 40-100ms after the onset of vibration and increased thereafter. The authors have additionally shown, through patient populations with spinal cord injury, that this depression does not require supraspinal input. It was suggested that the results seen in this paper were due to continued activation of the group I afferent fibres (primarily Ia). However, in some cases a tonic contraction developed due to the vibration, and therefore the activation of Ib fibres cannot be excluded. Additionally, it was demonstrated that re-enforcement through a Jendrassik manoeuvre was able to overcome some of the depression seen. These findings have been replicated using Achilles tendon reflexes and H-reflexes (Arcangel et al., 1971). Using microneurography, it has been shown that during tendon vibration, the muscle spindle response to a tendon tap is reduced (Burke et al., 1976b).

The two explanations that have been used to describe this phenomenon is that the tendon taps could have been delivered during the unloading phase of the vibration cycle when the spindle ending was less responsive or that it occurred during the discharge phase of the cycle, and there was an occlusion between the tendon tap response and the vibration response. In summary, during tendon vibration, there may be a reduced ability of the muscle spindle to respond to a stretch and the α-motoneuron pool may be less responsive to a given Ia afferent input.

The phenomena of the suppression of the monosynaptic stretch reflex due to tendon vibration was further studied in a feline model (Gillies et al., 1969). First, Gillies et al. confirmed previous findings by demonstrating that the monosynaptic stretch reflex was depressed to less than 30% of control reflex levels by vibration of the Achilles tendon. They found no differences in intact anaesthetized, decerebrate and spinal animals, confirming that supraspinal structures are not required for the suppression. The H-reflex was reduced in amplitude across a wide range of frequencies from 50-500 Hz vibration. Additionally, when an F-wave was present (indicator for α-motoneuron excitability), there were no significant changes, indicating that general α-motoneuron excitability was unchanged by vibration. The authors were able to demonstrate that one of the mechanisms responsible for the vibration-induced suppression of the monosynaptic stretch reflex was presynaptic inhibition of the Ia afferents due to primary afferent depolarization. This was further confirmed by the administration of picrotoxin (a drug known to abolish presynaptic inhibition (Eccles et al., 1963), which eliminated the reflex suppression that was observed.

The finding that vibration induces a suppression of the stretch reflex has been studied extensively; however, the mechanisms are still not fully understood in humans. In addition to tendon taps and H-reflexes this effect has also been seen when a muscle is mechanically

perturbed to produce both short and long latency responses. The results are somewhat varied in these studies. In the lower limb (Soleus), it has been shown that both the short latency and long latency response were reduced in amplitude during tendon vibration, while the latency was increased (Bove et al., 2003). The authors suggest that the results seen are likely a combination of presynaptic inhibition of the Ia terminals, and a "busy-line" effect reducing the Ia afferent input into the spinal cord. One interesting finding of this study was that they were able to demonstrate no changes in α-motoneuron pool gain. In the upper limb (Flexor carpi radialis), it has been shown that only the short-latency response was affected by vibration, while the longer latency responses were unaffected (Hendrie & Lee, 1978). Additionally, Hendrie and Lee were able to provide evidence (through radial nerve block) that the antagonist muscle spindles likely do not contribute to the depression of the stretch reflex. However, the participants in this study were asked to respond to the perturbation as fast as possible, which is known to modulate the activity of the long-latency response. Since the vibration-induced suppression can be diminished or even abolished with a Jendrassik maneuver, it is possible that the intent to respond was sufficient to diminish the long latency effects seen in the upper limb. One study which contradicts previous findings has shown that during acute vibration (1-5 seconds), there are no changes in amplitude of a patellar tendon tap (Pope & DeFreitas, 2015). However, this study removed the vibration immediately before the tendon tap, and additionally performed the Jendrassik maneuver, which is known to reduce the vibration-induced suppression (De Gail et al., 1966). Therefore, the lack of suppression seen in this study may be at least in part due to facilitation from the Jendrassik maneuver.

The main mechanisms that could cause a depression of the stretch reflex during tendon vibration are direct influences on the Ia afferent fibre transmission of a stimulus and changes in

the α-motoneuron pool response to a given Ia afferent input. Changes in the Ia afferent transmission of the stretch could be due to changes in presynaptic inhibition, γ-motoneuron activation, hyperpolarization of the Ia afferents, or homosynaptic depression. There is direct evidence in felines that during tendon vibration there is significant primary afferent depolarization, presumably due to presynaptic inhibition of the Ia afferents (Gillies et al., 1969). However, evidence of the presence of presynaptic inhibition of the Ia afferent fibres does not exclude other potential contributing mechanisms. Changes in the muscle spindle response, due to changes in the level of γ-motoneuron activity seems unlikely as qualitatively similar results are seen with both H-reflex and T-reflexes (Arcangel et al., 1971; De Gail et al., 1966). Since the H-reflex bypasses the muscle spindle, changes in γ-motoneuron activation could not describe these results. Hyperpolarization of the Ia afferents occurs after repetitive action potentials in the Ia afferents, which in turn results in an increase in the threshold to electrical stimulation. However, it is thought that this may actually increase the amount of neurotransmitter released at the Ia terminal (Pierrot-Deseilligny & Burke, 2012), and therefore would not explain the depression observed. Homosynaptic depression however could explain the results seen, particularly in a passive muscle. Both H-reflex and tendon reflexes would be susceptible to homosynaptic depression and could explain why both are depressed during tendon vibration. However, during a voluntary contraction, homosynaptic depression can be reduced (McNulty et al., 2008). It has been suggested the reason for these results is that during a contraction there is a background level of homosynaptic depression, and therefore it cannot increase as much as it can in a passive muscle state (Pierrot-Deseilligny & Burke, 2012). However, during tendon vibration there are likely large amounts of Ia afferent firing, and therefore, an increase in homosynaptic depression. Overall, multiple mechanisms could contribute to the suppression of the Ia afferent pathway

during tendon vibration, but presynaptic inhibition and homosynaptic depression seem to be the most likely contributors.

Input from antagonist Ia afferents (reciprocal inhibition) or from agonist Ib afferents may also reduce the α-motoneuron response to a given Ia input. In the upper limb (FCR), it was shown that the vibration-induced suppression was the same when the antagonist muscle nerve was blocked, indicating that reciprocal inhibition is not the cause of the suppression seen (Hendrie & Lee, 1978). Additionally, the Ib afferents typically only respond to vibration when the muscle is contracting (Burke et al., 1976a). However, during a contraction the inhibition from the Ib afferent reflex pathway to the contracting muscle can be significantly suppressed (Fournier et al., 1983). Since the effects are seen in both active and passive muscles, Ib afferents likely do not play a major role. Lastly, in both human and feline models, it has been demonstrated that there are little to no changes in α-motoneuron pool excitability (Bove et al., 2003; Gillies et al., 1969). Therefore, while direct α-motoneuron mechanisms could play a role, the current evidence suggests that it is not the major contributor.

1.7 Summary

While the suppression of the stretch reflex circuit with tendon vibration has been consistently demonstrated, several questions remain unanswered. Suppression of the reflex has been demonstrated with numerous different frequencies; however, it has never been investigated using aperiodic frequency vibration. That is, are the effects still present when the vibration is aperiodic, and not periodic? Single-frequency (periodic) vibration would cause large afferent volleys to synchronize and enter the spinal cord at the same time, while aperiodic vibration would most likely cause more sporadic Ia afferent inputs. Large synchronized afferent volleys would increase the probability that the motor output becomes synchronized. It has been

demonstrated that single frequency tendon vibration does cause increases in the firing probability of α-motoneurons during the vibration cycle (Burke & Schiller, 1976; Mildren, Peters, Carpenter, Blouin, & Inglis, 2019). However, the single motor units did not show large amounts of non-linear phase locking (Mildren et al., 2019). That is, while the afferent volleys produced by vibration did influence the probability of α-motoneuron firing, it did not lock the α-motoneurons to the vibration cycle. This lack of non-linear phase locking is likely due to increases in presynaptic inhibition during the vibration, and therefore a reduction in the influence of the Ia afferents on α-motoneuron firing. During normal physiological conditions, synchronizing motor output to a periodic afferent input would be detrimental to completion of the task as it would result in large force fluctuations in phase with the synchronized output. It could be argued therefore, that the suppression of the Ia afferent input onto the α-motoneuron pool during tendon vibration is functional in origin to reduce the probability of phase locking motor output. Therefore, if the vibration (and subsequent afferent volleys) were aperiodic in nature, they would not increase the probability of motor neuron synchronization and therefore may not induce the same amount of suppression seen.

While it has been shown that the Jendrassik manoeuvre can reduce the amount of suppression of the stretch reflex vibration (De Gail et al., 1966), the ability of the central nervous system to modulate this depression has not been fully studied. Hendrie and Lee (1978) have demonstrated that when a participant is asked to resist the perturbation there were no changes in the long latency responses, but there was still a suppression of the short latency response. However, in this study they did not test participants in both a “do not intervene” and a “resist” or “intervene” paradigm. Therefore, it is unknown if during a do not intervene condition if the long latency response is affected similarly by tendon vibration. Additionally, in a “compensate” or

"resist" paradigm can the vibration induced suppression of the short latency response be reduced?

1.8 Purpose and Hypotheses

Therefore, the purpose of the current study was to investigate the periodic dependence (periodic vs aperiodic) of vibration-induced suppression of the stretch reflex, and whether or not a participant's intent to respond to a perturbation may influence the stereotypical suppression seen. It was hypothesized that when the vibration and subsequent afferent volley are aperiodic, there would be less or no suppression of the stretch reflex, as this would not increase the probability of phase locking the motor output. It was additionally hypothesized that with an intent to respond, there would be a reduction of the vibration-induced suppression in both the short and long latency responses.

Chapter 2: Methods

2.1 Participants

15 participants (age: 24.7 ± 3.75 years), free of any neurological or musculoskeletal disorders were recruited to participate in this study. Ethics was approved through the University of British Columbia behavioural research ethics board (H17-00145). Informed written consent was obtained from all subjects. Participants were renumerated $10 for their participation.

2.2 Set Up

Participants were seated in a height adjustable chair, with their right elbow flexed at ~100˚ and their wrist secured into an apparatus, which prevented movement of the forearm, but allowed for wrist flexion and extension (Figure 1). Their hand was placed so that the wrist joint aligned with a manipulanda rotational axis, which was connected to a torque motor (Aeroflex, TQ 82W). The torque motor was driven via a motor amplifier, driven by an analog signal from a Cambridge Electronic Design data acquisition board, generated in Spike2 software (Cambridge Electronics Design, Cambridge, UK). Participants' metacarpophalangeal joints were aligned with a metal handle, connected to the motor shaft. Surface electromyography (EMG) electrodes were placed over flexor carpi radialis (FCR), flexor carpi ulnaris (FCU), and extensor carpi radialis (ECR) muscle bellies. EMG was collected using bipolar pre-amplified surface electrodes connected to an external amplifier (model DS-80; Delsys, Natick, MA). EMG was amplified at 3K and bandpass filtered between 20-450 Hz. Signals were sampled at 2000 Hz in Spike2 (Cambridge Electronic Designs, Cambridge, UK). An ~1-cm diameter probe attached to a linear motor (Ling Dynamics V203 Vibrator, Ling Electronics) was positioned against the right FCR tendon (Figure 1). An analog signal generated from Spike2 was sent from the data acquisition board and amplified via a motor amplifier (LPA 100 Amplifier) and sent to the linear motor.

Probe contact force was recorded using a force transducer (Honeywell, Model 31) attached in series with the end of the probe. An oscilloscope monitor was placed in front of the participants which gave online information about wrist joint angle from a potentiometer (model 6637S-1-103, Bourns, Riverside, CA).

2.3 Protocol

Participants underwent a series of rapid (150ms) wrist extension perturbations to generate muscle stretch responses in the wrist flexor muscles. There were 8 conditions with 25 perturbations per condition, resulting in a total of 200 perturbations. Each perturbation began with a slow ramp (500ms) to a preload of 0.25 newton meters (Nm) which stayed on until after the extension perturbation. Participants were asked to hold the wrist joint angle at ~10 degrees of wrist flexion defined by aligning a vertical red line with a marking on the oscilloscope monitor. A 1.5 Nm perturbation occurred randomly 2-3 seconds after the preload reached 0.25 Nm. Stretch responses were generated in 2 separate prior instruction sets for the participant. The instruction sets were as follows; “Do not intervene” (DNI) and “Compensate” (Comp). In the do not intervene condition, participants were asked to not intervene with the perturbation, while in the compensate condition they were asked to respond to the perturbation with a flexion movement as fast as they can. Participants performed the “Do not intervene” and “Compensate” conditions with no vibration, 20 Hz vibration, 100 Hz vibration, and aperiodic (noisy) vibration, which was composed of white noise bandpass filtered between 20-80 Hz (see Figure 2 for time series of signals). The periodic vibration frequencies were chosen to control for the highest and lowest frequencies within the aperiodic signal. The instruction set-vibration pairs were presented in a blocked manner (25 trials per block). Participants either completed all the “compensate” or the “do not intervene” blocks first, and this was counterbalanced across participants. Within each

instruction set the vibration blocks (25 trials) were randomized. After each vibration block participants were given a 1-2-minute break where they could remove their hand from the apparatus if they wanted. Between each instruction set participants were given a 5-minute break. Before each instruction set block, participants did 5-10 practice trials to ensure they could complete the task properly. Additionally, before any testing, participants were given the opportunity to experience the perturbations and all the vibration conditions. A diagrammatic representation of the protocol is displayed in Figure 3.

2.4 Analysis

Data analysis was conducted offline using MATLAB (Mathworks, Massachusetts, USA). EMG was DC bias removed, full-wave rectified, and averaged 250ms before to 500ms after the start of the perturbation. Ensemble averages were then created for each participant for each condition (25 trials per condition). To investigate latency differences between conditions, timing of the EMG responses was calculated based on the ensemble averages. Mean and standard deviation (SD) were calculated for the baseline EMG from -200 to 0ms relative to the perturbation onset. The short latency response onset was determined as the point at which the EMG increased above 2 SD above baseline levels and stayed above for at least 3ms. As the short and long latency response commonly merge, the same statistical criteria was not used to determine the onset of the long latency response as was used with the short latency response. Therefore, the onset of the long latency response was determined as the lowest local minimum in the EMG ensemble occurring around between 45 and 60ms. However, this value should be interpreted with caution, as there was not always a clear distinction between the short and long latency responses and sometimes multiple local minima could be present within the time range. As voluntary activation can overlap with the end of the long latency response, the end of long

latency response was determined where EMG activity returned to below 2 SD and stayed below for at least 3ms in the DNI condition.

To analyze the magnitude of the short and long latency response, the EMG was divided into 3 epochs: R1 (25-50ms), R2 (50-75ms), and R3 (75-100ms). R1 corresponds to the short latency response, while R2 and R3 correspond to the long latency response. To determine total EMG activity between conditions, integrals for R1, R2, and R3 were calculated on a trial-by-trial basis. The integral for the background activation was taken from -100 to 0ms relative to perturbation onset and divided by 4, resulting in an average for a 25ms window. R1, R2, and R3 integrals were then normalized by the background integral. Therefore, a value of 1 corresponds to a value equal to the background activation, and any value above 1 would correspond to more activation than the background. The data were then averaged across participants and compared between conditions. To investigate the level of force into the tendon for each vibration condition, the mean value from the load cell was determined from -1000 to 0ms for each trial and averaged for each condition and compared across conditions.

2.5 Statistical Analysis

All statistical analyses were completed in JASP, Version 0.14.1. To determine if background EMG was different between conditions, the EMG integrals were analyzed using a two-way repeated measures ANOVA, with factors intent (do not intervene; compensate), and vibration (no vibration; 100 Hz; 20 Hz; Noisy). To examine differences in EMG responses the normalized integrals and latencies for each epoch were submitted to separate two-way repeated measures ANOVAs, with factors intent (do not intervene; compensate) and vibration (no vibration, 100 Hz, 20 Hz, and Noisy). To determine if background levels of force were different between conditions, the mean values of the force were analyzed using a two-way repeated

measures ANOVA, with factors intent (do not intervene; compensate), and vibration (no vibration; 100 Hz; 20 Hz; Noisy). Statistical significance was set at $p < 0.05$ for all measurements and a Greenhouse-Geisser adjustment was applied when sphericity was violated. Uncorrected degrees of freedom are reported in the text. Post-hoc pairwise comparisons to decompose main effects and interactions were calculated using the Bonferroni method.

Chapter 3: Results

3.1 Background EMG Activation

The background FCR EMG activation (100ms prior to stretch) was found to be statistically different between vibration conditions [F (3, 42) = 5.384, p = 0.003, η_p^2 = 0.278], with no main effect or interactions with the instructions set (p > 0.05). Bonferroni adjusted pairwise comparisons indicated that the background EMG for the 100 Hz vibration was significantly higher compared to the no vibration condition (p = 0.045) but was not different from the 20 Hz vibration condition (p = 0.059) or the noisy vibration condition (p = 0.676). Specifically, the 100 Hz vibration resulted in an ~18% increase in background activation compared to control. Additionally, 20 Hz and noisy vibration were not significantly different from control (p > 0.05). To further investigate these differences, the analysis was re-run to compare the background EMG for the 2 seconds prior to the perturbation. As with the 100ms prior, there was a statistically significant effect of vibration [F (3, 42) = 4.189, p = 0.011, η_p^2 = 0.230], with no main effect of intent or interaction (p >0.05). While there were no significant differences between vibration conditions in the Bonferroni adjusted pairwise comparisons, qualitatively a similar trend in the data was present, with 100 Hz having higher values compared to the control (no vibration), with no noticeable difference when comparing 100 Hz to 20 Hz or noisy vibration.

3.2 Group EMG Amplitudes

3.2.1 Instruction Set

To investigate the effects of instruction set on the muscle response to stretch, the FCR EMG integrals for the compensate instruction set were compared with the do not intervene

instructions set. The results indicate that the participants' instruction set significantly modulated the EMG amplitude in R3 [F (1, 14) = 8.309, p = 0.012, η_p^2 = 0.372], but not in R2 [F (1, 14) = 4.390, p = 0.055, η_p^2 = 0.239] or R1 [F (1, 14) = 2.832, p = 0.115, η_p^2 = 0.168]. Specifically, the amplitude in the R3 (75-100ms) EMG response during the compensate instruction set increased to ~2.4 times that of the do not intervene instruction set (Figure 4). While the amplitude in R2 was consistently higher in the compensate compared to the do not intervene condition, this did not reach statistical significance (p = 0.055). Additionally, this increase in EMG amplitude in the compensate instruction set was not influenced by tendon vibration, as seen as no interaction in the two-way ANOVA for any epoch.

3.2.2 Vibration

The data comparing the different vibration conditions indicated that tendon vibration resulted in a significant reduction in the amplitude of the FCR EMG response to the wrist extension perturbation for the R1 [F (3, 42) = 15.108, p < 0.001, η_p^2 = 0.519], R2 [F (3, 42) = 13.050, p < 0.001, η_p^2 = 0.482] and R3 [F (3, 42 = 3.585, p = 0.021, η_p^2 = 0.204] epochs (Figure 5). This reduction in amplitude was not influenced by the participant instruction set for any epoch, as indicated by the lack of significant interactions between vibration and instruction set (p > 0.05). Bonferroni adjusted pairwise comparisons for R1 and R2 epochs indicated that 100 Hz, 20 Hz, and noisy vibration all resulted in significant reductions in the EMG amplitude compared to control (no vibration), and that the vibration conditions were not significantly different between each other (Table 1; Figure 5). Specifically, R1 was decreased to ~75% of control in the 100 Hz condition, ~72% of control in the 20 Hz condition, and ~70% of control in the noisy condition. In R2, the decrease in response amplitudes were similar, with a decrease to ~74% of control in the 100 Hz condition, ~79% of control in the 20 Hz condition, and ~68% of control in

the noisy condition. R3 was decreased to 78% of control in the 100 Hz condition, 95% of control in the noisy condition, and 80% of control in 20 Hz condition, however, the pairwise comparisons for R3 were not statistically significant ($p > 0.05$).

3.3 Individual Participant EMG Amplitudes

To investigate the responses in individual participants, the mean FCR EMG integral data were compared for each vibration condition separately. The following data have been normalized to the control (no vibration) condition for a given epoch and are presented as percentages. Since there were no significant interactions between vibration and instruction set for any epoch, values have been collapsed across instruction set for each participant. Data have been divided into four categories as followed: greater than 99%, between 90-99%, less than 90%, and less than 70% of control. Summary measures of the individual participant data can be seen in Figure 6.

3.3.1 R1

The data in the R1 response epoch (25-50ms) were relatively similar across the vibration conditions. In the 100 Hz vibration condition, 12/15 participants had a reduction in EMG amplitude to less than 90% of their control values, while three of these participants had reductions below 70% of control. The remaining three participants had values between 90 - 99% of control values. In the 20 Hz vibration condition, 13/15 participants had a reduction in their EMG amplitude to below 90% of control values, with four of these participants having a reduction below 70% of control. In the remaining two, one had a reduction between 90-99% and one showed no change relative to control (101%). Lastly, in the noisy vibration condition, 12/15 participants had a reduction in amplitude to below 90% of control, and six of these participants had a reduction to less than 70%. Two participants showed reductions in the 90-99% range, and one showed no change (100% of control).

3.3.2 R2

In the R2 response epoch (50-75ms), the data were also relatively similar between vibration conditions. In the 100 Hz vibration condition, 11/15 participants had a reduction in EMG amplitude to less than 90% of control, with five of the participants showing a reduction to less than 70% of control. Of the remaining four participants, two had reductions in amplitude to values between 90-99% of control, and two had values greater than control (108% and 122%). Finally, in the noisy vibration condition, 12/15 participants had reductions to less than 90% of control, with seven participants showing a reduction to less that 70% of control values. One participant had a reduction to a value between 90-99% of control, and two participants showed no change compared to control (102% and 103%).

3.3.3 R3

In R3, the 100 Hz vibration resulted in a decrease in amplitude to below 90% for 9/15 participants, with five of these participants showing a reduction to below 70%. Two participants had values between 90-99%, and four participants had values greater than 99% (highest 114% of control). In the 20 Hz vibration condition, only 6/15 participants had reductions to less than 90% of control, and two of these participants to values below 70% of control. Three participants had reductions to values between 90-99% and six had values greater than 99%. Of these six who had values greater than 99%, three of them had values greater than 110%. Lastly, in the noisy vibration condition, 8/15 participants had a reduction to below 90% of control, and five of these participants showed reductions to below 70% of control. Three participants had reductions to values between 90-99% and four showed values greater than 99%. Two of these four had amplitudes of greater than 110%.

3.4 EMG Latencies

In the no vibration condition, the first EMG response after the perturbation (R1) occurred at 31.5 ± 3.0ms in the DNI instruction set and 30.8 ± 2.8ms in the Comp instruction set. The onset of the long latency (start of R2) in the no vibration condition occurred at 50.3 ± 4.2ms in the DNI instruction set and 51.3 ± 4.9ms in the COMP instruction set. Finally, the end of the long latency response (end of R3), as determined only in the DNI condition was 106.4 ± 12.4ms in the no vibration condition. The R1 onset was significantly delayed with vibration [F (3, 42) = 4.717, p = 0.006, η_p^2 = 0.252], while both the start and end of the long latency response were unaffected by vibration (p > 0.05). Pairwise comparisons indicated that 100 Hz, 20 Hz, and noisy vibration significantly delayed the R1 onset relative to control (p < 0.05). Specifically, 100 Hz resulted in a ~1.6ms delay, 20 Hz in a ~1.8ms delay, and noisy in a ~2.2ms delay. These delays were not statistically different from each other (p > 0.05). Additionally, there were no interactions or main effects of intent on the response latencies for any epoch.

3.5 Force Characteristics

To determine if mean forces into the tendon were different between conditions, the mean force level before the perturbation (1 second average) were compared across vibration and instruction set conditions. The two-way repeated measures ANOVA indicated that there were no statistically significant differences in mean force level for vibration [F (3, 42) = 0.644, p = 0.525, η_p^2 = 0.044] or instruction set [F (1, 14) = 0.698, p = 0.417, η_p^2 = 0.048]. Sphericity assumption was violated for the vibration factor, therefore the Greenhous-Geisser adjustment was applied.

3.6 Flexor Carpi Ulnaris

The previous sections described the results for the vibrated muscle (FCR), and the following will describe data for FCU, a synergist to FCR. In the background activation for FCU,

there was a statistically significant effect of vibration [F (3, 42) = 3.509, p = 0.023, η_p^2 = 0.200] and instruction set [F (1, 14) = 16.882, p = 0.001 η_p^2 = 0.547], but no interaction. Specifically, in the compensate instruction set there were higher levels of background EMG. While all three vibration conditions resulted in higher amplitudes in background EMG, only the noisy vibration condition reached significance (p = 0.042*)*. The results for the stretch response integrals were qualitatively similar to the FCR results, with a significant effect of vibration for R1 [F (3, 42) = 18.021, p < 0.001, η_p^2 = 0.563], R2 [F (3, 42) = 12.811, p < 0.001, η_p^2 = 0.478], and R3 [F (3, 42) = 4.284, p = 0.030, η_p^2 = 0.234]. Sphericity was violated for R3, therefore, the Greenhouse-Geisser adjustment was applied. Pairwise comparisons for R1 indicated that the EMG response was significantly reduced with 100 Hz vibration (p < 0.001), 20 Hz vibration (p < 0.001), and noisy vibration (p < 0.001), and that the vibration conditions were not different from each other. In R2, the pairwise comparisons indicated that the EMG response was reduced significantly with 100 Hz vibration (p = 0.031), 20 Hz vibration (p < 0.001), and noisy vibration (p < 0.001), and that the noisy vibration EMG response was significantly reduced compared to the 100 Hz vibration (p = 0.013). Lastly, in R3, only the noisy vibration condition significantly reduced the EMG amplitude (p = 0.006). Unlike FCR, there was no significant effect of instruction set on the FCU EMG response for any epoch (p > 0.05), however R3 was trending towards significance [F (1, 14) = 3.806, p = 0.071, η_p^2 = 0.214]. There were no significant interactions between vibration and instruction set for any epoch. While there was no interaction, since the EMG response data are normalized by the background integrals and there was a significantly greater amplitude in the compensate instruction set background EMG, the instruction set differences in response epochs are difficult to directly compare. The data from FCU were not further analyzed due to a few

methodological issues. First, the vibration was likely sufficiently large enough to activate the FCU muscle spindles and therefore cannot be considered a non-vibrated muscle. Secondly due to the placement of the EMG electrode, it was positioned between the arm and the apparatus which may have induced some artifacts. Therefore, the data should be interpreted with caution.

3.7 Extensor Carpi Radialis

As changes in the background activation of the ECR could induce changes to the FCR motoneuron pool, the background activation was compared between conditions. There were no significant differences in background activation between vibration conditions [F (3, 42) = 0.853, p = 0.473, η_p^2 = 0.057]. The level of background activation of ECR was between 10-20% of the FCR values. Additionally, there were no significant differences in any analyzed epoch (R1, R2, and R3) between vibration conditions.

Chapter 4: Discussion

4.1 Hypotheses

The original hypotheses in this thesis were that the noisy tendon vibration would result in less suppression of the stretch response in comparison to the 100 Hz and 20 Hz vibration and that a participant's intent to respond to the perturbation would decrease the vibration induced suppression. The data from this thesis do not support these hypotheses, as all forms of vibration induced a reduction in EMG response to stretch and a participant's intent to respond to the perturbation did not modulate this reduction.

4.2 Short latency response

The data from the current thesis suggests that the short latency EMG response to stretch is reduced in amplitude regardless of vibration type. The short latency response is thought to be primarily mediated via monosynaptic and short polysynaptic Ia and potentially group II afferent fibres (Burke et al., 1984; Pierrot-Deseilligny & Burke, 2012). While other studies that investigated the effects of tendon vibration on stretch responses to mechanical perturbations also found suppressions of the short latency response (Bove et al., 2003; Hendrie & Lee, 1978), the data from the current thesis can also be compared to the larger body of literature investigating tendon taps and H-reflexes. There have been numerous studies using a variety of vibration parameters and protocols to test the effects of tendon vibration on the short latency response (e.g. Arcangel et al., 1971; De Gail et al., 1966; Gillies et al., 1969).The current understanding is that while tendon vibration results in a suppression of the short latency response, the mechanism is still not fully understood. The main mechanisms that could explain the suppression of the stretch response are presynaptic inhibition of the Ia afferent terminals, homosynaptic depression, a

"busy-line" effect, or changes in motoneuron excitability. While changes in gamma motoneuron activity could also explain the suppression, this is unlikely as similar results are seen with both tendon taps and H-reflexes.

4.2.1 Presynaptic Changes

There are a few presynaptic changes that could result in a suppression of the stretch response. Presynaptic inhibition via primary afferent depolarization would act to decrease the amplitude of the Ia afferent action potential, resulting in less neurotransmitter release and a smaller EPSP on the motoneuron (Rudomin, 1990; Rudomin & Schmidt, 1999). If there was significant presynaptic inhibition of the Ia afferent terminals during tendon vibration, it could explain the results seen in this thesis. There are strong animal data to suggest that one of the main mechanisms that would contribute to the suppression of the short latency stretch response is presynaptic inhibition of the Ia afferent terminals (Gillies et al., 1969). Specifically, these authors found that in a feline model, during tendon vibration there was significant depolarization of the Ia afferents, which would indicate presynaptic inhibition via increased activity in primary afferent depolarization neurons. In humans however, the mechanisms are not as well understood. One study demonstrated that the during soleus tendon vibration the soleus homonymous Ia connection is depressed while the heteronymous soleus response from quadriceps Ia afferents is unaffected (Abbruzzese et al., 1997). The authors then argue since the depression of the Ia afferent input is only seen for the vibrated muscle, this would indicate that the effect is presynaptic in origin and is not due to changes in the motoneuron excitability. It was further demonstrated using heteronymous conditioning stimuli on the homonymous H-reflex, a technique which is thought to assess presynaptic inhibition (Hultborn et al., 1987), that during vibration there was increased presynaptic inhibition of the Ia afferents. In another study, it was

demonstrated that continuous vibration over the tibialis anterior muscle reduced the facilitation of motoneuron firing from large muscle afferent (mainly Ia) input but did not affect facilitation from cutaneous receptors (Ashby et al., 1987). This finding supports the idea that the vibration induced suppression is happening at a presynaptic level and is not affecting the motoneuron excitability. It has additionally been demonstrated that very short vibration (3 cycles at 200 Hz), induced a depression of subsequent H-reflexes for 300-500ms, which, based on the time course was argued to arise from presynaptic inhibition (Hultborn et al., 1987). With reference to the current thesis results, presynaptic inhibition of the Ia afferents could certainly explain the suppression of short latency stretch responses seen. Since it is known that presynaptic inhibitory effects can occur in the millisecond range (Hultborn et al., 1987; Pierrot-Deseilligny & Burke, 2012), the 2-3 seconds of vibration in this study should allow for more than enough time for presynaptic inhibition of the Ia afferents to occur.

Since homosynaptic depression (HD) occurs with repetitive activation of Ia afferents with short interstimulus intervals, during tendon vibration this may play a key role in the suppression seen. It is thought that the homosynaptic depression is due to a decrease in the amount of neurotransmitter released at the Ia afferent terminal after repetitive activation (Kuno, 1964), which would result in a smaller EPSP on the motoneuron. While this could certainly explain the results seen with tendon vibration, it has been demonstrated that homosynaptic depression demonstrates a frequency dependence (Luscher et al., 1983). Specifically, Luscher et al., (1983) found that at low (1-10 Hz) and high (> 20 Hz) frequencies there was a depression of the motoneuron response, but between 10-20 Hz there was no change and potentially an enhancement of the motoneuron response. If this is the case, it may be expected that the 20 Hz vibration would have resulted in less suppression compared to 100 Hz vibration. However, there

are a few key issues in extrapolating the findings from Luscher et al., (1983) to the current thesis. First, Luscher et al.'s study was done by electrically stimulating single Ia afferents in an anesthetized feline, which makes direct comparisons with humans difficult. Second, since their study used electrical stimulation of single Ia afferents, they could be certain that a 20 Hz stimulus would result in 20 Ia afferent impulses per second, while with 20 Hz vibration, multiple Ia afferents would respond and some Ia afferents may fire multiple impulses per vibration cycle (Burke et al., 1976a, Burke et al., 1976b). Nevertheless, since Luscher et al., (1983) found a relatively constant decrease in motoneuron response with increasing frequencies past 20 Hz, it would still be expected that in the paradigm used in this thesis 100 Hz vibration would result in greater depression of the stretch response compared to 20 Hz vibration. Overall, homosynaptic depression could explain the reduction in amplitude of the short latency response but based on the lack of differences between frequencies it is unlikely to be the primary contributing mechanism.

The "busy-line" effect may also be contributing to the effects seen in this thesis. It has been demonstrated that during tendon vibration, the muscle spindle response to a tendon tap is reduced (Burke et al., 1976b). The authors suggest that during vibration the spindle response to stretch may either be occluded due to the spindle responding to vibration at the same time, or that the spindle may be unresponsive to the stretch if it is in an unloading phase from the vibration cycle. Both potential mechanisms would act to reduce the amount of Ia afferent impulses related to the stretch and therefore cause a reduction in the size of the stretch response. How much this effect contributes to the response is difficult to assess as it requires direct recordings from the Ia afferents during tendon vibration and a subsequent stimulation (H-reflex, Tendon taps, or mechanical perturbations). In a study investigating the effects of tendon vibration on stretch

responses, it was suggested that since no differences were seen in vibration frequencies above 40Hz, that Ia afferent occlusion is likely not the main contributing factor (Ashby et al., 1987). This would be in agreement with the findings from this thesis that there were no differences between 100 Hz and 20 Hz vibration. If occlusion of the Ia afferents was the main driving mechanism, it would be expected that 20 Hz would result in less suppression due to less occlusion of Ia impulses related to the stretch. Additionally, tendon taps evoke short duration stretches to the muscle which may be more vulnerable to occlusion compared to the large mechanical stretch applied in the current thesis. Overall, it is likely there may be some occlusion of the muscle spindle response to stretch but is likely not playing a major role in the results seen in this thesis based on the lack of frequency differences and the potential differences in protocol to evoke responses.

4.2.2 Postsynaptic (Motoneuron) Changes

While the current evidence suggests that the vibration induced suppression is presynaptic in origin, it is important to consider postsynaptic changes as well. The two main mechanisms that may decrease the motoneuron response to stretch would be input from Ib afferents of the agonist muscle (FCR) or Ia afferents from the antagonist muscle (ECR). Since both of these inputs may provide inhibitory inputs to the motoneuron pool (Pierrot-Deseilligny & Burke, 2012), if either afferent were significantly activated with vibration, the motoneuron response to agonist Ia afferent input could be suppressed. However, most data suggest that the motoneuron excitability is not changed during tendon vibration. First, studies that investigated the effects of homonymous Ia afferents of the vibrated muscle and compared this response to responses from Ia afferents from other muscles and cutaneous receptors found that only the homonymous Ia afferent response was reduced (Abbruzzese et al., 1997; Ashby et al., 1987). This would indicate

that the suppression of Ia afferent response is limited to the Ia afferents of the vibrated muscle. Secondly, a few studies that investigated the gain changes in motoneuron response to vibration found no differences between vibration conditions and control (Bove et al., 2003; Gillies et al., 1969). This lack of gain change would indicate that there are no noticeable differences in general motoneuron excitability, and the reduced amplitude of response is due to reduced amounts of afferent input and not changes in motoneuron excitability. However, it is still important to consider how motoneuron changes may explain the results seen, particularly in the current study, since tendon vibration was applied to an active muscle and therefore, there is likely a strong response from the Golgi tendon organs (Burke et al., 1976a). Activation of Ib afferents could result in inhibition of the agonist motoneuron pool and explain the smaller motoneuron response during vibration. However, there are data to suggest that Ib afferent inhibition during a voluntary contraction can be significantly suppressed (Fournier et al., 1983), and therefore Ib activation may not result in large amounts of inhibition to the motoneuron pool during a voluntary contraction, such as was used in this thesis. The other mechanism that may influence the motoneuron response is input from antagonist (ECR in this thesis) muscle spindle input. Since antagonist Ia afferent activation can result in reciprocal inhibition (Pierrot-Deseilligny & Burke, 2012), this could explain the results with tendon vibration. In this thesis, a reasonably large amplitude vibration was used, so it is plausible that this could have activated the ECR muscle spindles and produce reciprocal inhibition of the agonist response to stretch. While data from the current thesis cannot rule this out, previous work has used a nerve block of the antagonist muscle and found no changes in the vibration induced suppression (Hendrie & Lee, 1978). The current understanding of the vibration induced suppression of the Ia afferent pathway suggests that motoneuron pool changes are not the main contributors; however, it cannot be fully ruled out. In

particular, activation of Golgi tendon organs from vibration could contribute to the suppression of stretch response seen.

4.2.3 Summary

There are many mechanisms that may affect the short latency stretch response and they can be broadly categorized into presynaptic and postsynaptic mechanisms. While both may be occurring, the current evidence suggests that the effects are presynaptic in origin, and specifically, likely due to presynaptic inhibition. In the context of the current thesis, presynaptic inhibition of the Ia afferents via primary afferent depolarization would explain the decreased amplitude of the short latency stretch response. If the Ia afferents were depolarized, a smaller action potential would reach the synaptic terminal and result in less neurotransmitter release, and subsequently a smaller motoneuron response. However, it is likely that the results seen are from a combination of the many presynaptic mechanisms. Further research is needed to delineate the different presynaptic mechanisms.

4.3 Long Latency Response

As with the short latency response, tendon vibration resulted in a reduction in amplitude in the long latency response. This reduction was most evident in the early components of the long latency response, between 50- 75ms (R2 in this thesis). This reduction in R2 was significant for all three types of vibration in comparison to the no vibration condition, which indicates that as with R1, R2 is depressed with tendon vibration regardless of vibration frequency characteristics. In R3 however, the effect of vibration was less robust, as there were no significant pairwise comparisons. This finding was in contrast with the previous literature in the upper limb that investigated the effects of tendon vibration on short and long latency stretch

responses (Hendrie & Lee, 1978). Specifically, Hendrie and Lee only investigated the vibration induced suppression in the compensate instruction set and found no effect in the long latency epoch (R2 and R3 in this thesis).

The participant's intent to respond to a perturbation in the compensate condition resulted in a significant increase in EMG amplitude in the long latency response, particularly in the later components (R3). This finding is in agreement with previous work investigating the effect of instruction set on the amplitude long latency response (Calancie & Bawa, 1985; Forgaard et al., 2015; Hammond, 1955; Pruszynski & Scott, 2012). In the context of the current thesis, this finding confirms that there was gain modulation in the long latency EMG response with a participant's intent to respond. Additionally, the lack of significant interaction between vibration and instruction set in any epoch, would indicate that the vibration induced suppression of stretch response was not different between the do not intervene and compensate conditions. With relation to the hypothesis that the participants intent to respond to the perturbation may influence the vibration induced suppression, the significant gain modulation in the long latency response confirms that the lack of interaction between vibration and instruction set was not due to the participants' inability to modulate the long latency response. Since the stretch used in this paradigm is longer in duration than the long latency response, there would be continued monosynaptic and short polysynaptic input from Ia afferents contributing to both the short and long latency response. Therefore, the reduction in amplitude of the long latency response may be similar in origin to the short latency response. As discussed in detail in section 4.2, the primary mechanisms involved in the suppression seem to be presynaptic in origin, and likely have a major presynaptic inhibition component. Therefore, it is plausible to assume that the reduction in the long latency response is due to presynaptic effects of the Ia afferent connections to the

motoneuron pool, while the supraspinal pathways may be unaffected by vibration. This is supported by the result that vibration and instruction set had no significant interactions during the long latency response, indicating that the main effect of instruction set was not dependent on vibration condition. However, while the data from this thesis suggest this may be the case, there is currently no direct evidence to demonstrate that these pathways are unaffected and therefore, more research is needed.

4.4 Latency

The results from this thesis indicate that tendon vibration increases the latency of the short but not the long latency stretch response. However, it is important to note, that due to overlap between the short and long latency response, it is difficult to accurately determine the onset latency of the long latency response. The findings from this thesis are in partial alignment with previous studies investigating tendon vibration on stretch response (Bove et al., 2003). Bove et al., found that both the short and long latency response latencies were delayed with vibration, however they were testing this response in the lower limb, which may explain the difference seen in the long latency response. Since there is likely a reduced amount of Ia afferent feedback onto the motoneuron pool with tendon vibration, regardless of the mechanism (presynaptic inhibition, homosynaptic depression etc.), it could be argued that the motoneuron is reaching threshold at a slightly later time point. With a reduced Ia afferent input, the incoming EPSPs may not depolarize the motoneuron to threshold in the same amount of time, as it would have in the control condition, which would cause a delay in motoneuron firing. This explanation would also explain the lack of delay seen in the long latency response, as the timing of the long latency response is likely not due to the direct monosynaptic connections but from supraspinal Ia afferent loops which may be less affected by vibration (see section 4.3).

4.5 Final Summary

Overall, tendon vibration, regardless of frequency characteristics results in a suppression of the EMG response to stretch. This suppression seems to affect both the short and long latency responses. Contrary to the hypothesis that a participant's intent to respond to the perturbation would reduce the amount of suppression seen, the vibration induced suppression was not influenced by a participants instruction set. This lack of significant interaction between vibration and instruction set during the long latency response also may indicate that vibration is not affecting a participant's ability to modulate the response with the intent to respond. As described in section 4.3, this may indicate that the supraspinal pathways involved for the long latency response may be unaffected vibration. However, it will be important in future studies to directly assess this. Therefore, it seems likely that during tendon vibration the direct monosynaptic and short polysynaptic components of the short and long latency response are primarily affected. This is likely due to a combination of a few factors. First, presynaptic inhibition of the Ia afferent terminals via primary afferent depolarization. If the Ia afferents were depolarized, the size of subsequent action potentials in the Ia afferents would be reduced and less neurotransmitter would be released, and therefore would generate a smaller motoneuron response. Secondly, homosynaptic depression could also explain this result. If the Ia afferents are repeatedly activated, there can be a decrease in the amount of neurotransmitter released at the Ia afferent terminal. Lastly, a "busy-line" effect due to the vibration could also be a potential contributor. Additionally, direct changes to motoneuron excitability may also be driving these results, particularly due to Ib afferent feedback. Based on the current understanding of the vibration induced suppression of the stretch response, the most likely contributors seem to be presynaptic mechanisms, with the most evidence for presynaptic inhibition. However, the changes in

homosynaptic depression with short vibration remain to be fully studied, so it is likely this is also playing some role.

The results from this thesis are the first to provide evidence that aperiodic (noisy) tendon vibration induces the same effect as periodic vibration. Additionally, the data from this thesis provide some evidence that the supraspinal pathways responsible for the long latency response may be unaffected by vibration, but this remains to be fully answered. Therefore, contrary to the original hypothesis, periodicity of tendon vibration does not seem the be the driving factor of the vibration-induced suppression. Additionally, this thesis found no evidence that the vibration-induced suppression could be reduced with a participant's intent to respond to the perturbation. This would indicate that the vibration-induced suppression is not modifiable by a participant's intent to respond. Lastly, as noisy tendon vibration has been used as a tool to probe the Ia afferent pathway (Eschelmuller et al., 2020; Mildren et al., 2017, 2019, 2020), it will be important to note for future studies using this technique that this stimulus is also likely reducing the motoneuron response to that input.

4.6 Limitations

One major limitation from this thesis is that the high frequency vibration resulted in higher background EMG. Firstly, increases in background levels of activation would produce a larger EMG response for a given perturbation (Calancie & Bawa, 1985; Matthews, 1986). However, in the current study, since vibration reduced the amplitude of the response, if this was affecting the results, it would have caused the 100 Hz vibration condition to have a larger amplitude and therefore brought the values closer to control. Secondly, since the data are normalized by the background EMG, this difference in background can make the direct comparisons between vibration conditions difficult. Therefore, further research is needed to

understand this change in background activity, and the potential that the vibration is generating a tonic vibration reflex. Additionally, since in this thesis surface EMG was used, the precise activation of individual motor units cannot be distinguished. Having a better understanding of the firing patterns of individual motor units between conditions would provide additional insight into the vibration-induced suppression.

4.7 Future Directions

Future studies could investigate other aspects of the vibration-induced suppression of the stretch response. One topic of relevance to the current thesis would be to directly investigate the gain of the stretch response during tendon vibration by either systematically varying the background muscle activation or the size of the stretch perturbation. A better understanding of the gain would provide insight into whether or not the motoneuron properties are changing with vibration. Varying when the vibration is turned off before stretch may help elucidate if a busy line effect is playing a role in the vibration-induced suppression. If the vibrator were turned off before the stretch, and the results are the same, it would provide more evidence that a busy line effect is not a major contributor. Along a similar route, directly testing presynaptic inhibition during short periods of vibration is another important avenue of future research. Additionally, since presynaptic inhibition is thought to last at most 400ms (Pierrot-Deseilligny & Burke, 2012), varying the stop time of the vibration could also help determine the contribution of presynaptic inhibition. Lastly, directly testing homosynaptic depression with a paired H-reflex protocol would also provide more mechanistic insight. With both presynaptic inhibition and homosynaptic depression, an important area of research would be the time course between its appearance and the suppression of the stretch response. Lastly, directly assessing how tendon

vibration is affecting the pathways mediating the gain compensation seen in the long latency response will be an important area to investigate. Overall, the data from this thesis provide a starting point for a variety of new research topics to better understand the vibration-induced suppression.

Tables

Vibration condition	Instruction Set	Mean	SD	N
R1 [25 – 50 MS]				
Control	Comp	3.068	1.091	15
	DNI	2.837	1.091	15
High	Comp	2.317	0.763	15
	DNI	2.115	0.524	15
Low	Comp	2.149	0.535	15
	DNI	2.093	0.404	15
Noisy	Comp	2.132	0.566	15
	DNI	1.975	0.437	15
R2 [50 – 75 MS]				
Control	Comp	8.253	3.598	15
	DNI	6.406	2.859	15
High	Comp	6.324	3.271	15
	DNI	4.465	0.948	15
Low	Comp	6.566	2.838	15
	DNI	5.036	2.018	15
Noisy	Comp	5.619	2.224	15
	DNI	4.339	1.404	15
R3 [75 – 100 MS]				
Control	Comp	12.695	8.611	15
	DNI	5.508	4.626	15
High	Comp	10.207	8.695	15
	DNI	3.929	1.901	15
Low	Comp	12.059	9.208	15
	DNI	5.291	4.522	15
Noisy	Comp	10.221	9.508	15
	DNI	4.328	2.579	15

Table 1: Mean and standard deviations for the four vibration and two intent conditions for the R1, R2, and R3. Data are presented as mean integrals values for each epoch, normalized by background activation. Therefore, a value of 1 indicates the same level of activation as background. "Comp" represents the compensate instruction set, and "DNI" represents the do not intervene instruction set.

Figures

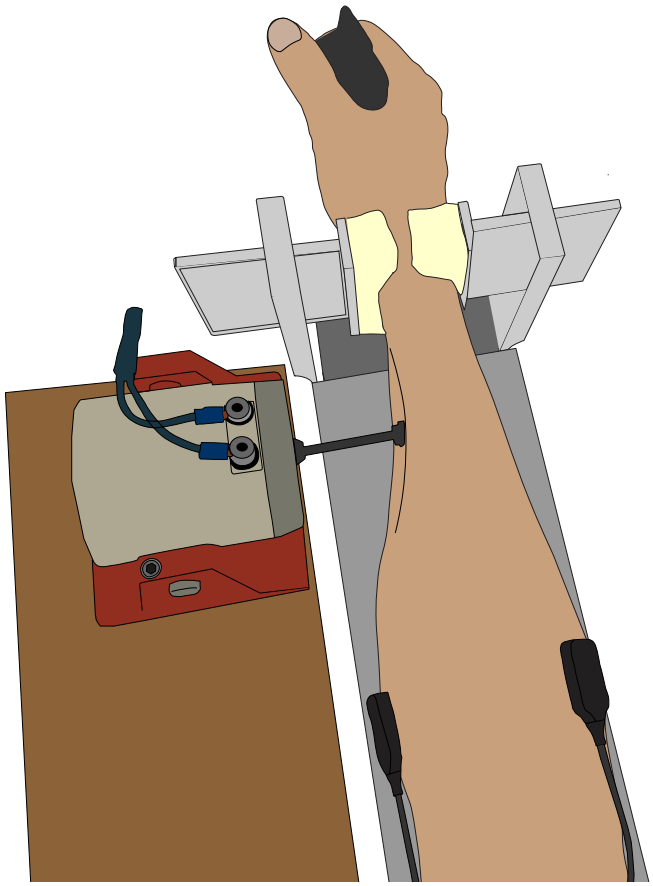

Figure 1: Participant set up. See text for details.

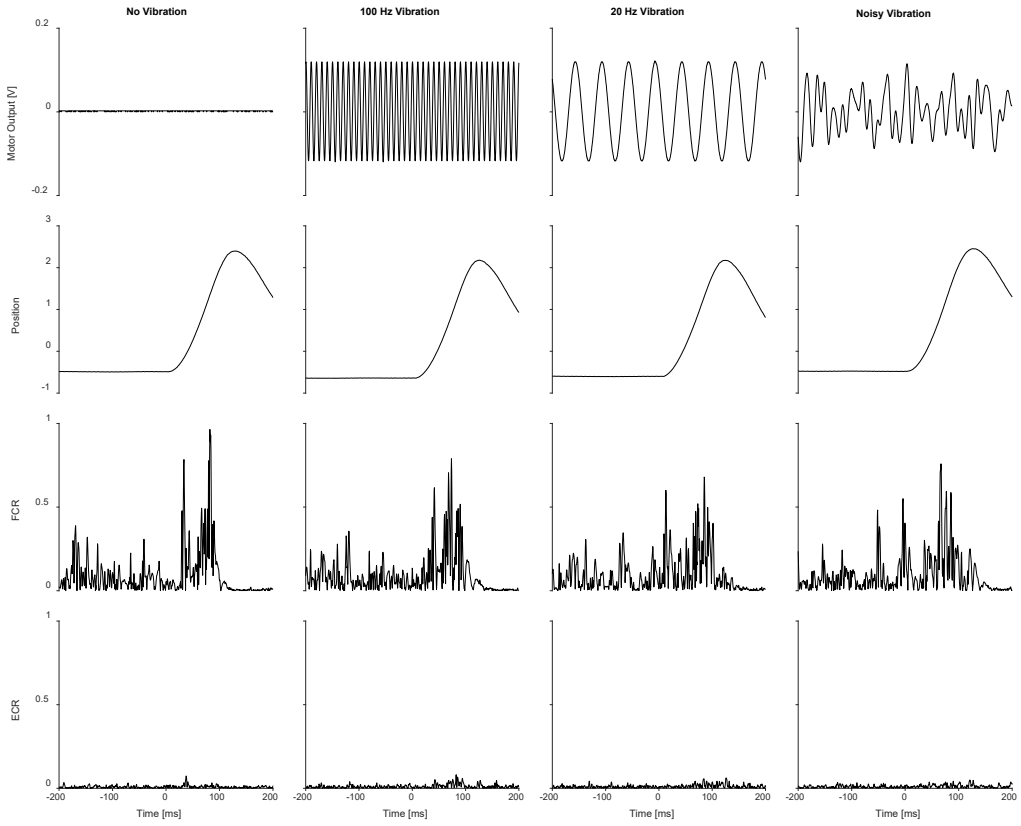

Figure 2: Example trial for each condition represented as a single column. Top row: Output in volts to the linear motor positioned against the tendon. Second row: Output in volts from a potentiometer measuring rotation of the wrist. Positive values indicate extension. Third row: EMG from the flexor carpi radialis, measure in volts. Bottom row: EMG from extensor carpi radialis, measured in volts. Time zero indicates the time the perturbation began.

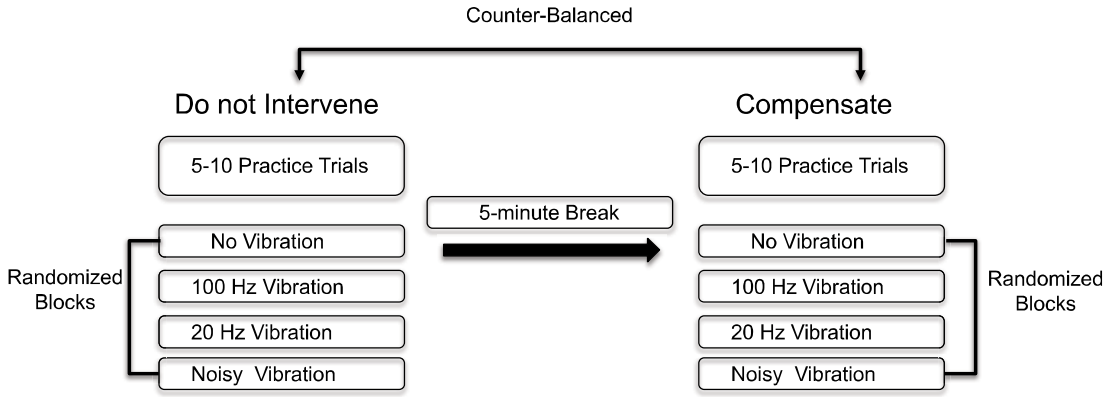

Figure 3: Diagrammatic representation of protocol.

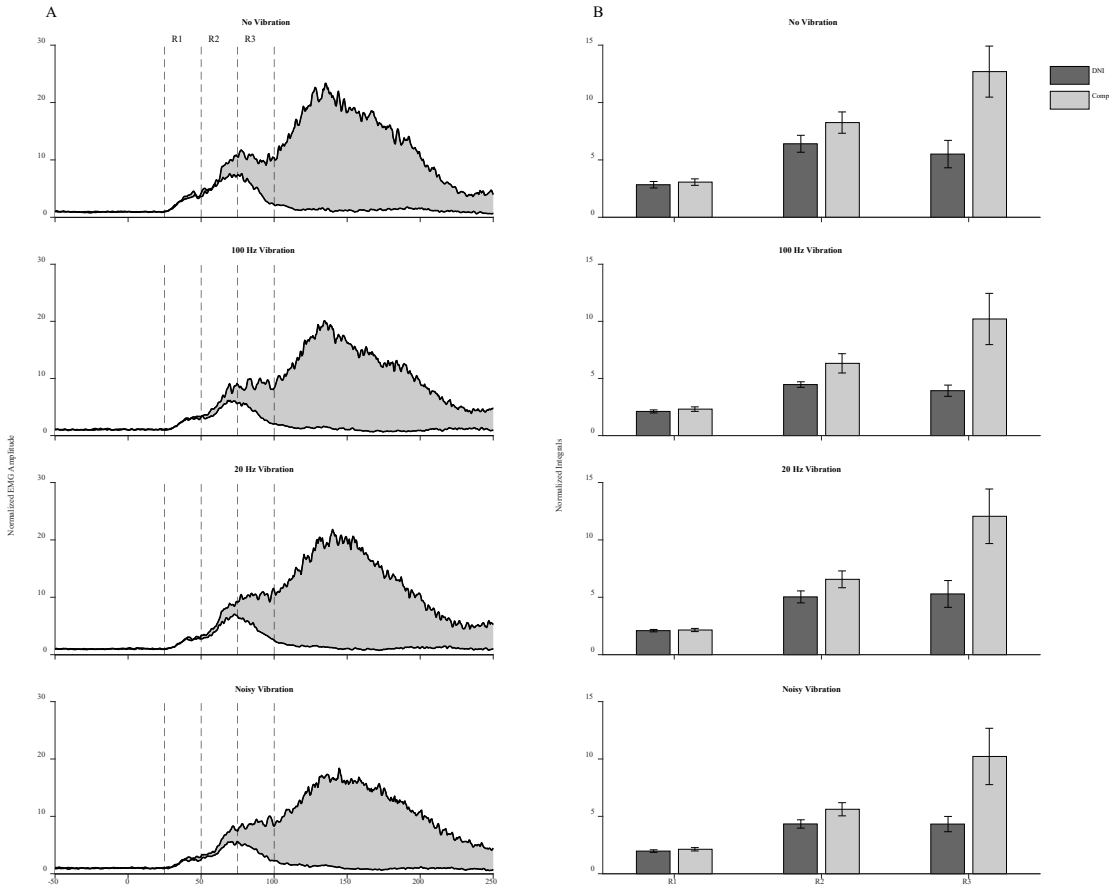

Figure 4: Do not intervene compared against compensate for each vibration condition for the FCR muscle, averaged across participants (15). A: Shaded area indicates time points in which compensate had a greater amplitude compared to do not intervene. Dividing lines indicate where R1, R2, and R3 were calculated. B: Mean normalized integrals for R1, R2, and R3 for each vibration condition. Error bars represent the SEM.

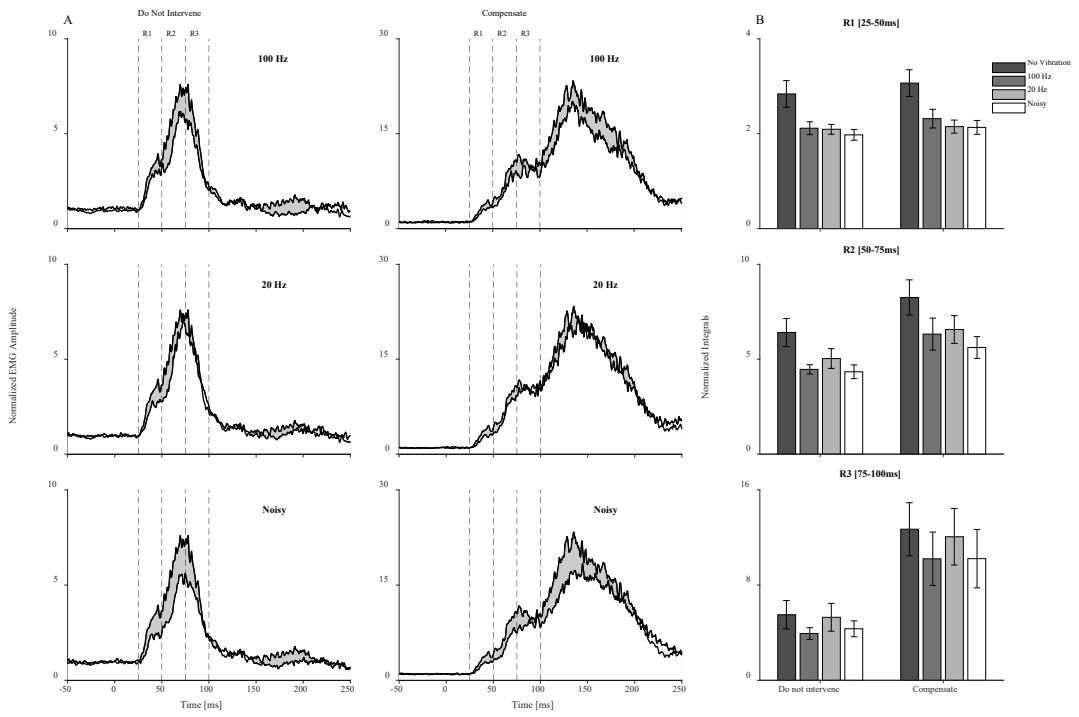

Figure 5: A: Ensemble FCR EMG responses for each condition [N=15] normalized to background activation. A value of one corresponds to equal activation compared to the background EMG. Grey shaded areas indicate time points where control is higher amplitude compared to vibration. The left most column represents the do not intervene condition, while the middle column represents the compensate instruction set. B: Normalized integrals for each condition and each epoch. Error bars represent the SEM.

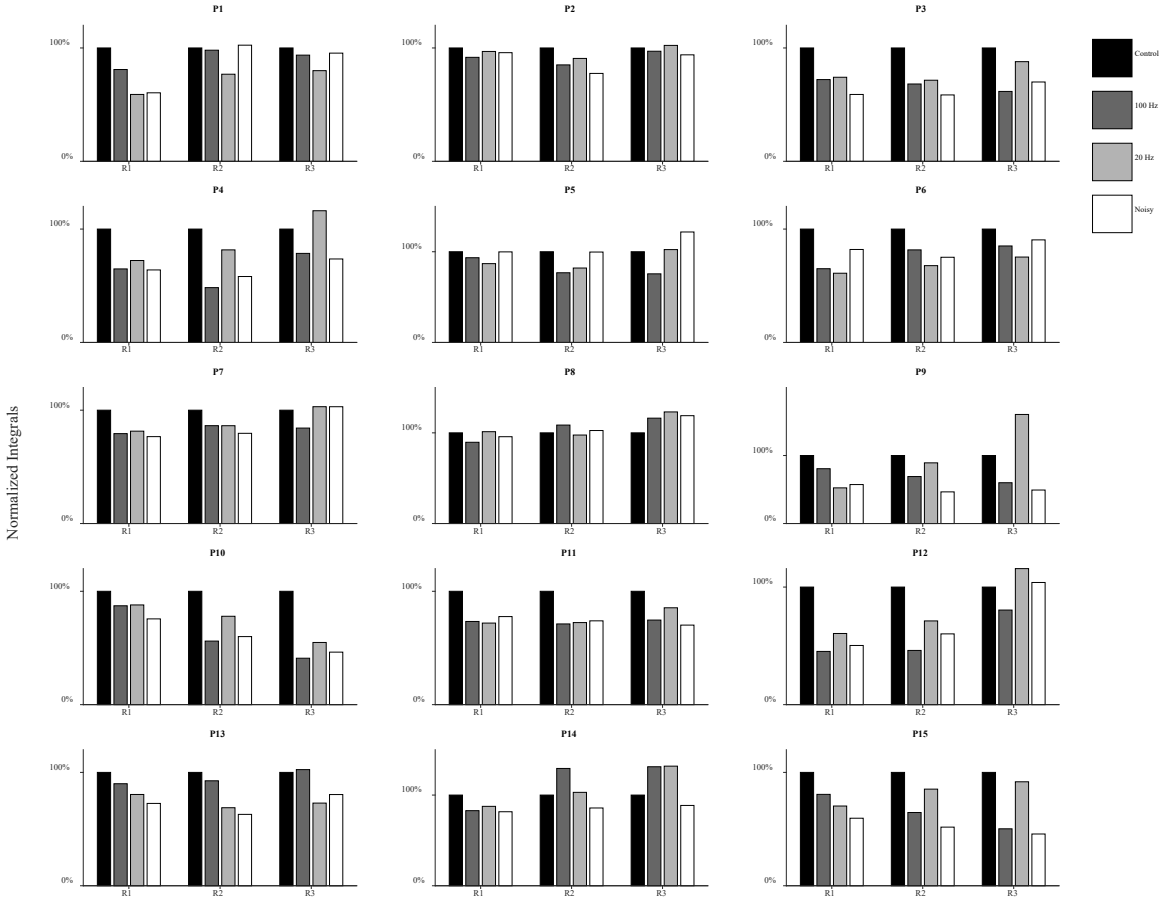

Figure 6: Single participant summary measures. Data for each epoch expressed as a percentage of the no vibration conditions. Data has been averaged across instruction set. For simplicity, only 0% and 100% have been marked on the y-axis. Control data has been included to aid in visualization of differences with vibration and will be 100% in all conditions.

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