

The Impact of Subclinical Neck Pain and its Treatment on Cerebellar Processing as Measured by the Cervico-ocular and Vestibulo-ocular Reflexes

by

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Title: The Impact of Subclinical Neck Pain and its Treatment on Cerebellar Processing as Measured by the Cervico-ocular and Vestibulo-ocular Reflexes

Abstract

Alterations in cerebellar processing, associated with subclinical neck pain (SCNP), have been demonstrated to improve following spinal manipulation. These alterations and improvements have only been demonstrated utilizing indirect measures of the cerebellum. The cervico-ocular and vestibulo-ocular reflexes (COR & VOR) are two measures that may be utilized to directly assess changes within the cerebellum.

Utilizing two eye-tracking protocols this thesis aimed examine differences in COR gain and VOR gain adaptation in a SCNP population prior to, and following, an 8-week chiropractic intervention. SCNP was demonstrated to alter COR gain but have a limited impact upon the VOR. These alterations within the COR gain were also observed to normalized following the chiropractic intervention. This may reflect that those with SCNP may have alterations in their proprioceptive input towards the cerebellum that may be normalized following spinal manipulation. However, SCNP may have a minimal impact on vestibular input towards the cerebellum.

Keywords: Cerebellum, subclinical neck pain, cervico-ocular reflex, vestibulo-ocular reflex, vestibulo-ocular reflex adaptation, spinal manipulation

Author's Declaration

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Statement of Contributors

I hereby declare that this thesis presents the research presents the thesis of Devonte Campbell in collaboration with his colleagues Praveen Sanmuganathan, Dr. Nicholas La Delfa, Dr. James Burkitt, and thesis supervisors Bernadette Murphy and Paul Yields.

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List of Abbreviations

ADHD	Attention Deficit Hyperactive Disorder
CBI	Cerebellar Inhibition
CNS	Central Nervous System
COR	Cervico-Ocular Reflex
DCML	Dorsal Column Medial Lemniscus
EEG	Electroencephalography
EHI	Edinburgh Handedness Inventory
GTO	Golgi Tendon Organs
HVLA	High-Velocity Low Amplitude
JPS	Joint Position Sense
LICI	Long-Interval Intracortical Inhibition
M1	Primary Motor Cortex
MEP	Motor Evoked Potential
NDI	Neck Disability Index
RPE	Rating of Perceived Exertion
SCNP	Subclinical Neck Pain
S1	Primary Somatosensory Cortex
SEP	Somatosensory Evoked Potential
SICI	Short-Interval Intracortical Inhibition
SMI	Sensorimotor Integration
TMS	Trans-Cranial Magnetic Stimulation
VAS	Visual Analog Scale
VPL	Ventroposterolateral Nucleus
VOR	Vestibulo-Ocular Reflex

Chapter 1. Thesis Introduction

As society progresses further into the digital age, technology has become more integral in everyday life; however, this increase in technology has shown a positive correlation with neck pain (Berolo et al., 2011; Green, 2008; Kim, 2015). Prior studies have demonstrated that neck pain affects 30-50% of the population and due to an overreliance on technology, these numbers are likely to increase (Hogg-Johnson et al., 2009). Neck pain can manifest in various forms such as chronic pain, traumatic acute pain (i.e. whiplash associated disorder), and non-traumatic acute pain (Ischebeck et al., 2017). One of the most unique, and understudied, forms of neck pain is subclinical neck pain (SCNP). SCNP is defined as recurrent episodes of moderate-to-low severity neck pain that has not yet been treated (Lee et al., 2008). One of the most common misconceptions regarding SCNP is the belief that, if left alone, the symptoms will reduce on their own and the neck will regain proper function (Haavik & Murphy, 2011; Karellas et al., 2019). However, literature has shown that, when left untreated, SCNP may turn into chronic neck pain due to alterations in neck muscle recruitment as well as altered movement patterns within the neck (Haavik & Murphy, 2012). Thus, there is a need to expand upon the current literature regarding SCNP. Individuals with SCNP present a unique population of study in regards to alterations in the neural pathways, and neural mechanisms, within the brain. Specifically, neck pain has been shown to alter incoming sensory information to the brain due to dysfunctional joints within the body (Haavik & Murphy, 2012). Furthermore, individuals with SCNP experience episodes of recurrent neck pain and, thus, can have periods of pain-free days (Lee et al., 2008). For these reasons, individuals with SCNP allow researchers to eliminate the confounding bias of pain and determine whether changes in sensory processing are due to alterations within the joints (Andrew et al., 2018).

SCNP can alter both the sensory and motor information to and from the brain. This process of converting sensory information into a motor output is known as sensorimotor integration (SMI) (Haavik & Murphy, 2012). SMI is defined as the ability of the central nervous system to integrate sensory information from the body and produce the proper motor commands in response (Andrew et al., 2018). However, joint and spinal dysfunction such as SCNP, have been demonstrated to impact SMI by altering the sensory information received from joints within the body (Andrew et al., 2018; Haavik-Taylor & Murphy, 2007a, 2007b). During SMI, sensory information is processed within the primary somatosensory and is then converted to motor information which is sent to the motor cortex (Andrew et al., 2018). The motor cortex then initiates the proper motor commands within the body (Haavik & Murphy, 2012). The cerebellum will also form connections with the primary motor cortex to make online movement corrections and ensure that an efficient motor command is elicited (Daligadu et al., 2013). Based on this information, it seems likely that SCNP may lead to chronic neck pain if left untreated. Due to alterations in SMI, the recruitment and movement of neck musculature may be impacted (Haavik & Murphy, 2012). Literature has shown that movement patterns within the neck muscles may be altered due to neck pain (Rogers, 1997). When movement patterns of musculature are disrupted, chronic pain and/or stiffness may develop within the muscles and, thus, lead to further alterations within the joints and muscles (Rogers, 1997). Furthermore, along with altering SMI, SCNP has also been shown to impact cerebellar processing (Baarbé et al., 2018; Daligadu et al., 2013). Utilizing transcranial magnetic stimulation and sensory evoked potentials, various studies have shown increases in cerebellar inhibition in individuals with SCNP when compared to healthy, asymptomatic, individuals (Andrew et al., 2018; Baarbé et al., 2018; Daligadu et al., 2013).

These alterations in cerebellar processing have also been associated with changes in motor control.

It is well known that the cerebellum is the primary area of the brain involved in the coordination of motor control (Daligadu et al., 2013; Knierim et al., 1997). When learning a novel motor task, the cerebellum consciously controls the motor output as it slowly adapts to the speed and direction of the task (Daligadu et al., 2013). As the cerebellum becomes accustomed to the task, it undergoes neural adaptation and can elicit the motor commands unconsciously (Baarbé et al., 2018). Two motor reflexes directly controlled by the cerebellum are the cervico-ocular reflex (COR) and vestibulo-ocular reflex (VOR). These oculomotor reflexes work in conjunction with one another to stabilize images upon the retina during trunk and head movements. The COR activates in response to trunk-on-head movements (i.e. the trunk is moving while the head is stable) and is stimulated by proprioceptive signals within the cervical muscles and joints (de Vries et al., 2016). Through various neural pathways, the cerebellum sends signals to the oculomotor muscles to stabilize the eyes within the orbit (Gdowski et al., 2001). The COR can be quantitatively assessed utilizing the measure known as COR gain, which is defined as the ratio of eye velocity to trunk velocity (de Vries et al., 2016). Research has also demonstrated that COR gain increases with age as a compensatory mechanism in the response to decreases in VOR gain. The VOR activates in response to head-on-trunk movements (i.e. the head is moving while the trunk is stable) and is stimulated by the vestibular system (Knierim et al., 1997). When the vestibular system senses movement of the head, it sends signals to the cerebellum which then stimulates the oculomotor muscles to move the eyes in the opposite direction, and at the same velocity, as the head (Gray, 2020b). However, when this movement of the eyes is no longer compensatory, the image starts to become distorted on the retina. This

phenomenon is known as a retinal slip (Schubert et al., 2008). When a retinal slip occurs, the cerebellum modifies the movement of the eyes by sending signals towards the oculomotor muscles to effectively adapt to the speed of the image (Knierim et al., 1997). This neural mechanism is known as VOR gain adaptation and may be used to examine cerebellar processing, and plasticity, within a research paradigm (Clopath et al., 2014; Montfoort et al., 2008).

Due to their relationship with the cerebellum, it is reasonable to believe that SCNP may alter the oculomotor reflexes as they are directly controlled by the cerebellum. These alterations may manifest in various ways such as cervicogenic dizziness, altered proprioception, and loss of balance/coordination (García-Pérez-Juana et al., 2018; Reid et al., 2014; Rogers, 1997). All of which are symptoms seen in individuals with SCNP. Previous studies have demonstrated increases in COR gain in individuals with various forms of neck pain when compared to healthy individuals without neck pain (de Vries et al., 2016; Ischebeck et al., 2018; Montfoort et al., 2006; Montfoort et al., 2008). However, these same studies were not able to demonstrate alterations in VOR gain. Although, this may have been due to an ineffective methodology utilized in these studies. Therefore, the first goal of this study is to determine whether SCNP alters cerebellar processing as demonstrated by alterations in COR gain and VOR gain adaptation. Given that there are likely to be differences between the healthy and SCNP populations, it would be viable to know whether spinal manipulation can restore the proper function of the oculomotor reflexes.

Spinal manipulation is a well-established technique in the treatment of SCNP (Baarbé et al., 2018). It involves high velocity, low-amplitude (HVLA) thrusts to dysfunctional joints within the spine (Baarbé et al., 2018). Prior studies have associated this treatment with improvements in SMI and cerebellar processing (Baarbé et al., 2018; Daligadu et al., 2013; Haavik & Murphy,

2011). As previously stated, altered SMI and cerebellar processing, are due to dysfunctional joints within the body. When treating SCNP, chiropractors direct HVLA thrust to these dysfunctional joints within the cervical spine and, thus, correcting the altered sensory input received from these joints. Hence, it is reasonable to believe that cervical spine manipulation may improve the oculomotor reflexes due to improvements in cerebellar processing. Therefore, the second goal of this study is to determine whether cervical spinal manipulation can improve cerebellar processing in individuals with SCNP as demonstrated by improvements in COR gain and VOR gain adaptation.

Chapter 2. Literature Review

Introduction to the literature review

As society progresses further into the digital age, technology has become pivotal in everyday life; this increase in technology has shown a positive correlation with neck pain (Berolo et al., 2011; Green, 2008; Kim, 2015). One of the most understudied forms of neck pain is known as subclinical neck pain (SCNP). It is defined as recurrent episodes of mild-to-moderate neck pain that has not yet received treatment (Lee et al., 2008). In general, neck pain has been demonstrated to alter the neural mechanisms and pathways within the body, such as sensorimotor integration (SMI), which is defined as the ability of the central nervous system to integrate sensory information from the body and produce the proper motor command (Holt et al., 2016). Thus, when examining individuals with acute or chronic neck pain, it may be difficult to determine whether alterations within neurophysiological systems are due to pain at the time of data collection or due to anatomical and functional changes in the neck (Haavik-Taylor & Murphy, 2007a). Unlike other forms of neck pain, individuals with SCNP experience pain-free periods, thus providing researchers with a unique study population when examining changes in the neural mechanisms, structures, and pathways that occur in response to recurrent episodes of neck pain. One of these neural structures that has been demonstrated to be altered by SCNP is the cerebellum (Baarbé et al., 2018). The cerebellum is a region within the brain responsible for the integration of motor plans and is integral in the process of motor learning and/or sensorimotor adaptations (Knierim et al., 1997). To examine these alterations, prior studies have implemented techniques such as transcranial magnetic stimulation (TMS), which is a technique that can be utilized to assess cerebellar inhibition (Baarbé et al., 2014; Daskalakis et al., 2004; Ugawa et al., 1995). However, TMS is an in-direct measure of cerebellar processing, and to our knowledge, no

prior studies have demonstrated alterations in cerebellar functioning utilizing direct measures of cerebellar processing.

Two direct measures that may be utilized to examine changes within cerebellar processing, are known as the cervico-ocular reflex (COR) and the vestibulo-ocular reflex (VOR) (Kheradmand & Zee, 2011). The COR and VOR are oculomotor reflexes that are directly controlled by the cerebellum to stabilize images on the retina (Gdowski et al., 2001). Furthermore, prior studies have demonstrated that both these reflexes may be altered due to neck pain (de Vries et al., 2016). Literature has shown that spinal manipulation may improve cerebellar processing in individuals with SCNP (Baarbé et al., 2018; Daligadu et al., 2013). Hence, it is reasonable to believe that spinal manipulation may also improve the neural responses controlled by the cerebellum such as the VOR and COR. This literature review will discuss the link between SCNP and alterations in cerebellar processing. Additionally, it will discuss how alterations in cerebellar processing may be examined utilizing the cervico-ocular and vestibulo-ocular reflexes. Finally, this literature review will discuss past studies of spinal manipulation and how it may be used to improve cerebellar processing in individuals with SCNP.

2.1 Neck Pain

Due to its biomechanical and neurophysiological connections to the upper limbs, the neck is one of the primary areas involved in the modulation of movement and sensation within the body (Kandel et al., 2000). The neck is responsible for transmitting motor signals from the cerebral cortex towards the skeletal muscles, as well as transmitting sensory information from various regions of the body towards the cerebral cortex (Kandel et al., 2000). In this way, the neck plays a vital role in sensorimotor integration (SMI) (Andrew et al., 2018). However, when exposed to a prolonged abnormal stimulus, the neck may experience anatomical changes which,

in-turn, commonly lead to pain. One common stimulus that has been associated with neck pain is an overreliance on technology. Hogg-Johnson and colleagues (2009) have demonstrated that neck pain affects 30-50% of the population and due to an overreliance on technology, these numbers are likely to increase. Neck pain can manifest in various forms such as chronic pain, traumatic acute pain (i.e. whiplash associated disorder), non-traumatic acute pain, and subclinical neck pain (SCNP) (Ischebeck et al., 2017). Chronic neck pain is defined as persistent low severity neck pain that has lasted, approximately, 7-12 weeks (Lee et al., 2005). Acute neck pain, not due to whiplash injury, is commonly referred to as a self-limiting disorder. It can be observed after a variety of activities such as improper form during resistance training or stretching (Vernon et al., 2005). Another form of acute neck pain are whiplash-type injuries (Vernon et al., 2005). These injuries commonly involve rapid flexion-extension or side-to-side forces that are directed towards the head or neck, and typically occur following motor vehicle accidents (Vernon et al., 2005). Whiplash also causes a disorder known as whiplash-associated disorder (WAD) which commonly represents with symptoms such as dizziness, mood disturbances, and sleep disturbances (Vernon et al., 2005). SCNP is a form of undiagnosed neck pain and typically consists of recurrent episodes of mild-to-moderate pain that has not yet been treated (Lee et al., 2005). Due to its unique symptomology, SCNP is one of the most understudied forms of neck pain. However, compared to individuals with chronic and acute neck pain, individuals with SCNP provide a unique area of study.

2.1.1 Subclinical Neck Pain

Unlike acute and chronic neck pain, individuals with SCNP experience periods of pain-free days (Lee et al., 2005). In this way, individuals present a unique population when examining alterations in the neural mechanisms and pathways within the body. In general, neck pain has

been shown to alter the neural mechanisms and pathways within the body (Haavik-Taylor & Murphy, 2007a). This is due to altered afferent input from joints and musculature within the cervical spine (i.e. the neck) (Haavik & Murphy, 2012). However, prior studies have demonstrated that pain itself can alter these neural mechanisms; hence, it is difficult to conclude whether changes in the neural mechanisms and pathways are due to altered neck anatomy or due to pain during the time of the study (Haavik & Murphy, 2012). Furthermore, individuals with SCNP experience periods of pain-free days, thus, allowing researchers to determine how changes to neck anatomy may alter these neural mechanisms and pathways while, simultaneously, eliminating the confounding bias of pain.

2.2 Sensorimotor Integration

To produce accurate and efficient motor responses, the body relies upon the brain's ability to process and integrate various forms of sensory input. This neurological process is known as SMI (Holt et al., 2016; Wolpert et al., 1995). SMI provides an individual with an estimate of the state of their body and their external environment (Wolpert et al., 1998). As illustrated by Treleaven (2007), proprioception heavily impacts SMI which is defined as an individual's bodily awareness in space, sense of limb position relative to other body parts.

2.2.1 Somatosensory evoked potentials

One commonly used methodology to assess SMI is somatosensory evoked potentials (SEP). SEPs are electrical potentials that are produced by stimulating afferent nerve fibers or their receptors in the periphery, which transmit along the dorsal column medial lemniscus tract of the spinal cord (DCML) (Crucchi et al., 2008). This action potential will travel along the DCML where it will synapse within the somatosensory cortex, resulting in electrical activity that

can be recorded from the scalp utilizing surface electrodes (Cruccu et al., 2008). These recorded electrical potentials then generate complex waveforms that represent the summation of axon potentials within the gray matter and the propagation of the action potentials along the peripheral nerve fibers (Passmore et al., 2014). These SEP peaks represent the arrival of the action potential from the peripheral nerves to the various cortical regions and the amount of time, in milliseconds, it takes for the action potential to reach the specific cortical area following peripheral nerve stimulation (Passmore et al., 2014). Additionally, the neurons that generate each individual SEP peak are referred to as neural generators (Cruccu et al., 2008). Each SEP peak is named based upon its polarity (negative or positive) and latency (milliseconds) (Cruccu et al., 2008). The polarity is represented by either an “N” or “P” in which a negative polarity, represented by an “N”, reflects an upward deflection on the SEPs waveform; whereas a positive polarity, represented by a “P”, reflects a downward deflection on the SEPs waveform (Nuwer et al., 1994). While the latency reflects the time, measured in milliseconds (ms) it takes for the action potential to reach the cortical area following the stimulation of the peripheral nerve (Passmore et al., 2014). In this way, the latency represents the cortical region that the neural generator originates from, after the peripheral nerve stimulation (Passmore et al., 2014). For example, the N24 SEP peak would represent a negative deflection on the SEPs waveform that occurred at 24ms. Additionally, the amplitude of the SEP peak reflects the electrical activity within the specific cortical area (Passmore et al., 2014). Thus, any changes in the amplitude of a given SEP peak may represent changes alterations within a specific cortical region. While changes in the amplitude of a given SEP peak may represent alterations in the rate of transmission along the peripheral nerve (Passmore et al., 2014). Prior literature that has examined changes within SMI and sensory processing have assessed changes within the N18,

N20, N24, and N30 SEP peaks (Andrew et al., 2018; Haavik & Murphy, 2012; Taylor & Murphy, 2008).

The neural generators for the N18 SEP peak are located within the inferior olive and dorsal column nuclei between the lower medulla and mid-brain-pontine regions (Noël et al., 1996; Sonoo et al., 1991). The N18 SEP peak represents the activity between the dorsal column nucleus and the interneurons of the cuneate nucleus that occur during cerebellar SMI (Sonoo, 2000). When learning a motor task, the cerebellum modifies extracerebellar output towards the M1 through inhibition of the inferior olive-cerebellar-M1 loop (Doyon et al., 2002). Due to the location of its neural generators, the N18 peak is representative of cerebellar inhibition during motor acquisition task.

The neural generators for the N20 SEP peak are located in Brodman's area 3b, within the somatosensory cortex, specifically in Brodman's area 3b (Desmedt & Ozaki, 1991). This peak represents the arrival of the earliest afferent volleys at the primary somatosensory cortex (S1) (i.e., earliest cortical processing within S1) (Nuwer et al., 1994).

The neural generators for the N24 SEP peak have been described to be localized near the wall of the central sulcus within the pathway between the cerebellum and S1 (Restuccia et al., 2006). This suggests that the N24 SEP peak represents somatosensory input towards S1 from the cerebellum (Restuccia et al., 2006).

The neural generators of the N30 SEP peak are located within the frontal lobe and reflex the activity within the cortical and subcortical loops that link with the basal ganglion, thalamus, pre-motor areas, and primary motor cortex (M1) (Passmore et al., 2014).

2.3 Proprioception

Proprioception provides individuals with information on their bodily orientation and spatial awareness (Kandel et al., 2000). Proprioceptive signals are commonly received from proprioceptors within the joints, skin, and muscles such as mechanoreceptors, joint receptors, golgi tendon organs, and muscle spindles (Matthews, 1988). However, research by Proske and Gandevia (2012) has demonstrated that joint receptors play a limited role in signaling proprioception for most joints; while muscle spindles are the bodies primary source of proprioception within the body. Muscle spindles act as stretch sensitive proprioceptors and are found in majority of skeletal muscle but are found in the greatest density in muscles where accuracy is vital (Macefield & Knellwolf, 2018). Muscle spindle density is very high within the neck musculature, where spindle feedback plays a key role in integrating the position of the head and neck (Cooper & Daniel, 1963). Each muscle spindle contains a bundle of straited intrafusal fibers that line fascicles of the extrafusal muscle fibers; thus, any change within the skeletal muscle cause a stretch of these intrafusal fibers (Kandel et al., 2000). This stretch of the muscle spindle is detected by the central nervous system (CNS) via two groups of sensory nerve fibers known as group Ia afferent (primary afferents) and group II afferents (secondary afferents) (Knierim, 2020). Primary afferents wrap around the central portion of the intrafusal fibers and sense change in both length and velocity within a muscle. While secondary afferents, innervate the ends of the nuclear chain and the static nuclear bag (Knierim, 2020). Since these secondary afferents innervate the static portions of the muscle spindle they only sense changes within muscle length (Knierim, 2020). Proprioceptive information is carried towards various regions of the brain via two ascending sensory tracts. The dorsal column medial lemniscus tract and spinocerebellar tract.

2.3.1 Dorsal Column Medial Lemniscus Tract

The dorsal column medial lemniscus tract (DCML) is a three order neuron pathway that is responsible for transmitting vibration sense, fine touch, two-point discrimination, and conscious proprioception from the periphery to the cerebral cortex (Al-Chalabi et al., 2018; Kandel et al., 2000). Signals are first detected by the deformation of various sensory receptors within the skin. This includes mechanoreceptors such as Meissner's corpuscles and Pacinian corpuscles, which are responsible for detecting fine touch and vibration sense, respectively (Al-Chalabi et al., 2018). Additionally, conscious receptors such as Golgi tendon organs (GTO), relay conscious proprioceptive information regarding the length and contraction of a muscle (Kandel et al., 2000). These receptors then relay this sensory information towards the medial dorsal root entry zone of the spinal cord via the central axons of the dorsal root ganglion, the first order neuron of this pathway (Kandel et al., 2000). Once in the spinal cord, some of these central axons will give off small collateral branches that will terminate within the gray matter of the spinal cord which will help the facilitation of the spinal reflexes (Al-Chalabi et al., 2018). However, majority of these central axons leave the gray matter in the dorsal horn and enter the dorsal funiculus to help form either the fasciculus gracilis or fasciculus cuneatus (Kandel et al., 2000). The fasciculus gracilis is located more medially within the dorsal column and transmits sensory information from the associated with the DCML from the lower limb (Kandel et al., 2000). While the fasciculus cuneatus is located more laterally within the dorsal column and transmits sensory information from the upper limb (i.e. nerve roots above the level of T6) (Al-Chalabi et al., 2018). The axons within the fasciculus gracilis and cuneatus will then ascend towards the caudal medulla and synapse within the nucleus gracilis and cuneatus, respectively, which act as the second order neurons on this three-order neuron pathway (Al-Chalabi et al., 2018). These second-order neurons then decussate, ventromedially, across the midline of the

medulla as internal arcuate fibers and come together to form the medial lemniscus (Al-Chalabi et al., 2018). The medial lemniscus then terminates within the ventroposterolateral nucleus (VPL) of the thalamus which is the third-order neuron in this pathway (Al-Chalabi et al., 2018). The thalamus contains a series of nuclei that relay information towards the various regions within the brain such as S1, cerebellum, basal ganglion, supplementary motor area, and M1 (Kandel et al., 2000). In this way, the thalamus serves as the control/relay center within the brain (Kandel et al., 2000). The third-order neurons of the VPL then travel laterally, out of the thalamus, and through the internal capsule, where they will then terminate within S1 (Al-Chalabi et al., 2018).

2.3.2 Spinocerebellar Tract

The spinocerebellar tract conveys unconscious proprioceptive information towards the spinocerebellar division of the cerebellum (Kandel et al., 2000). This tract is divided into four divisions, all of which are responsible for projecting proprioceptive information from different regions of the body (Röijezon et al., 2015). This includes the dorsal spinocerebellar, ventral spinocerebellar, rostral cerebellar tract, and cuneocerebellar tracts (Kandel et al., 2000). Both the dorsal spinocerebellar and cuneocerebellar tracts share similar neural processes as both tracts act as a two-order neuron pathways that project unconscious proprioceptive information from muscle spindles and joint receptors within the upper limb (above the level of C8) and lower limb (between the levels of C8-L2), respectively (Röijezon et al., 2015). Additionally, both tracts will enter the spinocerebellar division of the cerebellum via the inferior cerebellar peduncle after, synapsing within the dorsal nuclei (dorsal spinocerebellar tract) and accessory cuneate nucleus (cuneocerebellar tract) (Knierim et al., 1997). In contrast, the ventral spinocerebellar and rostral cerebellar tracts transmit information from descending motor and premotor pathways, during movement, towards the spinocerebellum (Bosco & Poppele, 2001). This allows for the

cerebellum to make online corrections during movements of the lower (ventral spinocerebellar) and upper limbs (rostral cerebellar) (Kandel et al., 2000) by comparing the motor command, to sensory feedback from the active muscles, a process known as feedback processing (Knierim et al., 1997). Majority of the projections from the rostral spinocerebellar tract ascend ipsilaterally; however, a small portion will project ipsilaterally (Matsushita & Xiong, 1997). Additionally, both of these tracts enter the spinocerebellum via the superior cerebellar peduncle (Kandel et al., 2000).

2.4 Body Schema

Over time the brain uses sensory feedback and motor commands to create internal representation of the body and the space surrounding it (Head & Holmes, 1911; Holmes & Spence, 2004). This neural process is known as body schema and it allows the body to perform a desired behaviour by navigating through 3D space, and to avoid and/or manipulate objects (Popper et al., 1977) Body schema is a multisensory process that integrates somatosensory, auditory, visual, and proprioceptive information (Holmes & Spence, 2004). In order for the brain to represent the space around the body in which the hands can reach, various regions of the brain will assess the location of the arms in space. This can be represented as reference frames; which can either be body-centered or eye-centered (Holmes & Spence, 2004). Body-centered reference frames represent the topography of the body surface and primarily originate from S1 and several other cerebral regions such as the secondary somatosensory cortex, premotor cortex, and M1 (Cohen & Andersen, 2002). While eye-centered reference frames assess the location of body parts utilizing eye-centered maps within the visual cortices (Cohen & Andersen, 2002). Depending upon the behavioural situation, the brain will utilize specific reference frame most suited to the task and environment (Holmes & Spence, 2004).

2.5 Cerebellum

The cerebellum acts as to coordinate and modify movements by comparing the actual movement to the intended movement (Knierim et al., 1997). In order to monitor and modify movement, it receives input from the various sensory systems such as the proprioceptive, vestibular, and visual systems (Knierim et al., 1997). It then sends these modified signals to various regions within the cerebrum such as the cerebellar nuclei and motor cortex. Specifically, the cerebrocerebellar division of the cerebellum forms a connection with the motor cortex via the pontine nucleus (afferent input to the cerebrum) and the ventrolateral thalamus (efferent output from the cerebrum), to modify motor output from the motor cortex (Knierim et al., 1997).

2.6 Cerebellar Anatomy

The cerebellum is divided into three functional regions (FIG. 2.1), all of which correspond to anatomical subdivisions within the cerebellum: the cerebrocerebellum, spinocerebellum, and vestibulocerebellum (i.e. flocculonodular lobe) (Knierim et al., 1997). Each division is responsible for integrating information from specific sensory systems and sends outputs to different regions of the brain (Kandel et al., 2000). The cerebrocerebellum is the largest of the three divisions and comprises the lateral hemispheres of the cerebellum as well as the dentate nucleus, one of the deep cerebellar nuclei (Knierim et al., 1997). It receives input, via the pontine nucleus, from the sensory and motor cortices as well as the premotor cortex and parietal cortex (Kandel et al., 2000; Knierim et al., 1997). Utilizing this sensory information, the cerebrocerebellum formulates an efficient motor plan and relays this information back towards the cortical areas, via the ventrolateral nucleus of the thalamus, resulting in smooth movements (Kandel et al., 2000; Knierim et al., 1997). In this way, the cerebrocerebellum is heavily involved in sensorimotor learning and control (Peterburs & Desmond, 2016).

The spinocerebellum is the most anterior of the three divisions and it encompasses the vermis and intermediate zones as well as the interposed and fastigial nuclei (Knierim et al., 1997). During movement, the spinocerebellum receives input from the cortical motor areas regarding the intended movement and feedback from the spinal cord (i.e., spinocerebellar tract), and periphery, regarding limb/body position (Kandel et al., 2000). Utilizing this sensory input, the spinocerebellum modifies movement by regulating peripheral musculature, to compensate for any disruptions that may occur during the movement such as changes in load (Kandel et al., 2000). Additionally, the spinocerebellum comprises of two deep cerebellar nuclei, the fastigial and interposed nuclei (Knierim et al., 1997). Purkinje cells within the spinocerebellum synapse on these two nuclei in order to modify the activity of the descending medial and lateral motor tracts (Kandel et al., 2000). In this way the spinocerebellum is able to modify the movements of the arms and legs, via the lateral pathways (i.e. lateral corticospinal tract and rubrospinal tract), and regulate posture and balance, via the medial pathways (i.e., reticulospinal tract, anterior corticospinal tract, tectospinal tract, & medial/lateral vestibulospinal tracts) (Knierim, 2016).

The vestibulocerebellum has been shown to be the oldest part of the cerebellum and constitutes the flocculonodular lobe of the cerebellum (Knierim et al., 1997). During head movements, the vestibulocochlear nerve projects signals from the vestibular labyrinth to the four vestibular nuclei located within the medulla and pons region (Knierim et al., 1997). The vestibulocerebellum then receives these signals from the vestibular nuclei and will then process the information and projects these signals back onto the vestibular nuclei (Kandel et al., 2000; Knierim et al., 1997). In this way, the vestibulocerebellum regulates the body's equilibrium by modifying the oculomotor reflexes via the medial longitudinal fasciculus, and maintains balance by controlling the axial and proximal limb muscles that are associated with

posture, via the medial and lateral vestibulospinal tracts (Gray, 2020c; Kandel et al., 2000; Knierim et al., 1997).

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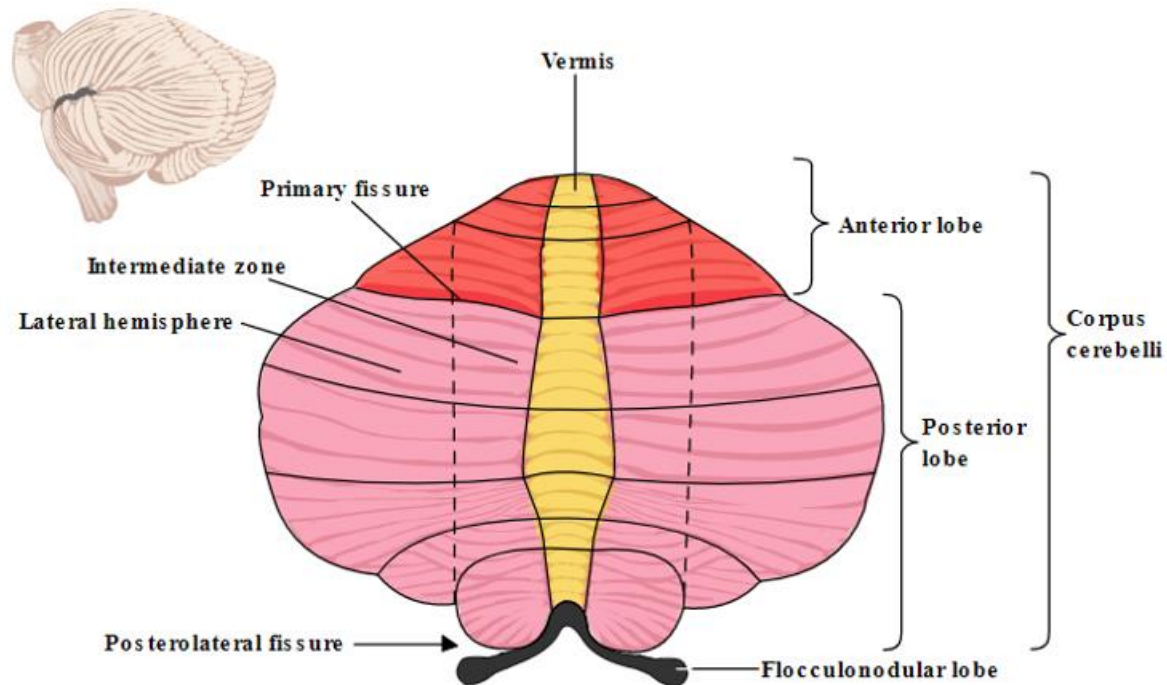


Figure 2.1. Unfolded diagram of the cerebellum (Knierim et al., 1997). Retrieved from <https://nba.uth.tmc.edu/neuroscience/m/s3/chapter05.html>

In summary, to transmit afferent and efferent information, the cerebellum utilizes three fiber bundles, known as peduncles; those being the inferior, middle, and superior cerebellar peduncles (Knierim et al., 1997). The inferior peduncle transmits four afferent tracts into the cerebellum (vestibulocerebellar, reticulocerebellar, posterior spinocerebellar, and olivocerebellar tracts) and one efferent tract away from the cerebellum (cerebellovestibular tract) (Snell, 2010). The middle peduncle is the largest of the three and only transmits afferent information into the cerebellum and is heavily involved in the corticocerebellar loop (Kim et al., 2014). Afferent fibers from the pontine nucleus enter the cerebrocerebellar division of the cerebellum via the

middle cerebellar peduncle (Snell, 2010). The superior peduncle mainly transmits efferent information away from the various cerebellar nuclei to the red nucleus, thalamus, and medulla regions (Snell, 2010). Additionally, it transmits some afferent input from the spinocerebellar tract (Knierim et al., 1997). The red nucleus is located within the midbrain region and receives cerebellar input from the various cerebellar nuclei and gives rise to the rubrospinal tract (Kandel et al., 2000; Knierim et al., 1997). The rubrospinal tract excites the alpha motor neurons, within the spinal cord, that act upon the flexor muscles (Kandel et al., 2000; Knierim, 2016). Also, due to its connection to the cerebellum, it plays a role in transmitting learned motor commands towards the musculature (Knierim, 2016).

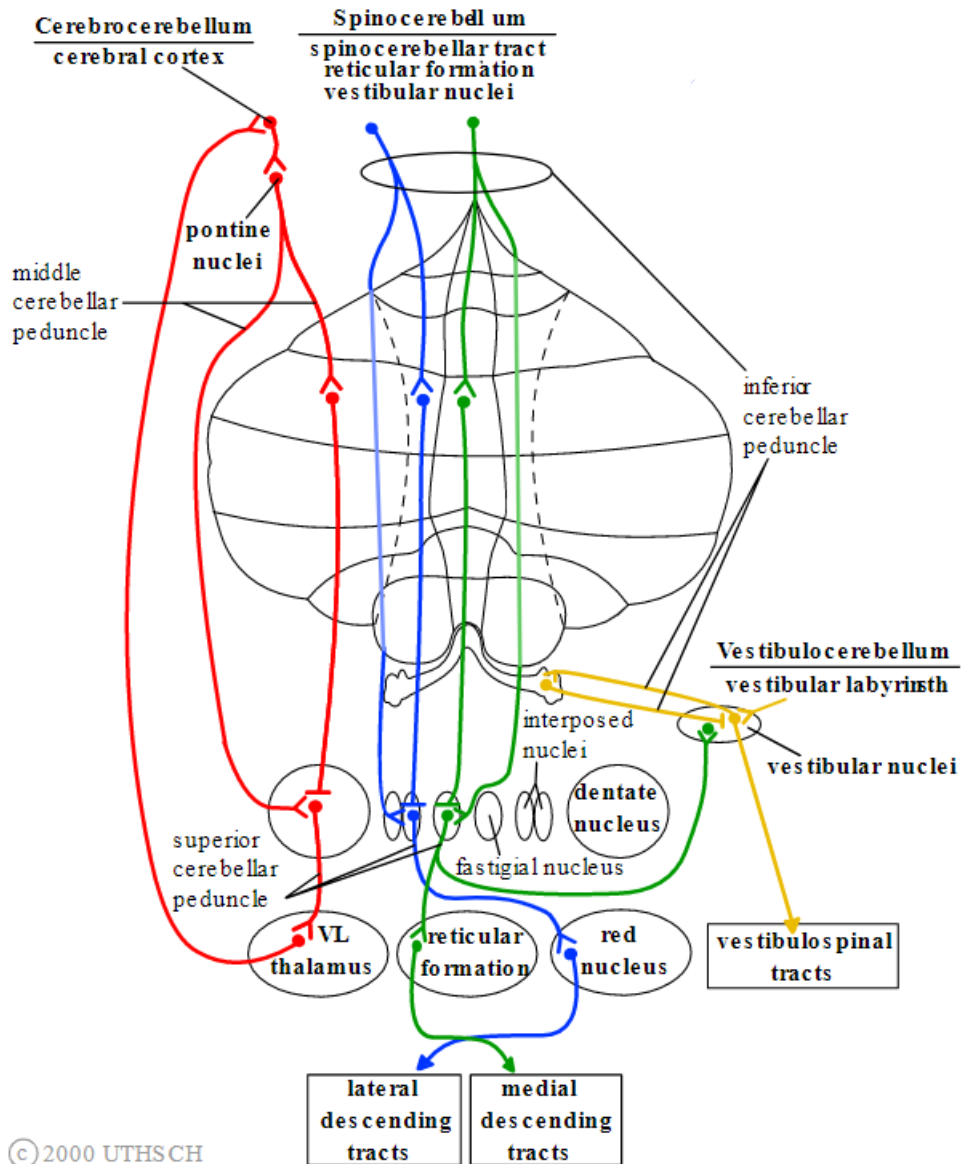


Figure 2.2. Summary of the various cerebellar pathways and four deep cerebellar nuclei (Knierim et al., 1997). Retrieved from <https://nba.uth.tmc.edu/neuroscience/m/s3/chapter05.html>

2.6.1 Cerebellar Cells

To communicate with different nuclei and the various area of the cerebral cortex there are numerous cells and fibers within the cerebellum (FIG. 2.3). These consist of granule cells, mossy fibers, Purkinje cells, and climbing fibers (Knierim et al., 1997). Granule cells are located within

the granule layer of the cerebellum and make up the majority of neurons/cells within the cerebellum (Knierim et al., 1997). They receive neural input primarily from mossy fibers and project this neural input onto Purkinje cells (Knierim et al., 1997). Mossy fibers originate from various structures within the mid brain regions such as the pontine nucleus, spinal cord, vestibular nuclei, and brainstem reticular formation (Knierim et al., 1997). The brainstem reticular formation is a set of interconnected nuclei located within throughout the brainstem (Kandel et al., 2000). These fibers carry sensory signals from these structures and project them onto the nuclei located within the cerebellum as well as granule cells (Knierim et al., 1997). Similar to mossy fibers, climbing fibers originate from structures outside of the cerebellum and, subsequently, carry sensory information into the cerebellum (Knierim et al., 1997). Specifically, climbing fibers originate from the inferior olivary nucleus, commonly referred to as the inferior olive, which is a nucleus located within the region of the medulla (Knierim et al., 1997). Similar to granule cells, Purkinje cells originate in the molecular layer of the cerebellum (Knierim et al., 1997). They utilize the inhibitory neurotransmitter gamma-Aminobutyric acid (GABA), and act as the primary output cells of the cerebellum by inhibiting the activity of the various nuclei within the cerebellar and brainstem region (Knierim et al., 1997; Warnaar et al., 2015). This output is completed in two ways: simple spike (SS) discharge and complex spike (CS) discharge (Knierim et al., 1997). During SS discharge, mossy fibers project excitatory signals onto the granule cells. Granule cells then send axonal projections, known as parallel fibers, towards the Purkinje cells in the molecular layer of the cerebellum (Knierim et al., 1997). They will then synapse with the Purkinje cells, triggering the release of a sodium dependent action potentials from the Purkinje cells which fire at a high resting rate of, approximately, 70 spikes/second (Knierim et al., 1997). During CS discharge, climbing fibers project excitatory signals directly

onto the Purkinje cells (Knierim et al., 1997). This will then trigger the release of a calcium dependent discharge from the Purkinje cells which tends to be more powerful than SS discharge (Knierim et al., 1997). However, these tend to fire at a slower rate than SS discharge, at, approximately, 1 spike/second (Knierim et al., 1997). To summarize: mossy fibers and climbing fibers originate from outside the cerebellum and carry sensory information into the cerebellum. In contrast, granule cells and Purkinje cells originate from within the cerebellum and receive input from various cells.

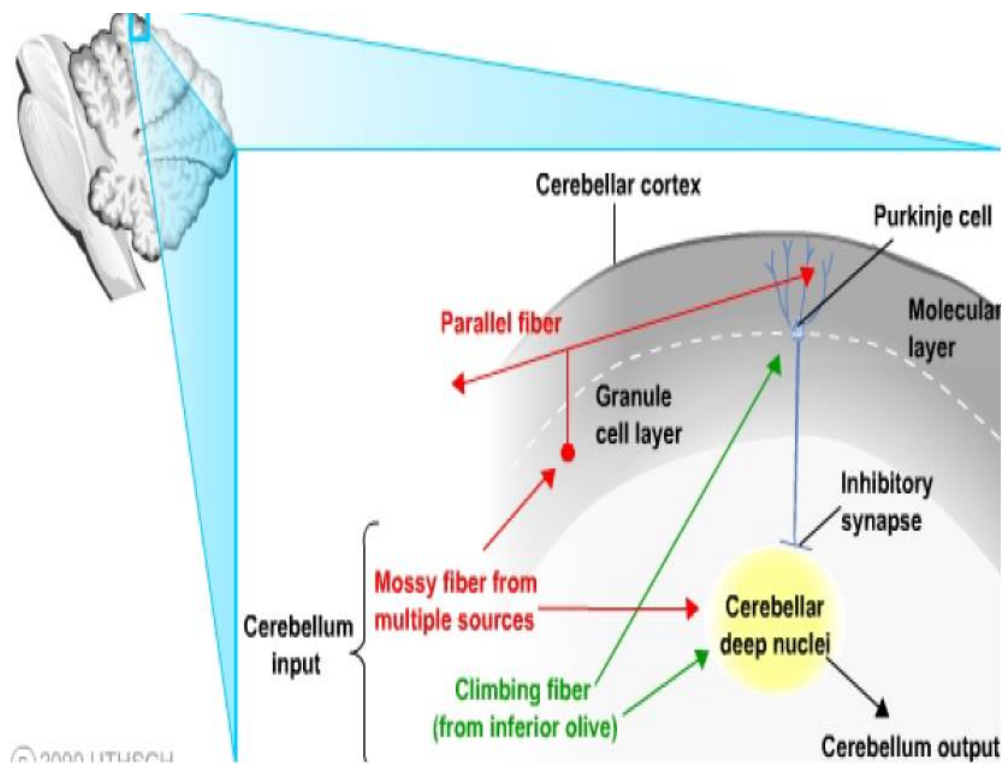


Figure 2.3. Summary diagram of cerebellar cells and their location (Knierim et al., 1997).

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2.6.2 Cerebellar Nuclei

All cerebellar outputs originate from the deep cerebellar nuclei (DCN) located in the various regions of the cerebellum (FIG. 2.2) (Kandel et al., 2000). In total, there are four DCN: the dentate nucleus, interposed nuclei which comprises the emboliform nucleus and globose nucleus, and the fastigial nucleus (Knierim et al., 1997). The dentate nucleus is the largest of the four DCN and is located in the lateral hemisphere of the cerebellum and is a key structure in the cerebrocerebellum (Knierim et al., 1997). It receives afferent input from the lateral hemisphere and the pontine nucleus and, thus, is heavily involved in the corticocerebellar loop (Knierim et al., 1997). It then projects efferent fibers onto the red nucleus and ventrolateral thalamic nucleus in order to help regulate fine motor control (de Leon & Das, 2021; Knierim et al., 1997).

The interposed nuclei is located in the spinocerebellum and receive afferent input in regards to proximal somatosensory, auditory, and visual information and subsequently projects efferent fibers onto the red nucleus (Knierim et al., 1997). In this way the interpose nuclei plays a key role in transmitting learned motor commands as the red nucleus is the origination site of the rubrospinal tract (Knierim, 2016; Knierim et al., 1997).

Similar to the interposed nuclei, the fastigial nucleus is also located in the spinocerebellum (Knierim et al., 1997). It receives proprioceptive input from the spinocerebellar tract regarding limb/body position and plays an integral role in modifying descending motor commands (Kandel et al., 2000; Zhang et al., 2016). Additionally, it projects proprioceptive information onto the vestibular nuclei (Knierim et al., 1997). Utilizing this proprioceptive information, the vestibular nuclei are able to modify the oculomotor reflexes in response to head and/or neck movements (Knierim et al., 1997). In this way the fastigial nucleus plays a key role in oculomotor control.

2.7 Vestibulospinal Tract

The vestibulospinal tract (VST) is one of the many descending motor tracts within the spinal cord and originates from the vestibular nuclei, specifically the medial and lateral vestibular nuclei (Gray, 2020b; Knierim, 2016). Its role is to coordinate and maintain the body's posture by innervating the anti-gravity muscles within the body, those being the extensor muscles (Lance & McLeod, 1981). The tract descends ipsilaterally within the spinal cord and synapses within the alpha and gamma motor neurons that are located in the anterior horn of the spinal cord (Lance & McLeod, 1981). In other words, the VST will send vestibular signals towards alpha and gamma motor neurons which help to maintain the tension and length of our muscles (Lance & McLeod, 1981). This tract can also be divided into medial and lateral portions with the lateral portion making up majority of the fibers (Gray, 2020b). The lateral portion originates from lateral vestibular nucleus, descends ipsilaterally, and supplies the extensor muscles of the axial and appendicular skeleton (Knierim, 2016). While the medial portion originates from medial vestibular nucleus, descends bilaterally, and supplies the extensor muscles of the neck and head (Knierim, 2016).

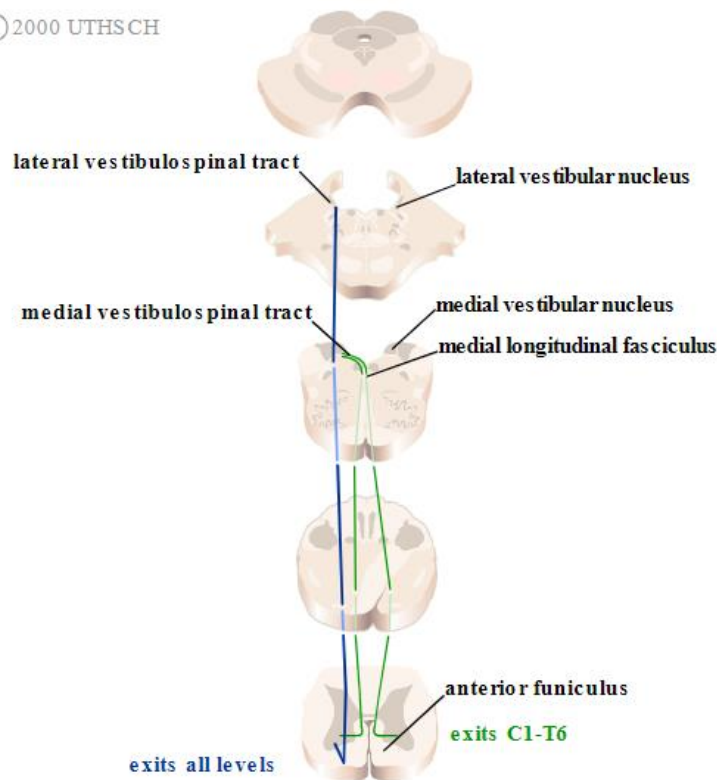


Figure 2.4. Pathway of the medial and lateral vestibulospinal tracts (Knierim, 2016). Retrieved from <https://nba.uth.tmc.edu/neuroscience/m/s3/chapter02.html>

2.7.1 Vestibular Nuclei

There are 4 pairs of vestibular nuclei, all of which are located within the pons and medulla area: the medial, lateral, inferior, and superior vestibular nuclei (Gray, 2020b). These second order nuclei transmit information regarding head/body position, and oculomotor control (Gray, 2020b). The lateral nucleus is located within the pons and gives rise to the lateral portion of the VST, commonly referred to as the lateral vestibulospinal tract (LVST) (Gray, 2020b; MacKinnon, 2018). The medial nucleus is located within the medulla and gives rise to the medial portion of the VST, also known as the medial vestibulospinal tract (MVST) (Gray, 2020b; MacKinnon, 2018). The inferior nucleus is located within the medulla and it supplies afferents to

the LVST (Gray, 2020b). Additionally, the inferior nucleus will work together with the medial nucleus to supply vestibular afferents directly into the cerebellum (Gray, 2020b). The superior nucleus is located within the pons and it gives rise to vestibular afferents which ascend towards the thalamus (Gray, 2020b). Additionally, the superior nucleus, along with the medial nucleus, give rise to a group of ascending vestibular fibers known as the medial longitudinal fasciculus (MLF) (MacKinnon, 2018). The MLF projects vestibular input from the medial and superior vestibular nuclei towards the oculomotor, trochlear, and abducens nuclei (Glover, 2004). These three nuclei give rise to three cranial nerves that act upon the oculomotor muscles, the oculomotor, trochlear, and abducens nerves (Glover, 2004). In this way vestibular information received from the vestibular labyrinth, located in the inner ear, is used to modify the movement of the eyes.

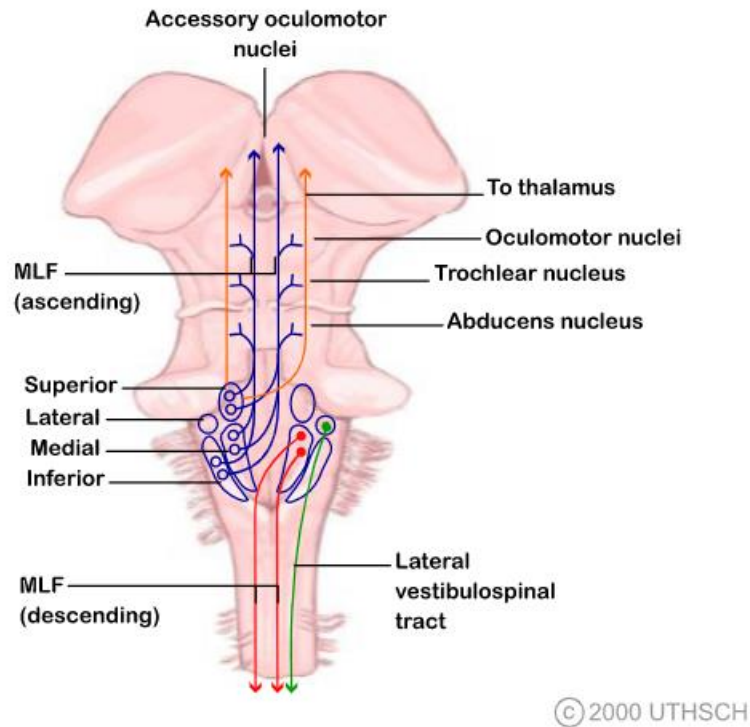


Figure 2.5. Summary of the various projections of the vestibular nuclei (Gray, 2020b). Retrieved from <https://nba.uth.tmc.edu/neuroscience/m/s2/chapter11.html>

2.8 Oculomotor Neuroanatomy

Movement of the eyeballs is a result of the extraocular muscles (i.e. oculomotor muscles) that surround the eye (Moore & Dalley, 2018). In total there are 7 oculomotor muscles (FIG 2.6); however, only 6 are involved the movement of the eyeball (Moore & Dalley, 2018). These consist of the superior oblique, superior rectus, medial rectus, lateral rectus, inferior rectus, and inferior oblique muscles (Moore & Dalley, 2018). The superior rectus muscle acts to turn the eye upwards, the medial rectus muscle acts to turn the eye medially, the lateral rectus muscle acts to turn the eye laterally, and the inferior rectus muscle acts to move the eye downwards (Moore & Dalley, 2018). While the superior oblique muscle acts to turn the eye downward when the eye is

turned medially and the inferior oblique muscle acts to turn the eye upwards when the eye is turned medially (Moore & Dalley, 2018). The seventh oculomotor muscle is known as the levator palpebrae superioris and it's involved in the movement of the eyelid (Moore & Dalley, 2018). The oculomotor muscles receive motor input from three different cranial nerves: the oculomotor, trochlear, and abducens nerves (Moore & Dalley, 2018). The oculomotor nerve supplies the superior rectus, medial rectus, inferior rectus, and inferior oblique muscles (Moore & Dalley, 2018), while the trochlear nerve supplies the superior oblique muscle, and the abducens nerve supplies the lateral rectus muscle (Moore & Dalley, 2018).

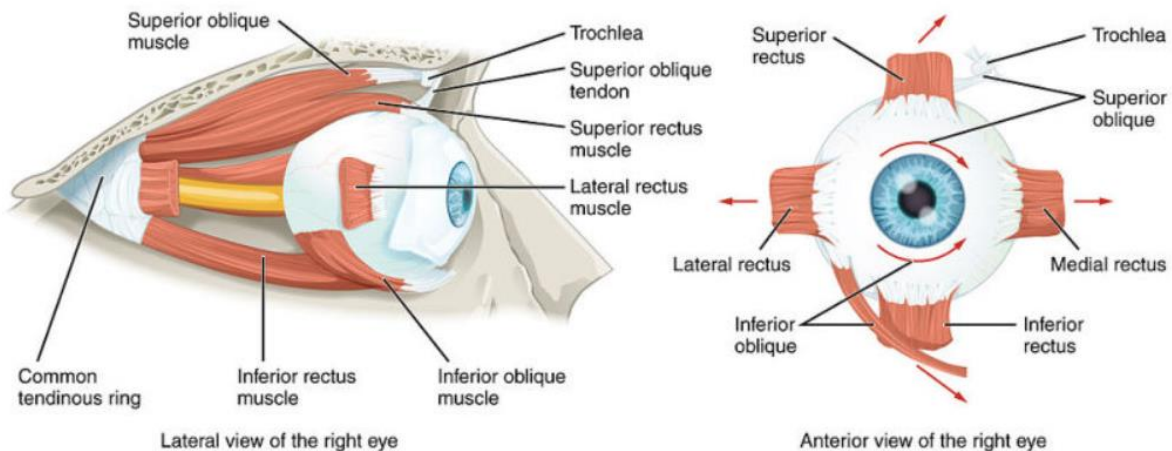


Figure 2.6. Summary of the extraocular muscles. By OpenStax College [CC BY 3.0 (<https://creativecommons.org/licenses/by/3.0>)], via Wikimedia Commons

2.8.1 Cranial Nerves

There are 12 pairs of cranial nerves that are exclusively located within the cranial and upper neck region of the body; which originate from various nuclei within the midbrain, pons, and medulla regions of the brain (Moore & Dalley, 2018). There are only five cranial nerves that are involved in oculomotor control: the second cranial nerve (optic nerve, CNII), the third cranial nerve (oculomotor nerve, CN III), the fourth cranial nerve (trochlear nerve, CN IV), the sixth

cranial nerve (abducens nerve ,CN VI), and the eighth cranial nerve (vestibulocochlear nerve, CN VIII) (Gray, 2020b).

2.9 Vestibulo-ocular reflex

The vestibulo-ocular reflex (VOR) is an oculomotor reflex that acts to stabilize gaze during head movements (Ranjbaran & Galiana, 2015). The VOR can be quantitatively expressed as VOR gain, which is the ratio of peak eye velocity to peak head velocity (Fadaee & Migliaccio, 2016). In a healthy population, this value is, approximately, 1.0; representing, a one-to-one ratio between head and eye movements (Hoshowsky et al., 1994). However, Shelhamer and colleagues (1994) suggests that VOR gain will increase in response to a retinal image slip that can be induced using a moving target. The VOR can also be represented by slow and fast phases (Ranjbaran & Galiana, 2015). The slow phase acts to move the eyes in the opposite direction and, almost, the same velocity of a head rotation in order to preserve a stable visual image on the retina (Bronstein et al., 2015; Ranjbaran & Galiana, 2015). However, when the VOR is significantly reduced (i.e., <50%), the slow-phase is no longer able to preserve vision and, thus, a corrective saccade is required to fixate on the visual target (Bronstein et al., 2015). While the fast phase occurs at higher speeds and causes the eyes to move in the direction of the head movement, then makes a corrective eye movement back towards the target (Ranjbaran & Galiana, 2015). However, majority of literature removes/ignores the fast phase when analyzing eye velocity to calculate VOR gain (Ranjbaran et al., 2016).

The reflex relies upon three different input pathways to produce an efficient response. This includes a vestibular, visual, and proprioceptive pathway, all of which are directly modified by the cerebellum (Gray, 2020c).

2.9.1 Vestibular input to the vestibulo-ocular reflex

The vestibular pathway begins with the vestibulocochlear nerve (CN VIII) as it passes through the internal auditory meatus where it picks up vestibular afferents from Scarpa's ganglion (Gray, 2020c). It then travels further into the membranous labyrinth of the inner ear into the three semicircular ducts (horizontal, anterior, and posterior) (Gray, 2020c). Within each semicircular duct is a localized dilation known as the ampulla (Gray, 2020c). This ampulla contains a small structure known as the crista where a patch of hair cells, known as the stereocilia, lay and are innervated by branches of the CN VIII (Gray, 2020a). When head rotation occurs, inertia causes movement of the fluid (i.e., endolymph) to lag which then causes movement within the semicircular duct, opposite to that of the head rotation (Gray, 2020c). This movement of the endolymph causes bending of the cupula which, in turn, bends the stereocilia (Gray, 2020a, 2020c). Depending on the direction in which the stereocilia are bent, an influx of potassium ions will be released causing a depolarization of the neuron which generates impulses that are sent along the CN VIII (Gray, 2020a). When the stereocilia are bent towards the kinocilium, potassium is released into the cell causing depolarization of the neuron and an increase in afferent activity (Gray, 2020a). When the stereocilia are bent away from the kinocilium, the neuron becomes hyperpolarized and inhibition of afferent activity occurs (Gray, 2020a). In this way, a head rotation will cause excitatory and inhibitory signals to occur simultaneously. For example, during a right head rotation, fluid within the right ampulla will move in the left direction causing excitation of the neuronal cell (Gray, 2020c). While fluid within the left ampulla will move in the right direction causing inhibition of the neuronal cell (Gray, 2020c).

The CN VIII will then project these vestibular afferents towards the four vestibular nuclei(Gray, 2020c). However, a small portion of these vestibular afferents directly enter the cerebellum via the inferior cerebellum peduncle (Gray, 2020b). Utilizing this vestibular input, the cerebellum will make adjustments to posture by sending descending signals, via the MVST and LVST, to the alpha and gamma motor neurons within the extensor muscles (Gray, 2020b). Additionally, the medial and inferior vestibular nuclei will utilize mossy fibers to send second order vestibular afferents into the cerebellum, via the inferior cerebellar peduncle, which will then synapse directly upon granule cells within the cerebellum (Gray, 2020b). Once the granule cells receive this input, they project their long axons, known as parallel fibers, onto the Purkinje cells within the flocculonodular lobe of the cerebellum (Gray, 2020b). When these parallel fibers synapse on the Purkinje cells they trigger the release of a SS discharge, in order to modify the activity of the vestibular nuclei (Gray, 2020b). Once the vestibulocerebellum has modified the activity of the vestibular nuclei, the medial and superior vestibular nuclei will project vestibular afferents towards the three oculomotor nuclei (i.e., the oculomotor, trochlear, and abducens nuclei), via the MLF (Gray, 2020b). After synapsing within the various oculomotor nuclei, vestibular afferents send excitatory and inhibitory signals along the motor neurons towards the extraocular muscles to coordinate eye movements during head rotations (i.e. VOR response) (Gray, 2020b). In this way, the cerebellum modifies the movement/velocity of the eyes and head, during the VOR response, by adjusting the output from the vestibular nuclei to the three oculomotor nuclei, via the MLF, and the neck musculature, via the MVST.

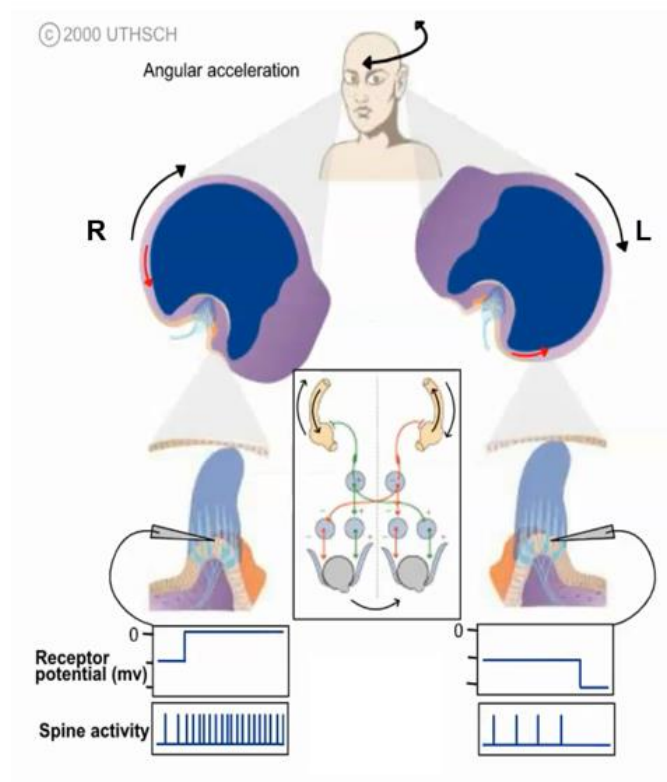


Figure 2.7. Activation pattern of oculomotor muscles during the VOR (Gray, 2020c). Retrieved from <https://nba.uth.tmc.edu/neuroscience/m/s2/chapter10.html>

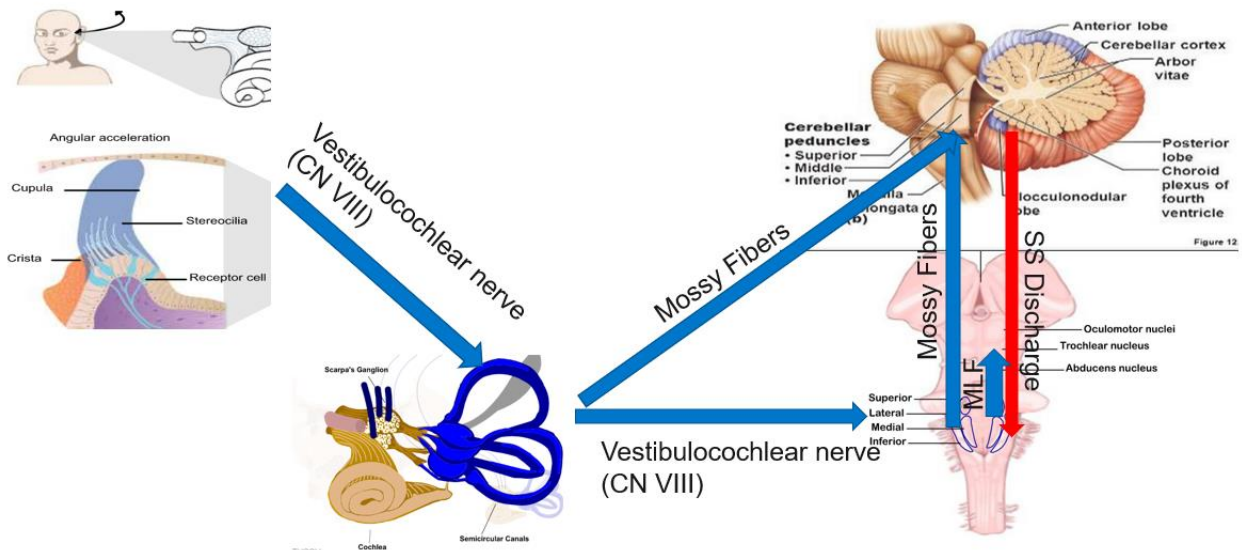


Figure 2.8 Pathway of vestibular input to the cerebellum to control COR and VOR

2.9.2 Proprioceptive input to the vestibulo-ocular reflex

During head rotations, muscle spindles within the cervical region send proprioceptive information towards the cerebellum via the spinocerebellar tract. However, since the VOR involves movement of the head and neck (i.e. upper limb), the majority of the proprioceptive input received is from the rostral cerebellar and cuneocerebellar divisions of the spinocerebellar tract (Röijezon et al., 2015). Once proprioceptive information reaches the cerebellum, it travels towards one of the four deep cerebellar nuclei, the fastigial nucleus (Gdowski & McCrea, 2000). The fastigial nucleus then projects this proprioceptive information out of the cerebellum and onto the four vestibular nuclei within the medulla and pons (Knierim et al., 1997; Zhang et al., 2016). The vestibular nuclei then utilize this proprioceptive information to modify the movement/velocity of the eyes and head, via the MLF and MVST, respectively (FIG 2.9). Additionally, during head rotations, some proprioceptive information is transmitted to the central cervical nucleus (CCN), which is made up of a column of cells from cervical afferents and is located anterior to the upper four cervical spinal cord segments (Gdowski & McCrea, 2000). The CCN sends afferent input into the flocculus of the cerebellum, via mossy fibers (Gdowski & McCrea, 2000). Similar to input from the vestibular system, proprioceptive input is utilized to modify the activity of floccule Purkinje cells (Gdowski & McCrea, 2000). In-turn, the floccular Purkinje cells modify the activity of the VOR via inhibitory signals which act upon the vestibular nuclei (Gdowski & McCrea, 2000). In this way, the cerebellum utilizes proprioceptive information to adjust the VOR response.

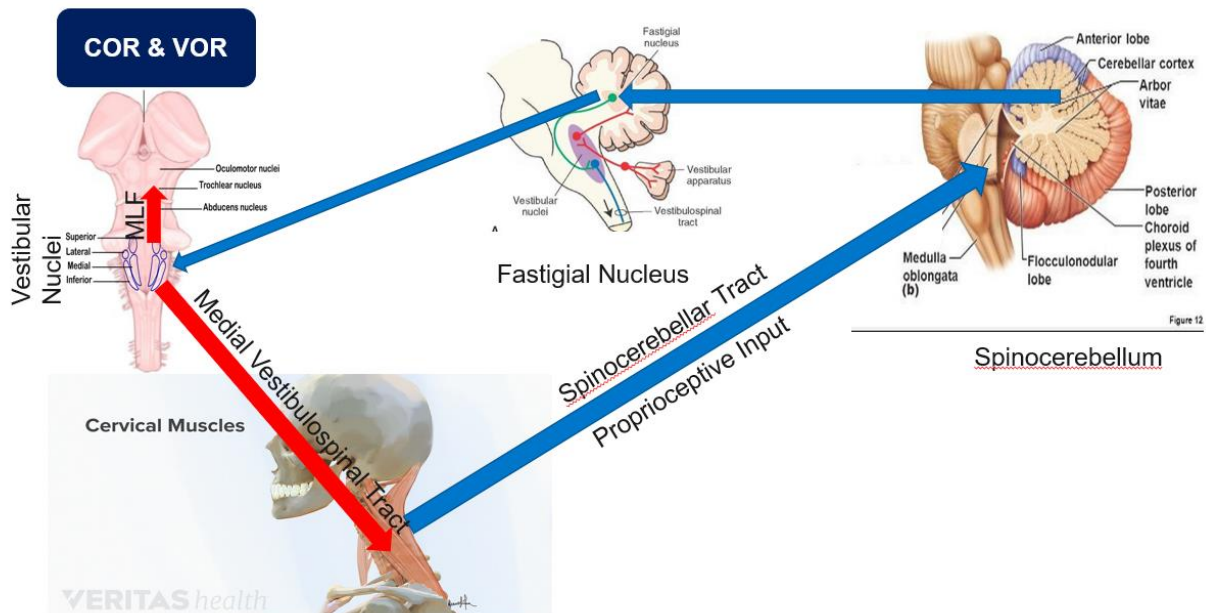


Figure 2.9 Pathway of proprioceptive input to the cerebellum to control COR and VOR

2.9.3 Visual input to the vestibulo-ocular reflex

When head rotation occurs, a compensatory eye movement is made in the opposite direction, and same velocity, of the head rotation to ensure images stay stable on the retina (Fadaee & Migliaccio, 2016). However, when this eye movement is no longer compensatory the image becomes distorted on the retina and, subsequently, an error signal is sent along the visual pathway (Ito, 1998). This error signal is first transmitted along the optic nerve towards the tectal plate in the dorsal portion of the brainstem (Ito, 1998). There the visual information synapses within the superior colliculus (SC) (Ito, 1998). The primary role of the SC is to orient the sensory structures of the head such as the eyes and ears, towards a stimulus (Corneil et al., 2002). In this way, the SC utilizes this visual error and work in conjunction with the cerebellum to re-orient the eyes to the image (Ito, 1998). After synapsing within the SC, this visual error is projected towards the inferior olivary nucleus (ION), located within the medulla (Ito, 1998). The role of

the ION is to transmit sensory signals between the cerebellum and various sensory pathways such as the ascending tracts and visual system, in this case, the visual error toward the cerebellum via climbing fibers within the ION (Knierim et al., 1997). Once in the cerebellum, these climbing fibers synapse on the Purkinje cells within the molecular layer of the cerebellum, triggering the release of a CS discharge which acts to inhibit the activity of the vestibular nuclei (Ito, 1998; Zucca et al., 2016). Utilizing this input, the vestibular nuclei modifies the movement of the eyes via the MLF, thus, leading to an adaptation of the VOR response. This neurophysiological phenomenon is known as VOR gain adaptation and may be used as a measure of cerebellar plasticity (FIG 2.8).

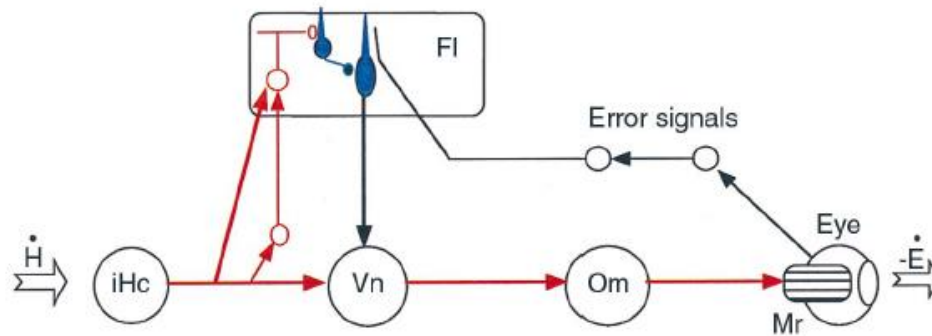


Figure 2.10. Summary of VOR adaptation within the flocculonodular lobe of the cerebellum (Ito, 1998)

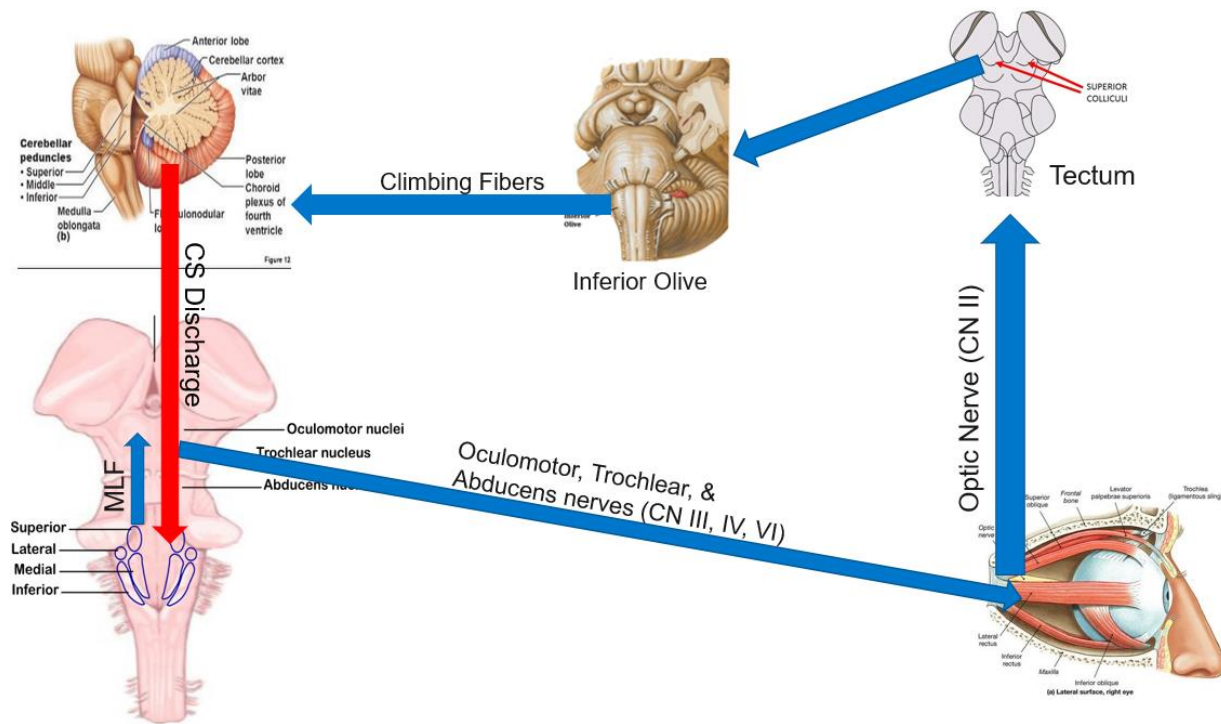


Figure 2.11 Pathway of visual input to the cerebellum to control COR/VOR and adapt the VOR response

2.9.4 Velocity Storage Mechanism

In daily life, the VOR is frequently active to maintain the body's balance and coordination. To ensure the VOR response is sufficient, the cerebellum cannot solely rely upon sensory feedback from the visual, vestibular, and proprioceptive systems (Bronstein et al., 2015). Thus, it creates an internal model, based upon previous sensory information, to maintain a sufficient VOR response (Bronstein et al., 2015). This neural phenomenon is known as the velocity storage mechanism and is defined as a polysynaptic loop between the cerebellum and perihyoglossal nucleus (Ito, 1998). Utilizing information obtain from prior head rotations, the cerebellum builds this internal model to prevent abnormal eye movements from occurring such as nystagmus (Ito, 1998).

2.10 Cervico-ocular reflex

The cervico-ocular reflex (COR) is a gaze stabilizing reflex that acts to stabilize images on the retina by keeping the eyes fixated in the orbits during trunk rotations while the head is stable (de Vries et al., 2016). Similar to the VOR the COR can be quantitatively expressed as VOR gain, which is the ratio of peak eye velocity to peak head velocity (Ischebeck et al., 2017). Additionally, literature has found that COR gain may be as low as 0.1 or completely absent within a healthy population (Schubert et al., 2004). The COR is typically much weaker than the VOR, and is most prominent in the absence of a visual target (Gdowski et al., 2001).

2.10.1 Neuroanatomy of the cervico-ocular reflex

Little is known surrounding the neural substrates that formulate the COR, as the specific details of the pathway are still unknown (Gdowski et al., 2001). However, literature suggests that it may share the same central processes as the VOR (Gdowski et al., 2001), specifically, those related to neck proprioceptive input towards the cerebellum (Gdowski et al., 2001). During trunk-on-head rotations, neck proprioceptors detect changes in neck velocity and transmit this information along the spinocerebellar tract (Röijejon et al., 2015). Some of this proprioceptive information enters the spinocerebellar division of the cerebellum while some of the information is transmitted to the CCN (Gdowski et al., 2001). Via mossy fibers, the CCN sends afferent input into the flocculus of the cerebellum (Gdowski et al., 2001). Similar to the VOR, the floccular Purkinje cells will modify the activity of the COR via inhibitory signals which act upon the vestibular nuclei (Gdowski et al., 2001). Also, since both reflexes share the same neural substrates, one must be suppressed during certain behavioural contexts in order to ensure gaze stability is maintained by the active reflex (Gdowski et al., 2001). It has been suggested that through floccular Purkinje cell input to the vestibular nuclei, the flocculonodular lobe is able to

suppress the activity of the VOR while the COR is active (Belton & McCrea, 1999; Gdowski et al., 2001).

2.11 Altered central processing with neck pain

One of the most common sensory systems that has been observed to be altered with neck pain is the vestibular system (Brandt & Bronstein, 2001; Wrisley et al., 2000). Disruptions within the vestibular system, due to neck pain, commonly manifest as cervicogenic dizziness which is characterized by dizziness and altered equilibrium, associated with neck pain (Wrisley et al., 2000). Additionally, Brandt and Bronstein (2001) demonstrated that altered cervical somatosensory input, due to neck pain, may lead to sensory mismatches between vestibular and cervical sensory inputs which may also result in cervical vertigo. This is commonly characterized by disorientation and imbalance, commonly associated with neck pain (Brandt & Bronstein, 2001). This could suggest that neck pain such as SCNP, may alter the VOR and COR as they both receive input from the vestibular system. As described by de Vries and colleagues (2019), these possible alterations within the oculomotor reflexes, may account for symptoms such as dizziness and postural instability, commonly seen in a neck pain population. These disruptions within the vestibular system, due to neck pain, are most likely due to the connections that the vestibular system forms with the cervical receptors such as the role of cervical proprioceptive input in modifying the oculomotor reflexes via the fastigial-vestibulocerebellar connection or the connection between the CCN and vestibulocerebellum (Treleaven, 2017). However, these alterations within the vestibular system seem to only be apparent within more severe forms of neck pain (Reid et al., 2014; Reid et al., 2008; Treleaven et al., 2003; Treleaven et al., 2008). Treleaven (2017) illustrates that low severity neck dysfunction such as SCNP, may not result in

vestibular dysfunction. The researcher also states that more severe forms of neck trauma such as whiplash, is required to elicit disruptions within the vestibular system (Treleaven, 2017).

Haavik and Murphy (2012), described that areas of joint/spinal dysfunction such as SCNP, represent areas of altered afferent input which made lead to alterations within central processing. In support of this, Paulus & Brumagne (2008) have demonstrated significant changes in head movement during passive movement of the shoulder when comparing persons with SCNP to asymptomatic controls. This suggests that alterations in head and neck proprioception may be due to disruptions within the muscle spindles located in their neck musculature. Zabihhosseinian and colleagues (2017) have built upon this concept by comparing the ability of asymptomatic control and SCNP participants to perform a humeral elevation task in the scapular plane, before and after a cervical extensor muscle (CEM) fatigue task. It was discovered that individuals with SCNP displayed altered scapular kinematics when compared to the asymptomatic control group (Zabihhosseinian et al., 2017). Interestingly, the researchers also found that CEM fatigue caused the asymptomatic control group to perform a humeral elevation task in a more adducted position; whereas the SCNP group performed the task in a more flexed position, and fatigue did not further alter their scapular kinematics (Zabihhosseinian et al., 2017). The authors suggested this was because the SCNP group was already adapted to altered neck input. This work suggests that SCNP alters sensory input received from the neck, during tasks involving the upper limb, leading to alterations in upper limb body schema. The research also suggests that these differences in scapular kinematics may represent alterations in neuromuscular recruitment strategies in individuals with SCNP. Additionally, research by Haavik and Murphy (2011) has demonstrated that individuals with SCNP have altered elbow joint position sense (JPS), which can be improved following a cervical spinal manipulation intervention. This

suggests that joint dysfunction, due to SCNP, results in altered afferent input towards the CNS; thus, altering SMI. Research by Andrews et al. 2018, supports this claim. Utilizing SEPs, the researchers were able to assess the neural markers of SMI, during a novel motor acquisition task, between an asymptomatic control group and a SCNP group. The researchers observed significant between group differences in the N18 and N24 SEP waveforms (Andrew et al., 2018). The researchers determined that individuals with SCNP may have alterations within SMI as demonstrated by a greater increase in the N18 SEP peak, during the novel motor acquisition task, when compared to the healthy control group (Andrew et al., 2018). This increase in the N18 SEP peak indicates increased altered sensory input towards the cerebellum from the inferior olive. Additionally, the researchers demonstrated an increase in the N24 SEP peak amplitude which may represent alterations in cerebellar-S1 inhibition (Andrew et al., 2018). The researchers also suggest that this may reflect decrease activity within the cerebellar nuclei that is associated with the later stages of learning (Andrew et al., 2018). These findings would also suggest that individuals with SCNP may also exhibit alterations within cerebellar processing (Cruccu et al., 2008).

2.12 Altered cerebellar processing

Daligadu and colleagues (2013) were one of the first groups of researchers to link alterations in cerebellar processing and SCNP. Utilizing transcranial magnetic stimulation (TMS), the researchers assessed the neural connectivity between the cerebellum and motor cortex by examining both cerebellar and cortical measures. The two cortical measures examined were short-interval intracortical inhibition (SICI) and long-interval intracortical inhibition (LICI); while the one cerebellar measure examined was cerebellar inhibition (CBI). All measures were taken prior to, and following, a combined intervention consisting of spinal manipulation

and a motor sequence learning task (Daligadu et al., 2013). It was determined that individuals with SCNPs had increased CBI, prior to completing a combined intervention. This would suggest that the altered afferent input from the cervical region may disrupt the output from the cerebellar nuclei towards M1 via the ventrolateral thalamic nucleus that occurs during the later stages of motor learning. Baarbé and colleagues (2018) have also demonstrated increased CBI in an SCNPs population during a more complex motor skill acquisition task. However, a limitation of these neurophysiological studies is that they assess processing in cerebellar pathways, but they do not directly measure cerebellar function.

The most common measure utilized to assess cerebellar processing, via TMS, is CBI which represents the level of inhibition the cerebellum exerts on M1 (Baarbé et al., 2018). CBI involves TMS that is applied over the ipsilateral cerebellum, followed by stimulation over the contralateral M1 (Daligadu et al., 2013). This results in an inhibited motor evoked potential (MEP) that is commonly recorded within the distal hand musculature (Daligadu et al., 2013). However, these recorded MEPs are an indirect result of stimulation towards the cerebellum and M1 and, thus, are an indirect representation of cortico-cerebellar connectivity. To this date, no prior study has examined alterations within cerebellar processing utilizing a direct measure of cerebellar processing. However, two direct measures that may be utilized are the VOR and COR as they are both directly controlled by the cerebellum.

2.13 Altered oculomotor reflexes

Prior literature has established a co-dependent relationship between the COR and VOR, in which one reflex will upregulate due to disruptions within the other (Gdowski et al., 2001). Zmysłowska-Szmytko and colleagues (2018) have describe an upregulation in the COR in individuals experiencing dizziness, accompanied by asymmetric neck pathophysiology. The

researchers suggest that increased neck muscle tension, and restricted neck rotation, may cause a mismatch between the proprioceptive and vestibular systems causing disruptions within the vestibular system. As a result, this may cause an upregulation in the COR to compensate for any possible disruptions that may be observed within the VOR due to its reliance on the vestibular system; however, disruptions within the VOR were not observed (Zamysłowska-Szmytko et al., 2019). Earlier research by Bronstein and colleagues (1995) have also demonstrated upregulation in the COR in individuals with bilateral vestibular labyrinth lesions. Kelders et al., (2003), have built upon this by demonstrating upregulation in the COR in response to decreases in the VOR within an older population. As demonstrated by Iwasaki and Yamasoba (2015), the vestibular system seems to deteriorate with old age, which can be demonstrated by measuring the VOR (Baloh et al., 1993; Paige, 1992; Peterka et al., 1990). Montfort et al., (2008) suggests that the cerebellum will modify either the COR or VOR in response to disruptions within the other reflex. This would suggest that the relationship between COR and VOR gain can be expressed as a negative correlation; in which increases in COR gain may reflect decreases in VOR gain. To build upon this concept, prior literature has demonstrated upregulation in the COR in individuals with various forms of neck pain such as whiplash and nonspecific neck pain (de Vries et al., 2016; Ischebeck et al., 2017; Kelders et al., 2005; Montfort et al., 2008). However, these same studies were unable to demonstrate alterations within the VOR; although, this may have been due to the methodology utilized to examine the VOR.

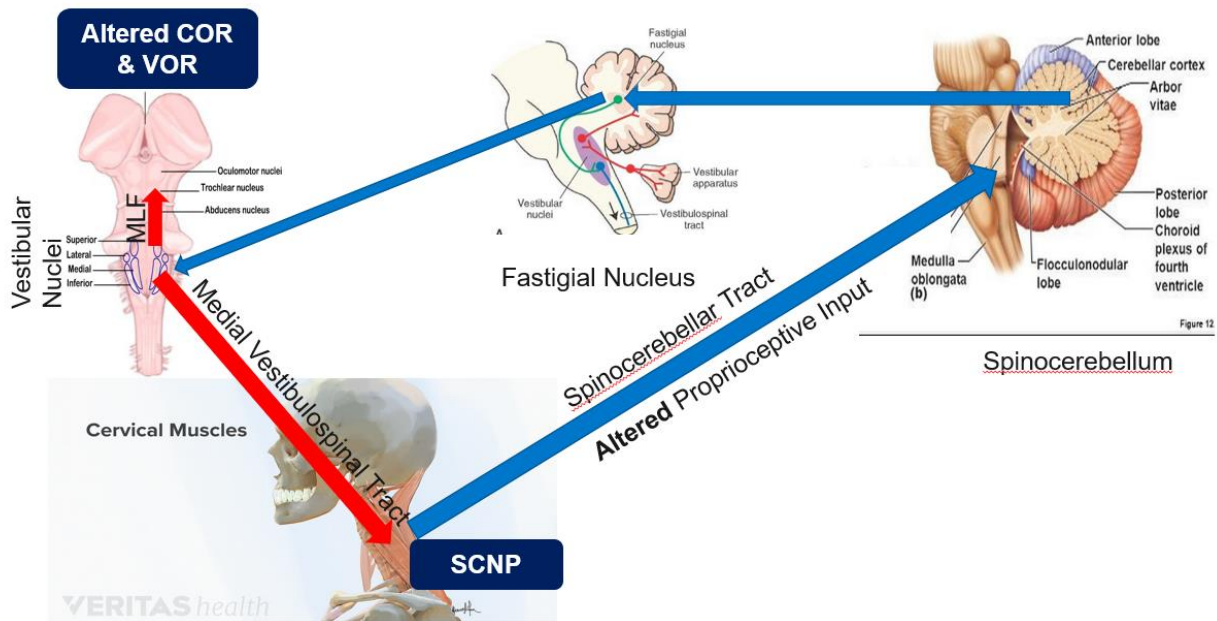


Figure 2.12 Pathway of altered afferent/proprioceptive input towards the cerebellum, altering the control of the COR and VOR

2.14 Methodology utilized to collect the COR and VOR

To assess changes within the COR, prior literature has had participants wear an Eye-Link-II eye-tracking device while tracking at a target projected on a monitor 3 meters ahead of them (de Vries et al., 2016; Ischebeck et al., 2017; Ischebeck et al., 2018; Kelders et al., 2005; Kelders et al., 2003; Montfoort et al., 2008). While tracking this target participants were seated within a motorized chair that oscillated at a frequency of 0.04 Hz to an amplitude of 5°, for 134 seconds. This led to a peak trunk velocity of 1.26°/second which occurred when the head and trunk are in-line with one another (i.e., the center position). To ensure the participants head was fixated during the chair rotations, the researchers utilized a bite board. However, research has demonstrated that a biting task may cause co-activation of the anterior and posterior neck muscles (Hellmann et al., 2012). Thus, this would activate the GTO's within the cervical

musculature as they are responsible for relaying proprioceptive information regarding length and contraction of the muscle (Kandel et al., 2000). Therefore, this may alter the proprioceptive information received from the neck musculature and thus, may alter the COR response.

To assess VOR gain and VOR gain adaptation prior literature has utilized an incremental angular VOR training methodology (Fadaee & Migliaccio, 2016; Schubert et al., 2008). In these protocols, participants were instructed to make 300 bilateral head rotations while tracking a laser target projected on a screen. Trials were evenly divided into 10 epochs in which the laser target moved in the opposite direction of the participants head rotation for each trial (Fadaee & Migliaccio, 2016; Schubert et al., 2008). During the first epoch, the target moved at 10% of the participants head velocity and subsequently increased, in increments of 10%, for each epoch. For example, in epoch 2 the target moved at 20% of the participants head velocity and in epoch 10 the target moved at 100% of the participants head velocity. In this way, the researchers elicit adaption of the VOR response. However, the issue with these studies is the lack of a “pre-adaptation epoch”, in order to measure the participants’ baseline VOR gain prior to adaptation. Additionally, these studies have only examined VOR gain and VOR gain adaptation within a healthy population and have yet to examine it within a neck pain population. Prior studies have addressed this issue by examining VOR gain in individuals with various forms of neck pain; however, these studies have yet to report alterations in VOR gain within a neck pain population (de Vries et al., 2016; Ischebeck et al., 2017; Kelders et al., 2005; Montfoort et al., 2008). Within these studies, the researchers utilized an oscillating chair to passively rotate the head, along with the body, as the participants stared at an image projected onto a screen. This chair rotated at a frequency of 0.16 Hz with an amplitude of 5°, leading to a peak velocity of 5.03°/second. However, Tabak and colleagues (1997) suggest that the VOR is most effective at high movement

speeds and, thus, cannot be elicited at low frequencies. Additionally, prior literature has demonstrated that the VOR can only be elicited at speeds greater than 50°/second (Gray, 2020c). Thus, the methodology utilized by these studies may have not been sufficient to elicit the VOR response, and these methodological deficiencies should be addressed in future work.

2.15 Spinal Manipulation

Spinal manipulation is a well-established technique in the treatment of SCNP (Baarbé et al., 2018). It commonly involves high velocity, low-amplitude (HVLA) thrusts to dysfunctional joints within the spine (Baarbé et al., 2018). Prior studies have demonstrated that the manipulation of dysfunctional joints within the cervical spine may improve cerebellar processing in individuals with SCNP (Baarbé et al., 2018; Daligadu et al., 2013). This improvement in cerebellar processing can be linked back to disruptions in SMI.

2.16 Neurophysiological effects of spinal manipulation

Utilizing a joint repositioning task, Haavik and Murphy (2011), demonstrated alterations in upper limb proprioception in an SCNP population. This would suggest that joint dysfunction, due to SCNP, results in altered afferent (i.e., proprioceptive) input towards the CNS. However, the researchers were able to demonstrate improvements in JPS following an intervention consisting of spinal manipulation directed towards dysfunctional joints within the cervical spine (Haavik & Murphy, 2011). This suggests that spinal manipulation may be able to improve proprioception within a SCNP population. The researchers also suggest that these changes in proprioceptive input are a result of normalized afferent input from the cervical spine following HVLA adjustments to dysfunctional areas. This would also insinuate that spinal manipulation may lead to improvements in SMI in a SCNP population. Utilizing SEPs, research by Haavik

and Murphy (2007) outline this concept. Following a single session of spinal manipulation, the researchers found significant attenuation in both the N20 and N30 SEP peaks. This decrease in amplitude of the N20 SEP peak would represent a decrease in processing within S1 (Haavik-Taylor & Murphy, 2007a). Additionally, the decrease in the N30 SEP peak may suggest a reduction in activity within the cortical and subcortical loops that link with the basal ganglion, thalamus, pre-motor areas, and M1 (Haavik-Taylor & Murphy, 2007a). The researchers suggest that this change within the N30 SEP peak may be due to alterations within afferent input following spinal manipulation (Haavik-Taylor & Murphy, 2007a). Additionally, prior literature has demonstrated that primary afferents (Ia) act as the mediators for the central neural changes that occur following spinal manipulation (Bolton & Holland, 1996; Murphy et al., 1995; Pickar & Wheeler, 2001; Zhu et al., 2000; Zhu et al., 1993). It has also been demonstrated that the N30 SEP peak is sensitive to changes within the Ia afferents (Hoshiyama & Kakigi, 2000). Thus, it can be suggested that HVLA manipulation may alter Ia afferent input towards the CNS; therefore, causing neuroplastic changes within SMI. Similar findings were observed in TMS studies that examined changes within CBI in a SCNP population (Baarbé et al., 2018; Daligadu et al., 2013). Daligadu, and colleagues (2013) were able to demonstrate significant reductions in CBI following cervical spinal manipulation. Similarly, Baarbé and colleagues (2018), were able to demonstrate decreases in CBI, as well as improvements in reaction time during a motor skill acquisition task (i.e. improved motor control), following a single session of spinal manipulation towards dysfunctional joints within the cervical spine. This would suggest HVLA manipulation, directed towards dysfunctional joints, normalizes afferent feedback from the neck (Daligadu et al., 2013). This would then improve the ability of the cerebellum to create an accurate internal body schema with which to process somatosensory information (Daligadu et al., 2013).

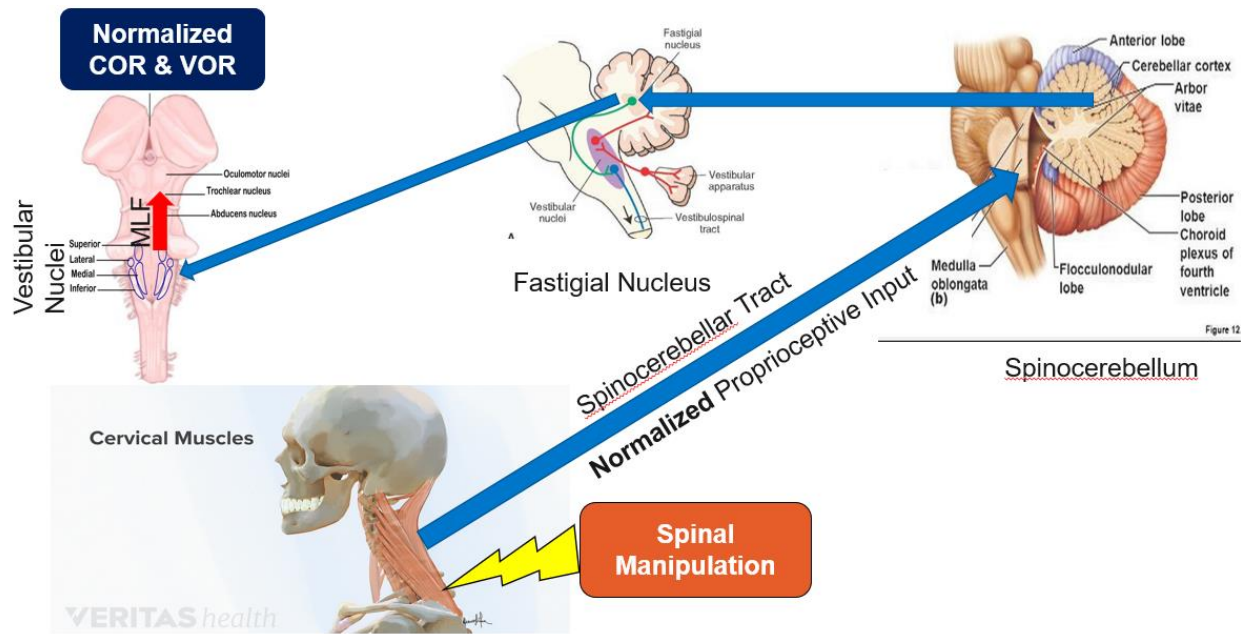


Figure 2.13 Normalization of afferent/proprioceptive input following spinal manipulation which may lead to a normalization of the COR and VOR within a SCNP population

2.17 Conclusion

In summary, individuals with subclinical neck pain seem to have alterations in sensorimotor integration as well as cerebellar processing. Alterations in cerebellar processing may be represented by disruptions in the oculomotor reflexes. Since the COR and VOR are directly controlled by the cerebellum, disruptions in these reflexes are direct representations of altered cerebellar functioning. However, due to spinal manipulation targeting areas of altered afferent input, these oculomotor reflexes may be able to improve following chiropractic treatment. Thus, representing improvements in cerebellar processing in individuals with SCNP.

Proposed Research Framework

The proposed research framework consisted of two related studies that sought to examine the relationship between the COR and VOR and the cerebellum in an SCNPN population. The first study aimed to determine whether there were differences in cerebellar processing assessed through COR gain and VOR gain adaptation, when comparing a SCNPN group to a healthy control group. The second study aimed to determine if an 8-week chiropractic intervention consisting of spinal manipulation and myofascial release would improve COR gain and VOR gain and/or VOR adaptation measures in an SCNPN population, which would be a direct reflection of improved cerebellar processing.

Thesis Objective and Hypothesis

Objectives of Thesis

1. To determine the effects of SCNP on cerebellar processing by measuring COR gain, VOR gain and VOR gain adaptation.
2. To determine if an 8-week chiropractic intervention consisting of spinal manipulation and myofascial release would lead to improvements in cerebellar processing, as demonstrated by improvements in COR gain, VOR gain and/or VOR gain adaptation, in individuals with SCNP.

Hypotheses of Thesis

1. Individuals with SCNP will have an increased COR gain and a diminished ability to adapt their VOR response, representing alterations in cerebellar processing.
2. Individuals with SCNP will demonstrate COR gain and VOR gain adaptation levels closer to healthy individuals following an 8-week chiropractic intervention, representing improvements in cerebellar processing.

Chapter 3. Manuscript 1

The effects of subclinical neck pain on cerebellar processing as measured by the cervico-ocular and vestibulo-ocular reflexes

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3.1 Abstract

Background: Subclinical neck pain (SCNP) refers to untreated, recurrent episodes of mild-to-moderate neck pain with pain-free days. Previous literature has found alterations in cerebellar processing in individuals with SCNP including disruptions in sensorimotor integration (SMI), motor control processes, proprioception, and cerebellar inhibition (CBI), all assessed indirectly. Cerebellar processing, which can be examined via the cervico-ocular and vestibulo-ocular reflexes (COR & VOR) has not been assessed directly in those with SCNP. These two oculomotor reflexes act to keep images stable on the retina in response to trunk and head movements. This study aims to investigate the relationship between SCNP and cerebellar function by measuring changes in COR gain and VOR gain adaptation in individuals with SCNP.

METHODS: 38 right-hand dominant participants (20 SCNP: 9M & 11 F; 18 Healthy controls: 8M & 10F) between the ages of 18 and 35 performed two eye-tracking tasks. COR: participants were seated in a motorized chair and fitted with an eye-tracking device. They were instructed to stare at a visual target projected on a monitor 3 meters away from them. Once the target appeared on the screen, the motorized chair began a series of oscillations at a frequency of 0.04 Hz, with an amplitude of 5°, for 120 seconds. 10 trials were completed, with each trial lasting two minutes. VOR: participants were seated 90 cm away from a monitor and were instructed to make active head rotations while tracking a target projected on the screen in-front of them. Participants performed 390 trials divided into 13 blocks (pre-adaptation, 10 adaptation, & 2 post-adaptation blocks) in which the target would move at different speeds during each block.

RESULTS: The SCNP group demonstrated significantly higher COR gain values than the healthy control group ($p = 0.006$, $D = 0.833$). No differences were seen in VOR gain adaptation between groups ($p = 0.771$, $\eta_p^2 = 0.015$). The healthy control group tended to have higher VOR gain baseline values but this was not statistically significant ($p = 0.487$, $D = 0.229$).

DISCUSSION: SCNP may alter proprioceptive input towards the cerebellum, thus altering cerebellar processing. It also appears that SCNP may have a limited impact upon processing of vestibular input by the cerebellum.

Keywords: Cerebellum, subclinical neck pain, cervico-ocular reflex, vestibulo-ocular reflex

3.2 Introduction

In recent years, there has been a greater reliance on technology during multiple activities of daily life such as working from a laptop, texting on a phone, or watching television. With this rise in technology use, there has been a subsequent rise in neck pain (Berolo et al., 2011; Green, 2008; Kim, 2015). Neck pain can present in various forms, dependent on the extent of injury or dysfunction on the mechanical and/or physiological structures of the neck. Neck pain may be classified as chronic pain, traumatic acute pain (i.e. whiplash associated disorder), and non-traumatic acute pain (Ischebeck et al., 2017), all of which have been shown to alter various neurophysiological pathways/systems within the body such as the proprioceptive and vestibular systems (García-Pérez-Juana et al., 2018; Kendall et al., 2018; Reid et al., 2014; Rogers, 1997). In order to assess the impact of this pain on neural mechanisms associated with sensory motor integration (SMI) and motor control, it is important to assess on pain-free days, as alterations in neural processing may occur in the presence of pain, and pain can also impact movement patterns (Rossi et al., 2003; Strutton et al., 2005; Waberski et al., 2008). A subclinical neck pain (SCNP) population is ideal to assess alterations in central processing without pain being a confounding factor. SCNP is defined as recurrent episodes of mild-to-moderate neck pain that has not yet received treatment (Lee et al., 2005). This population experiences pain-free periods, permitting researchers to examine changes in the neural mechanisms and pathways that may have developed over time (Lee et al., 2005).

Prior literature has demonstrated that SCNP may alter proprioceptive input towards the central nervous system (CNS) (Haavik & Murphy, 2011; Lee et al., 2008; Zabihhosseinian et al., 2017). Literature has noted alterations within upper limb joint position sense, head and neck movements, as well as altered shoulder and scapular kinematics in a SCNP population (Haavik

& Murphy, 2011; Paulus & Brumagne, 2008; Zabihhosseinian et al., 2017). Haavik and Murphy (2012), suggest that these alterations may be due to altered afferent input received from areas of joint/spinal dysfunction such as SCNP, towards CNS. This then alters the CNS' ability to process sensory information and produce an efficient motor command in response; which is known as sensorimotor integration (SMI). Utilizing somatosensory evoked potentials prior literature has demonstrated that this joint dysfunction alters the processing of sensory information within the primary somatosensory cortex, as reflected by alterations within the N20 SEP peak (Haavik-Taylor & Murphy, 2007a). SEPs are complex wave forms that are recorded from the scalp, following the stimulation of afferent nerve fibers or their receptors in the periphery (Cruccu et al., 2008). The N20 SEP peak represents the arrival of the afferent volleys at the primary somatosensory cortex, reflecting earliest cortical processing within the primary somatosensory cortex (Nuwer et al., 1994). Additionally, the researchers noted alterations within the N30 SEP, prior to a spinal manipulation intervention (Haavik-Taylor & Murphy, 2007a). The N30 SEP peak is reflective of neural connectivity between the motor, pre-motor and pre-frontal cortexes, thalamus and basal ganglion (Cebolla et al., 2011; Cebolla & Chéron, 2015; Manguiere, 2005; Passmore et al., 2014), all areas which are heavily involved in SMI. Building upon these results, Andrews et al. (2018) demonstrated alterations in both the N18 and N24 SEP peaks following a motor acquisition task, in those with SCNP. Changes in these peaks reflect alterations in cerebellar processing. The N18 SEP peak represents the arrival of the first afferent volleys from the brainstem, specifically the inferior olive and dorsal column nuclei, towards the cerebellum, and is a key area of SMI (Sonoo, 2000). The N24 SEP peak represents somatosensory input conveyed towards the primary somatosensory cortex from the cerebellum (Restuccia et al., 2006). This suggests that SCNP alters the processing of sensory input travelling towards the

cerebellum, as well as somatosensory output from the cerebellum towards the primary somatosensory cortex (S1), during SMI (Andrew et al., 2018). Additionally, literature has demonstrated alterations within the cerebellar processing utilizing transcranial magnetic stimulation (TMS), within a SCNP population (Baarbé et al., 2018; Daligadu et al., 2013). Daligadu and colleagues (2013) were able to demonstrate increased cerebellar inhibition (CBI), prior to completing a combined intervention consisting of spinal manipulation and a motor skill acquisition task. CBI represents the level of inhibition the cerebellum exerts on the primary motor cortex (M1) and involves the application of TMS over the ipsilateral cerebellum, followed by stimulation over the contralateral M1 (Ugawa et al., 1995). This results in an inhibited motor evoked potential (MEP) that is commonly recorded within the distal hand musculature which represents the connectivity between the M1 and the cerebellum (Daskalakis et al., 2004). Thus, an increase in CBI would suggest that the altered afferent input from the cervical region may disrupt the output from the cerebellar nuclei towards M1 via the ventrolateral thalamic nucleus, that occurs during the later stages of motor learning (Daligadu et al., 2013). Baarbé and colleagues (2018) have also demonstrated an increased CBI in an SCNP population, during a more complex motor skill acquisition task. This would also suggest that SCNP may cause neuroplastic changes within the cerebellum (i.e., altered cerebellar processing); thus, leading to altered movement patterns. However, the issue with SEPs and CBI-TMS, is that they are indirect measures of cerebellar processing, as they reflect the sensory input and motor output from the cerebellum, respectively. Thus, while these studies demonstrate likely changes in cerebellar processing, there is a need to determine if cerebellar function is impacted in those with SCNP.

Two direct measures of cerebellar function are the cervico-ocular reflex (COR) and vestibulo-ocular reflex (VOR). Both the COR and VOR rely upon visual, vestibular, and

proprioceptive inputs in order to produce an efficient reflex response (Gdowski et al., 2001; Gdowski & McCrea, 2000; Gray, 2020c; Ito, 1998). All of these responses are coordinated and modified within the flocculonodular lobe of the cerebellum (Gdowski et al., 2001; Gdowski & McCrea, 2000). The COR is a gaze stabilizing reflex that acts to stabilize images on the retina by keeping the eyes fixated in the orbits during trunk rotations while the head is stable (de Vries et al., 2016). The COR can be quantitatively expressed as COR gain, which is the ratio of peak eye velocity to peak trunk velocity (Ischebeck et al., 2017). Prior literature has demonstrated that this value is, approximately, 0.2 within a healthy population. However, other literature has found that COR gain may be as low as 0.1 or completely absent within a healthy population (Schubert et al., 2004). The VOR acts to stabilize gaze during head movements (Ranjbaran & Galiana, 2015). Similar to the COR, the VOR can be quantitatively expressed as VOR gain, which is the ratio of peak eye velocity to peak head velocity (Fadaee & Migliaccio, 2016). In a healthy population, this value is, approximately, 1.0; representing, a one-to-one ratio between head and eye movements (Hoshowsky et al., 1994). Additionally, Shelhamer and colleagues (1994) suggest that VOR gain will increase in response to a retinal image slip that can be induced using a moving target. This neurophysiological phenomenon is known as VOR gain adaptation (Shelhamer et al., 1994). Furthermore, prior literature has established a co-dependent relationship between the COR and VOR, in which one reflex will upregulate due to disruptions within the other (Gdowski et al., 2001).

To assess changes in VOR gain adaptation, prior literature has utilized an incremental angular VOR training methodology (Fadaee & Migliaccio, 2016; Schubert et al., 2008). In these protocols, the participant's ability to adapt their VOR was assessed by having them make bilateral head rotations while tracking a target moving at varying velocities (Fadaee &

Migliaccio, 2016; Schubert et al., 2008). A key issue with these studies is the lack of a “pre-adaptation epoch”, in order to measure the participants’ baseline VOR gain prior to adaptation. Prior studies have examined VOR gain in individuals with various forms of neck pain; however, these studies have yet to report alterations in VOR gain within a neck pain population (de Vries et al., 2016; Ischebeck et al., 2017; Kelders et al., 2005; Montfoort et al., 2008). Within these studies participants stared at a target while being passively rotated, in an oscillating chair, at a peak velocity of 5.03°/second. However, Tabak and colleagues (1997) suggest that the VOR is most effective at high movement speeds and, thus, can not be elicited at low frequencies. Additionally, prior literature has demonstrated that the VOR can only be elicited at speeds greater than 50°/second (Gray, 2020c). Thus, the methodology utilized by these studies may have not been sufficient to elicit the VOR response. Additionally, there may have been issues in the methodology these studies utilized to assess the COR (de Vries et al., 2016; Ischebeck et al., 2017; Kelders et al., 2005; Montfoort et al., 2008). Within these studies participants stared at a target while being rotated within an oscillating chair with their head fixated. To ensure the participants head was fixated during the chair rotations, the researchers utilized a bite board. However, research has demonstrated that biting task may cause co-activation of the anterior and posterior neck muscles (Hellmann et al., 2012). Thus, this would activate muscle spindles and golgi tendon organs (GTO) within the cervical musculature as they are responsible for relaying proprioceptive information regarding length and contraction of the muscle (Kandel et al., 2000). Therefore, the use of a bite board to hold the head still could alter the proprioceptive information received from the neck musculature and thus, may alter the COR response.

Zamysłowska-Szmytke and colleagues (2019) has demonstrated an upregulation of the COR in individuals experiencing dizziness, accompanied by asymmetric neck pathophysiology.

The researchers suggested that this upregulation may be due to increased neck muscle tension and restricted neck rotation which may cause a mismatch between the proprioceptive and vestibular systems, leading to disruptions within the vestibular system that may be observed with a diminished VOR response (Zamysłowska-Szmytke et al., 2019). However, disruptions within the VOR were not observed in their study (Zamysłowska-Szmytke et al., 2019). Additionally, Bronstein and colleagues (1995) have also demonstrated upregulation in the COR in individuals with bilateral vestibular labyrinth lesions. Kelders et al., (2003), have built upon this by demonstrating upregulation in the COR in response to decreases in the VOR within an older population. The vestibular system seems to deteriorate with old age, which can be demonstrated by measuring the VOR (Baloh et al., 1993; Paige, 1992; Peterka et al., 1990). It has been suggested that the cerebellum will modify either the COR or VOR in response to disruptions within the other reflex (Montfoort et al., 2008). This would suggest that the relationship between COR and VOR gain can be expressed as a negative correlation; in which the cerebellum will upregulate the COR in response to a diminished VOR. Prior literature has also demonstrated upregulation in the COR in individuals with various forms of neck pain (de Vries et al., 2016; Ischebeck et al., 2017; Kelders et al., 2005; Montfoort et al., 2008). The researchers suggest that this alteration within the COR may be due to altered afferent input from the neck towards the central processors. While past studies have not found VOR changes in those with neck pain, this may have been because the neck rotations were not fast enough to elicit the VOR or the fact that the presence of pain may have affected neck movement speed, and thus the ability to elicit the VOR.

The current study aims to compare direct measures of cerebellar processing (i.e. the COR and VOR) in those with SCNPs vs healthy controls. It will also address the potential limitations of previous studies by monitoring neck movement speed for the VOR, and eliminating the bite

board when measuring the COR. It is hypothesized that individuals with SCNP will have an increased COR gain and a diminished ability to adapt their VOR response, representing alterations in cerebellar processing.

3.3 Methodology

3.3.1 Participants

38 right-hand dominant participants, with and without SCNP, were recruited from the Ontario Tech University student population and were all between the ages of 18 – 35 years old. 20 participants (9M & 11F; 21.8 ± 2.35 years) were assigned to the SCNP group. While 18 participants (8M & 10F 22.25 ± 3.59 years) were assigned to the healthy control group. The study was approved by the University's research Ethics Board (add approval number).

Before being deemed eligible for the study, participants completed the neck disability index (NDI), Edinburgh Handedness Inventory (EHI), and electroencephalography (EEG) safety screening checklist. The NDI was utilized to determine the presence or absence of reoccurring neck pain, within the previous three months. Prior literature has demonstrated that the NDI is a valid, and objective, measure for the assessment of neck disability in both clinical and research settings (Vernon, 2008). Additionally, previous work has often utilized the NDI to help determine the presence of SCNP (Baarbé et al., 2018; Daligadu et al., 2013). The EHQ was utilized to confirm right-hand dominance for each participant (Oldfield, 1971). Participants had to score $> +40$ to be considered right-hand dominant (Oldfield, 1971). The EHQ has been demonstrated to be a reliable and valid tool in the determinacy of right-hand dominance (Oldfield, 1971). Additionally, on the day of data collection, participants also completed the visual analog scale (VAS). The VAS is a continuous 10 cm line, which is a commonly used tool

for the assessment of chronic and acute pain (Bijur et al., 2001). To eliminate the confounding effect of acute pain on movement and neural processing, data collection took place on days when participants were experiencing minimal pain. Participants were required to have a score of 3 cm, or lower, on the 10 cm VAS. Clinically, scores of 3 cm or lower typically indicate an individual is currently experiencing an acceptable level of pain (i.e. minimal acute pain) (Tashjian et al., 2009). The EEG safety checklist was utilized to determine if the participant used medication that might alter their balance or alertness, had been diagnosed with attention deficit hyperactive disorder (ADHD), or had a history of neurological disorders or visual problems, which could impact the outcome measures. Participants were also excluded if they had received treatment for their neck in the past six months. The 10-point Borg rating of perceived exertion (RPE) scale was administered at different timepoints during both protocols, to assess level of fatigue within the head, neck, eyes and low back, at that instant of time (Borg, 1982).

3.3.2 Instrumentation and Data Acquisition

The Eye-Link-II eye-tracking device (SR-Research, Ottawa, Canada) was utilized to record movements during the experimental conditions, for both COR and VOR. Monocular eye movement (left eye) was recorded during the COR protocol using a sampling frequency of 250 frequency, consistent with past literature (de Vries et al., 2016; Ischebeck et al., 2017). Binocular (both) eye movements were recorded during the VOR protocol with a sampling frequency of 500 Hz, as opposed to using a scleral search coil to record monocular (left) eye data (Fadaee & Migliaccio, 2016; Schubert et al., 2008). Data from both eyes was collected as the Eye-Link-II eye-tracker was unable to track the corneal reflection (CR) signal on the left eye during right head turns and vice versa for the right eye during left head turns. As a result, binocular eye

movement was recorded; however, the ipsilateral eye with respect to the head movement was used in the analysis, e.g. left eye data for left head turns and right eye data for right head turns.

A custom-built motorized chair was utilized during the COR protocol, in order to stimulate the COR response by rotating the individual's trunk. For technical details on development of this chair please refer to Sanmuganathan et al, (2021). This chair was also fitted with three infrared markers, with a marker power frequency of 1000 Hz, to record the degree of chair rotation and angular velocity during the protocol. Similarly, during the VOR protocol the eye-tracking device was fitted with three infrared markers, with a marker power frequency of 1000 Hz. These were utilized to record the degree of head rotation and angular velocity for each trial. Two *Northern Digital Incorporated Optotrak* cameras were utilized to record trunk rotation (COR protocol only) and head rotation (VOR protocol only) data. The cameras were placed, approximately, 275 cm (COR protocol) and 255 cm (VOR protocol) away from the participant and sampled at a frequency of 50 Hz. The analog trunk and head rotation data were recorded as digital trunk and head displacement signal and stored as a Matlab files for further analysis.

3.3.3 COR Protocol

While seated in a custom-built motorized chair, participants were fitted with an Eye-Link-II eye-tracker and be in front of a 50-inch monitor 3 meters away from them. Once fitted with the eye-tracker, the participant's head was secured to a headrest behind the chair utilizing two cloth bandanas (FIG 3.1). This ensured that no movement of the head occurs during trunk rotations. Following the setup of the eye-tracker, eye position was calibrated utilizing a built-in 9-point calibration system. Once calibration was completed, participants were instructed to fixate their eyes on a fixation target that was projected on the screen. This was utilized to accurately fixate the position of the participant's eye before the trial began. Once the position of the left eye

was fixated, a circular target appeared on the screen for three seconds and then disappeared. The participant was instructed to stare at this target, and where they last saw the target after it disappeared, for the duration of the trial. Prior literature has demonstrated that the COR seems to be much stronger in the absence of a visual stimuli (Gdowski et al., 2001). Thus, by having the target disappear, a more prominent COR response can be elicited. Simultaneously as the target appearing on the screen, the motorized chair began to rotate the participant's trunk for five full oscillations. The chair rotated at a frequency of 0.04 Hz to an amplitude of 5°, for, approximately, 120 seconds. This led to a peak stimulus velocity (i.e., trunk velocity) of, approximately, 1.5°/second which occurred when the head and trunk were in-line with one another (i.e., the center position). In total, 10 trials were completed in which one trial consisted of 5 oscillations over the 120-second window. Once each trial was completed, the participants reported level of RPE was recorded for their head, neck, eyes, and lower back. Additionally, participants were offered a break at the end of each trial; although, if the participant did not want a break the next trial began. However, to ensure the protocol did not elicit acute neck pain, participants were given a mandatory break if they reported an RPE of 4 or more in either their head, neck, or lower back, following two consecutive trials. Participants were also given a mandatory break once they completed the 5th trial. During which the eye-tracker and bandanas were removed from the participants head and the next trial didn't begin until the participant was ready to continue. Following RPE recordings, the fixation target re-appeared on the screen, indicating that the next trial could begin.



Figure 3.1. Participants head secured into the head rest utilizing bandannas

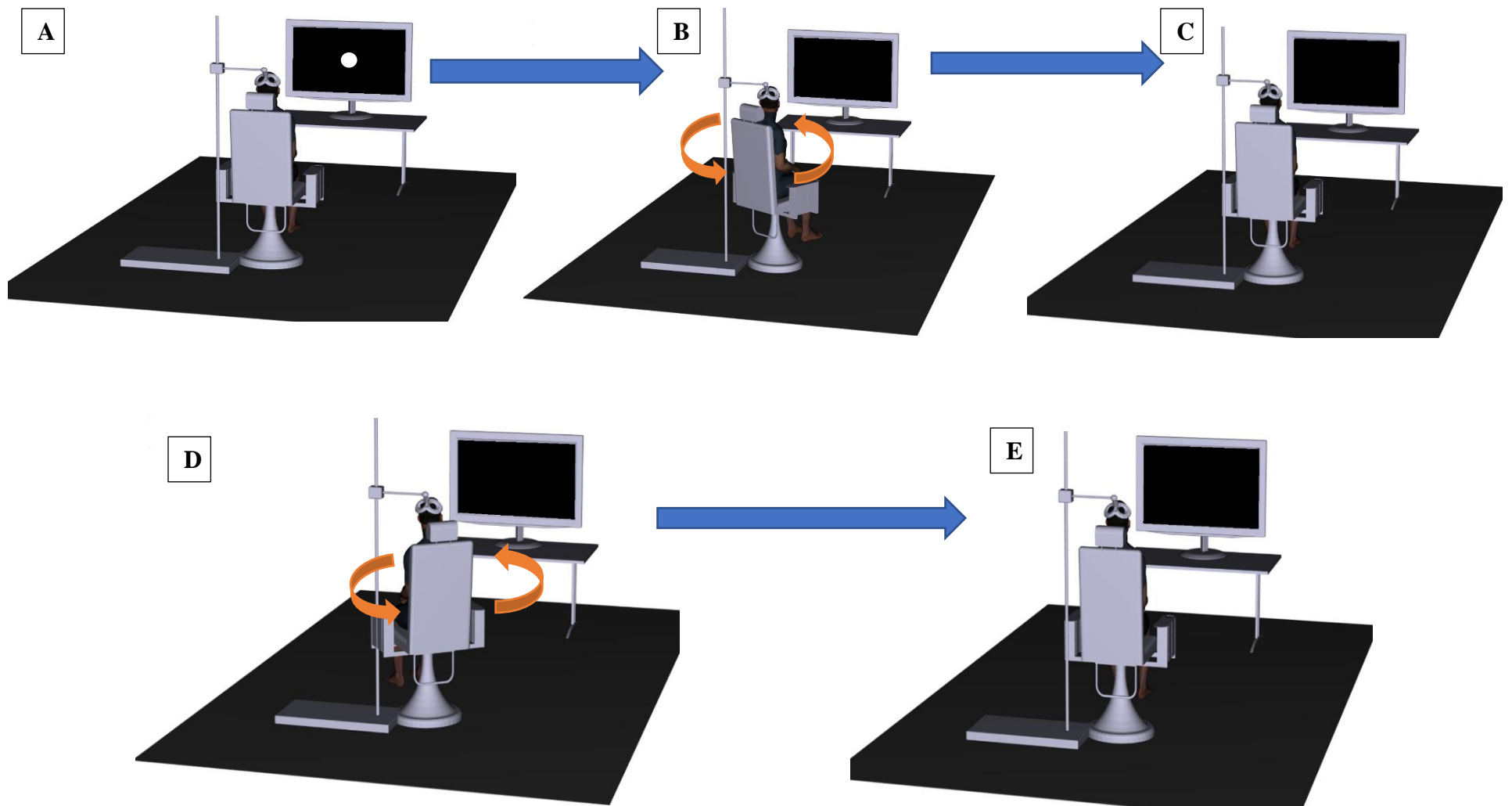


Figure 3.2. Illustration of COR Protocol: (a) Starting position of the chair with target projected on the screen for 3 seconds, (b) Chair rotating to 5° in the clockwise direction, (c) Chair rotating 5° back towards the center position, (d) Chair rotating 5° in the counter-clockwise direction, & (e) Chair rotating 5° back towards the center position

3.3.4 VOR Protocol

Participants were seated 90 cm away from a 26-inch monitor and fitted with the Eye-Link-II eye-tracker. Once setup was completed, eye position was calibrated using a built-in 3-point calibration system. Following the completion of the calibration, participants were instructed to fixate on a fixation target that was projected on the screen, in order to accurately fixate the position of the eyes before the trial. Once the position of the eyes was fixated, a circular target appeared on the screen and the participant was instructed to rotate their head to either the right or left (counterbalanced between participants), by 15° from the center position while keeping their eyes fixated on where they last observed the target. Prior studies have utilized an end range of 25° (Schubert et al., 2008); however, pilot results demonstrated that participants tended to overshoot the end angle by $5^\circ - 10^\circ$. For this reason, the end angle was reduced to compensate for this overshoot. Once participants reach the 15° mark, a grey screen appeared indicating to the participant that they have reached the end range of their rotation. At this grey screen, participants were instructed to pause their rotation for three seconds, until the grey screen disappeared on its own, and then return back to the center position. Once back in the center position, the fixation target reappeared, and the next trial began once the circular target was projected on the screen again. In total, each trial lasted, approximately, 5 seconds and participants were instructed to alternate their head movements between each trial (i.e. left then right head turn or right then left head turn).

In total, participants completed 390 trials, evenly divided over 13 epochs. In the first epoch, the target remained in the center of the screen, during the first $\pm 2^\circ$ of head rotation, and consisted of 30 trials. This epoch was used to measure the participants' baseline VOR gain and was known as the pre-adaptation block. Epochs 2-11 consisted of the target moving in the

opposite direction of the head rotation and contained 30 trials per epoch. These epochs were known as the adaptation blocks. In each adaptation block, the target increased in velocity by increments of 10% of head angular velocity. For example, the target moved at 10% of the participants head angular velocity in adaptation block 1, while in adaptation block 10, the target moved at 100% of the participants head angular velocity. These epochs were utilized to induce a retinal slip and thus, were used to measure the participants ability to adapt their VOR response (i.e., VOR gain adaptation). In epochs 12-13, the target remained in the center of the screen, during the first $\pm 2^\circ$ of head rotation, and consisted of 30 trials each. These two epochs were used to measure the participants ability to re-adapt their VOR back to baseline levels and were known as post-adaptation blocks 1 and 2. During each head rotation, participants also received feedback, in the form of audible beeps, regarding the peak angular velocity of their head rotation. When the participant received two low pitched beeps, it indicated that they were moving too slowly (i.e., below $140^\circ/\text{second}$), two high pitched beeps indicated that they moved too quickly (i.e., above $170^\circ/\text{second}$), and one medium pitched beep indicated that the participant moved at a good speed ($140^\circ/\text{second} - 170^\circ/\text{second}$). Additionally, at the end of each epoch, participants received a 45 second break to rest their eyes and ensure neck fatigue did not accumulate. During these breaks the participants RPE within their head, neck, and eyes was taken. Similar to the COR protocol, to ensure acute neck pain did not occur, if participants reported an RPE of 4 or more in either their head or neck following two consecutive epochs, the eye-tracker was loosened for 30 seconds.

Prior to beginning the VOR protocol, participants completed 25 practice trials in order to familiarize themselves with the task. The parameters for the first 20 trials of the practice were the exact same as the pre-adaptation block. While the parameters for the last 5 trials of the practice

were the same as adaptation block 1. This was to ensure the participant did not adapt prior to beginning the experimental protocol.

Additionally, an uncontrollable technical error was experienced at random times throughout the protocol. It was assumed to be a result of an interruption in the connection between the Matlab script used to run the protocol and the Optotrak cameras which resulted in the visual target no longer responding to the participant's head rotation, so that the grey screen no longer appeared when the participant reached the end range of their rotation, and the audible beeps were no longer being elicited. When this error occurred, it led to a loss of data in the trials following the error, as the Optotrak cameras were no longer able to record head rotational data and there was no change in the visual stimulus to elicit VOR gain adaptation. To minimize this loss of data, the Matlab script had to be divided into three separate scripts where the first script contained the first four blocks (Pre – AB3; 120 trials in total), the second script contained blocks 5 – 8 (AB4 – AB7; 120 trials in total), and the third script contained the last five blocks (AB9 – Post 2). However, it took ~2.5 minutes to transition between scripts.

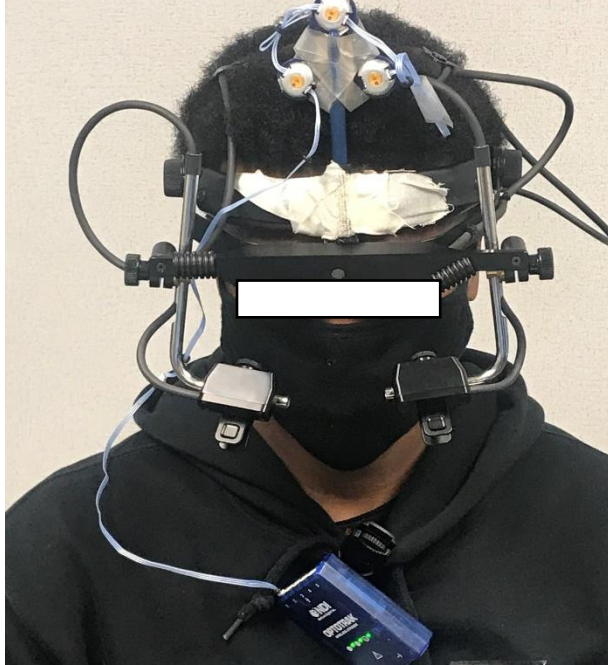
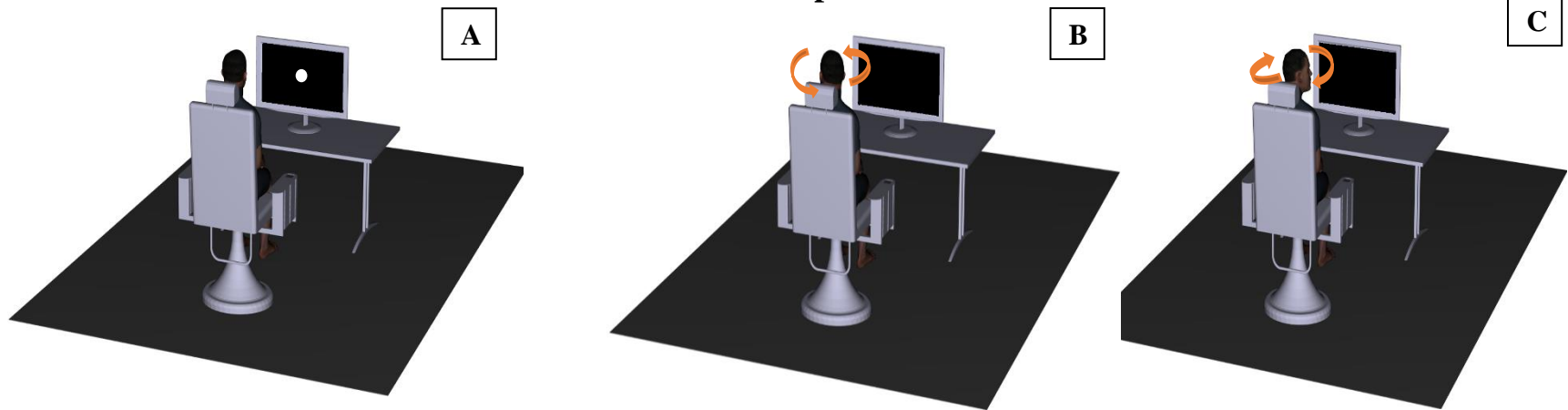


Figure 3.3. Eye tracker setup for VOR protocol

Pre/Post-Adaptation Block Trials



Adaptation Block Trials

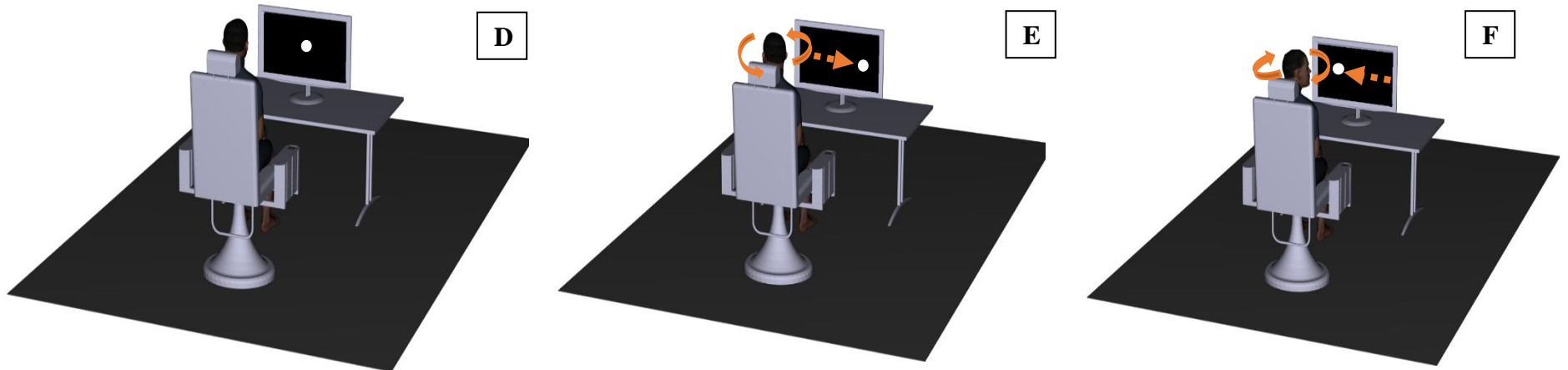


Figure 3.4. Illustration of VOR protocol for **Pre-/Post-adaption blocks**: (a) Target in the starting position with head in center position, (b) Left head turn with target disappearing at -2° of head rotation, & (c) right head turn with target disappearing at $+2^\circ$ of head rotation; **Adaptation blocks**: (d) Target in the starting position with head in center position, (e) Left head turn with target moving towards the right at set percentage of head velocity, & (f) Right head turn with target moving towards the left at set percentage of head velocity

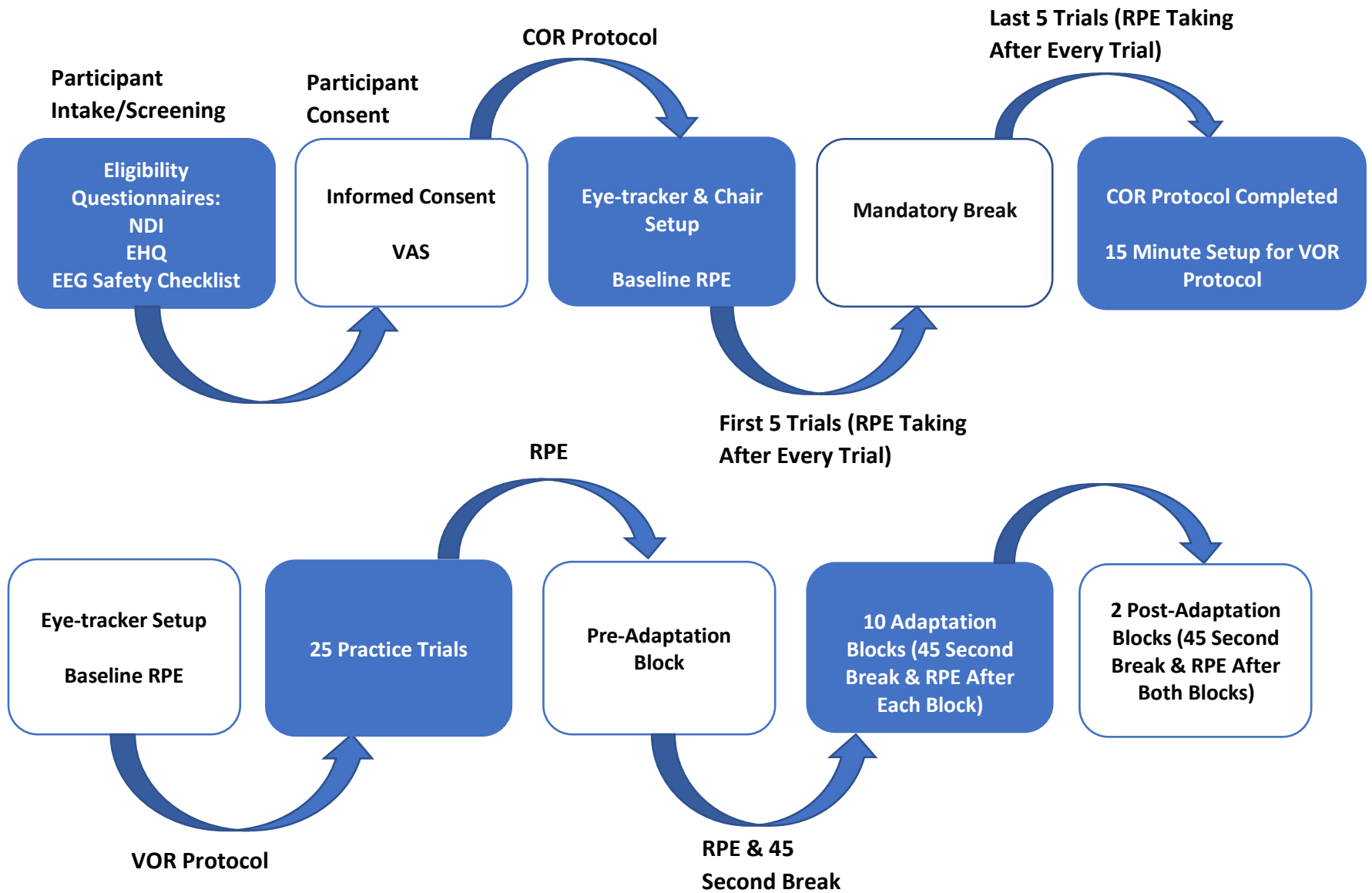


Figure 3.5. Flow of COR and VOR protocols

3.3.5 Data Analysis

All data was analyzed utilizing customized MATLAB R2021a codes (The MathWorks Inc., Natick, MA).

COR Analysis

The raw chair angular velocity data was filtered utilizing a low-pass, second-order Butterworth filtered with a cut-off frequency of 0.5 Hz. A moving average was then utilized to smooth the chair angular velocity. From there, the maximum chair velocity for each trial was outputted. Following this, blinks, saccades, and fast-phases were all identified by the custom written Matlab script and were subsequently removed by this script. A piecewise cubic hermite interpolating polynomial (PCHIP) was then utilized to interpolate and fill in the missing data points within the set. Raw eye angular velocity was filtered utilizing a low-pass, second-order Butterworth filtered with a cut-off frequency of 0.25 Hz. Once the raw eye velocity data had been filtered, a sinusoidal wave was fit through the filtered eye angular velocity data. This sine wave was created utilizing an open source Matlab script provided by Seibold (2022). The amplitude of this sine fit was then outputted for each trial. COR gain was then calculated by dividing the amplitude of the sine fit by the peak chair angular velocity and was, subsequently, averaged out for all ten trials.

$$\text{COR Gain} = \frac{\text{Amplitude of sine fit}}{\text{Peak chair angular velocity}}$$

VOR Analysis

Head displacement and angular velocity signals were filtered using a low-pass, second-order Butterworth filtered with a cut-off frequency of 10 Hz. Additionally, any missing head

angular velocity data points were interpolated utilizing a cubic spline. Blinks, saccades, and fast-phases were all identified and, subsequently, removed. A PCHIP was then utilized to interpolate the slopes of these missing data points. Raw eye displacement and angular velocity signals were low-pass, second-order Butterworth filtered with a cut-off frequency of 6 Hz. Once completed, VOR gain was calculated by taking the ratio of average eye angular velocity to average head velocity during the 120ms before and following, peak head velocity. Prior literature has calculated VOR gain by taking the ratio of eye velocity to head velocity during the 30ms prior to peak head velocity (Schubert et al., 2008). However, early pilot data demonstrated this window was too small and, occasionally, did not capture the point at which peak eye velocity occurred at. Additionally, trials were removed from individual participants' data set if the following occurred during the trial: loss of corneal reflection signal during the 120ms window utilized to calculate VOR gain, participant did not reach the 15° mark for head rotation, or participants changed head rotation direction mid trial. On average, 17.5% (68/390 trials) of trials were removed in the healthy control group, while 15.9% of trials (62/390 trials) were removed in the SCNP group. However, since each epoch consisted of 30 trials, the number of missing of trials was relatively distributed among the 13 epochs and, thus, was robust enough to resist any biases or type II errors. VOR gain was calculated for each trial and then averaged out for each epoch.

$$\text{VOR Gain} = \frac{\text{Average eye velocity 120 ms prior to \& following peak head velocity}}{\text{Average head velocity 120 ms prior to \& following peak head velocity}}$$

3.3.6 Statistical Analysis

Descriptive Statistics

Utilizing a sample size calculation on G*Power 3.1.9.7 statistical software, it was determined to have a large effect size (0.40), an alpha (α) of 0.05, and a power ($1 - \beta$) of 0.95 a

sample size of 15 individuals per group would be required. Statistical analysis was completed utilizing SPSS version 26 (IBM Corp., Armonk, NY, USA). The variable analyzed for the COR protocol was the difference in COR gain between the two groups. The variables analyzed for the VOR protocol were VOR gain, head peak velocity, constant error (CE), and variable error (VE). Shapiro-Wilk test was utilized to test for normality in the data sets for COR gain, VOR gain, head peak velocity, CE, and VE. Mauchly's test of sphericity was also utilized to test sphericity for the variables VOR gain, head peak velocity, CE, and VE. All statistical analyses were run assuming a p value of 0.05.

COR Gain

Levene's Test of Homogeneity revealed that there was not equal variance in COR gain values between the healthy control and SCNP group. Therefore, an independent samples t-test, with equal variance not assumed, was run to determine the differences in means between the two groups. Additionally, outliers were removed from the data set if participants' COR gain value was 2 standard deviations away from the interquartile range (IQR), plus or minus the 75th or 25th percentile range, respectively. Effect size was reported utilizing Cohen's D, in which 0.2 is considered a small effect size, 0.5 is considered a medium effect size, and 0.8 is considered a large effect size (Cohen, 2013).

VOR Gain, Head Peak Velocity, Constant Error, & Variable Error

Due to the uncontrollable Matlab error that led to the adaptation of the Matlab script into three different scripts, only the first four blocks were included in the statistical analyses for VOR gain, head peak velocity, constant error, and variable error. As seen within figure 3.7 (c), the 2.5-minute breaks to transfer between scripts, which occurred at the end of AB3 and AB7, seemed to

result in the loss of an VOR adaptation response; specifically, following the break at AB3. Therefore, the data following this 2.5-minute break is most likely representative of participants attempting to regain the adaptation response and may not be a true representative of a VOR adaptation profile.

Levene's Test of Homogeneity revealed that there was equal variance between the healthy control and SCNP groups for all four variables. Sphericity was only assumed for VE ($p = 0.836$) and was not assumed for VOR gain ($p < 0.001$, $\epsilon = 0.662$), CE ($p < 0.001$, $\epsilon = 0.647$), and head peak velocity ($p = 0.003$, $\epsilon = 0.725$); thus, the greenhouse-geisser correction was applied for those three variables. Additionally, the Shapiro-Wilk test revealed that the data sets for VOR gain, CE, and VE were all normally distributed. However, head peak velocity was not normally distributed at adaptation block 1 – adaptation block 3; thus, a logarithmic transformation was applied to this data set. A 2 x 4 repeated measures analysis of variance (ANOVA) was utilized for each of the four variables, with pre-planned contrast to baseline for both VOR gain and head peak velocity. The between subjects' factor was set to the two groups (healthy control vs SCNP), while the within group factor was set to either the average VOR gain, head peak velocity, CE, or VE for each of the 4 epochs (pre-adaptation block and adaptation blocks 1 – 3). Additionally, outliers were removed from the data set if their VOR gain or head peak velocity value was 2 standard deviations away from the IQR, plus or minus the 75th or 25th percentile value, respectively. These outliers also had to be present in 3 or more epochs to be removed. However, outliers were not removed for CE and VE as they were not the main outcome measures for the VOR protocol. Effect size was reported utilizing partial eta squared, where 0.0099 is consider a small effect size, 0.0588 is considered a medium effect size, and 0.1379 is considered a large effect size (Richardson, 2011).

An independent samples t-test was also conducted to compare the difference in baseline VOR gain (i.e. VOR gain during the pre-adaptation block), between the two groups. Levene's test of homogeneity was not statistically significant; thus, equal variance was assumed. Effect size was reported utilizing Cohen's D.

Correlation between COR gain and VOR gain

To examine the relationship between the two reflexes a correlation analysis was run between COR gain and baseline VOR gain (i.e., VOR gain during the pre-adaptation block). Shapiro-Wilks test revealed that both variables were normally distributed, thus Pearson's correlation test was utilized. Two Pearson correlation tests were run; one for the SCNP group and one for the healthy control group.

3.4 Results

Demographic

37 participants were included in the analysis of COR gain: 17 healthy controls (7M & 10F, 22.40 ± 3.66 years) and 20 SCNP (9M & 11F, 21.89 ± 2.38 years). 36 participants were included in the analysis of VOR gain, head peak velocity, constant error, variable error, and the correlation between COR gain and VOR gain: 17 healthy controls (7M & 10F, 22.40 ± 3.66 years) and 19 SCNP (9M & 10F, 21.78 ± 2.39 years). One male healthy control participant was removed from both the COR gain and VOR gain analysis as they had mentioned that they suffer from motion sickness and the protocols had aggravated it. Thus, they would not be considered a true healthy control participant as prior literature has demonstrated that motion sickness occurs due to disruptions within the vestibular system (Bertolini & Straumann, 2016). One female SCNP participant was removed from the VOR protocol as their VOR gain value was considered

an outlier (i.e., more than 2 standard deviations away from the IQR plus the 75th percentile value) for 3 epochs. Additionally, this participants' peak head velocity value was also an outlier (i.e., more than 2 standard deviations away from the IQR minus the 25th percentile value) for 3 epochs. This would indicate that the participant was rotating their head too slowly during the protocol which would then lead to a falsely increased VOR gain value. The healthy control group ($\bar{X} = 0.765 \pm 1.091$; $\bar{X} = 0.141 \pm 0.180$) demonstrated lower NDI and VAS values than the SCNP group ($\bar{X} = 7.950 \pm 5.53$; $\bar{X} = 1.474 \pm 1.050$).

COR Gain

There was a statistically difference in COR gain between the healthy control group and the SCNP group ($p = 0.006$), in which the SCNP group ($\bar{X} = 0.239 \pm 0.122$) showed significantly higher values than the healthy control group ($\bar{X} = 0.159 \pm 0.053$). A large effect size was also observed for COR gain ($D = 0.833$).

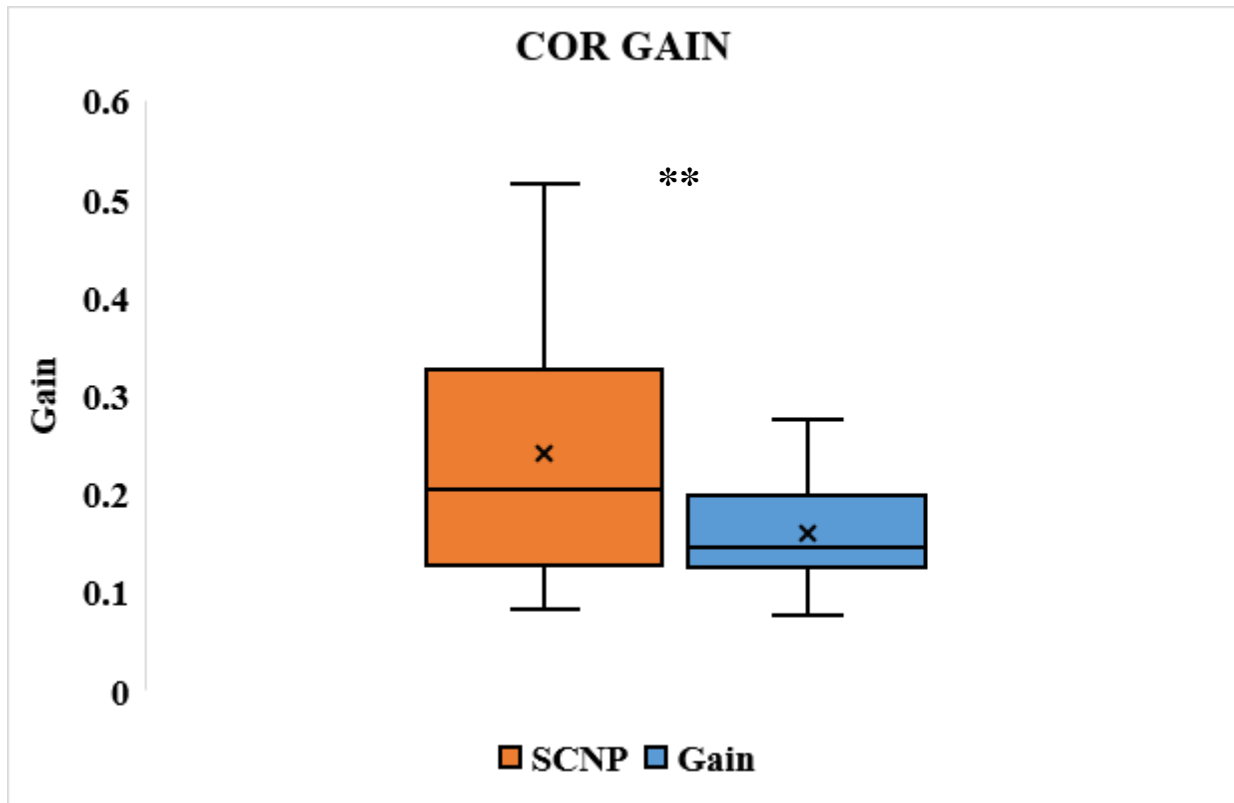
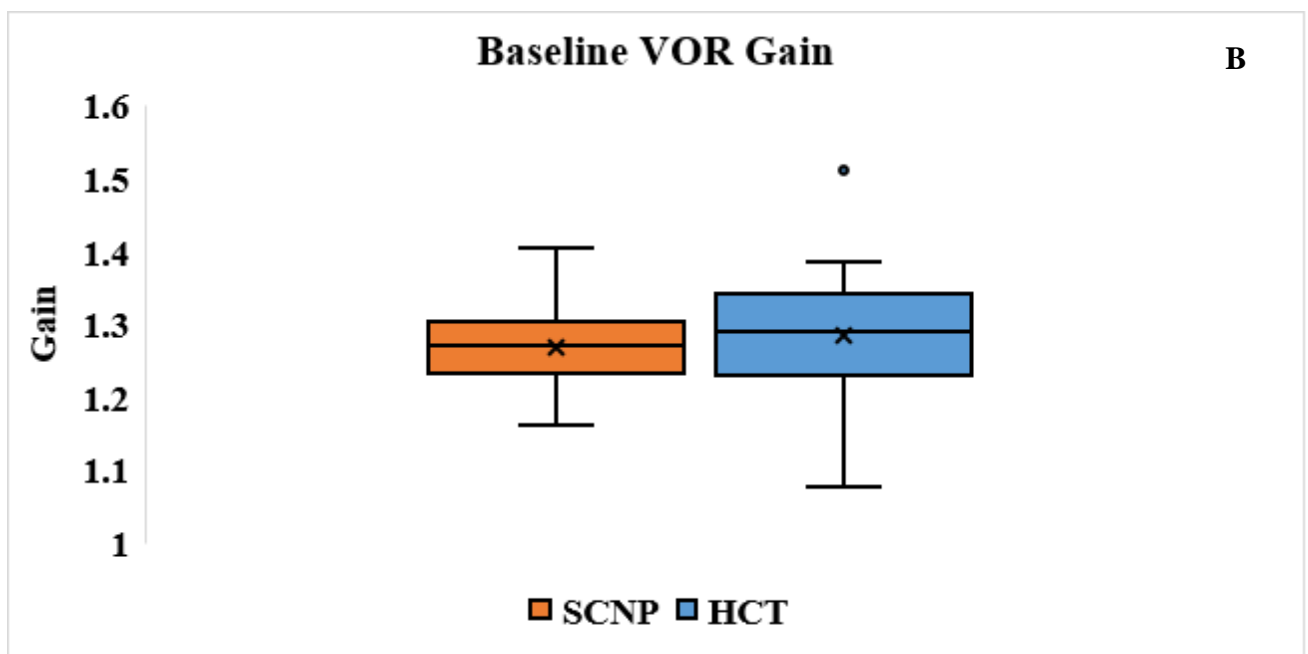
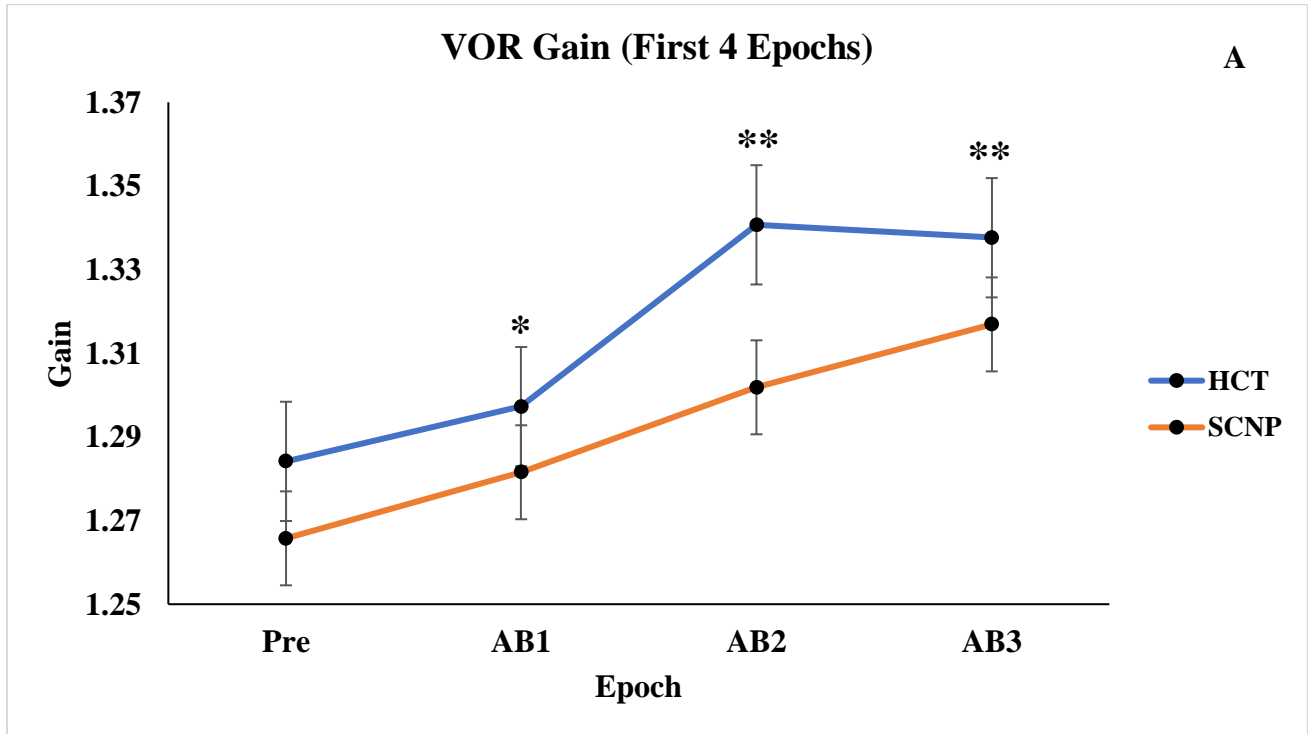


Figure 3.6. Average COR gain of SCNP and healthy control groups. * $p < 0.05$, ** $p < 0.01$

VOR Gain & Head Peak Velocity

For VOR gain, a statistically significant within-group effect was observed for epoch alone ($p < 0.01$). A large effect size was also observed for VOR gain ($\eta_p^2 = 0.252$). This indicates that regardless of the participant group, individuals were able to adapt their VOR response. Additionally, the test of within-subjects contrasts revealed statistical significance during the first 3 adaptation blocks. This would indicate that participants were able to adapt their VOR response during the first 3 adaptation blocks, regardless of what group they were in. However, no significant between-group differences were observed between the SCNP and healthy control groups ($p = 0.608$, $\eta_p^2 = 0.014$). Although, the healthy control participants, on average, had higher VOR gain values than the SCNP group for majority of the epochs (FIG 3.7.a). When

compared to the SCNP group ($\bar{X} = 1.266 \pm 0.059$), the healthy control group ($\bar{X} = 1.284 \pm 0.099$) also demonstrated higher VOR gain values at baseline, though this was not statistically significant ($p = 0.487$, $d = 0.229$).



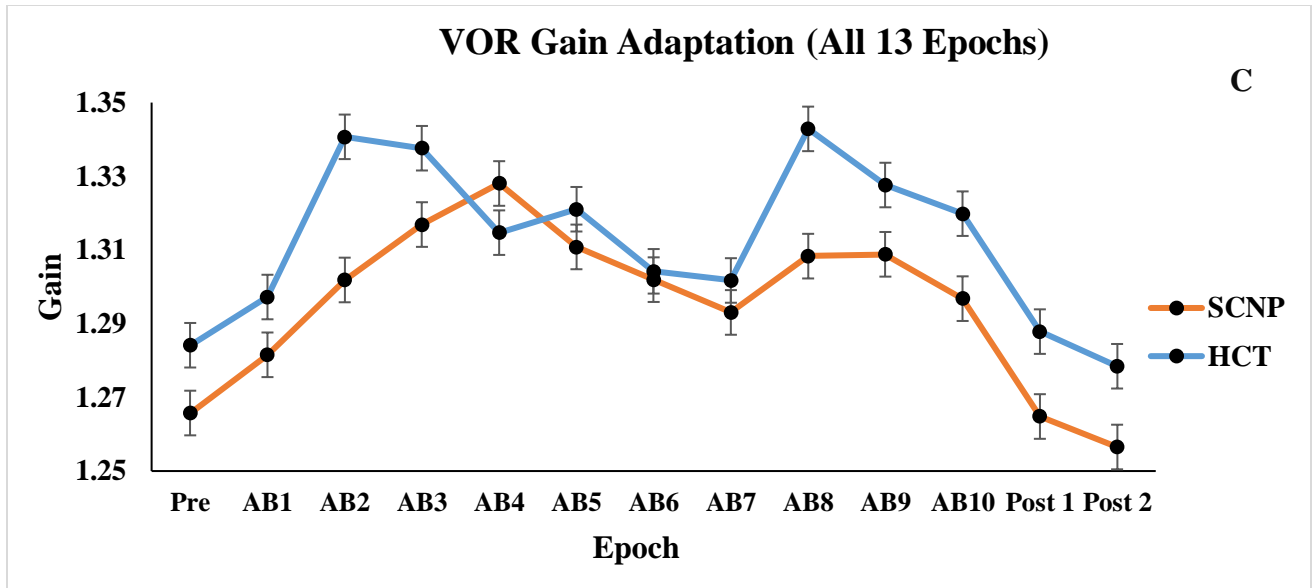


Figure 3.7. (A) Trend in average VOR gain adaptation over the 4 epochs for the SCNP and healthy control groups. Asterisks denotes significant effect of time, with respect to the pre-adaptation block (i.e. baseline). * $p < 0.05$, ** $p < 0.01$. (B) Average VOR gain of SCNP and healthy controls at baseline (i.e. pre-adaptation block). (C) Trend in average VOR gain adaptation over all 13 epochs for the SCNP and healthy control groups; reflecting the drop in VOR gain during the 2.5-minute transfer period, specifically following AB3.

Similar results were observed for head peak velocity, as a statistically significant within-group difference was observed for epoch alone ($p = 0.028$), while a medium effect size was also observed ($\eta_p^2 = 0.097$). This would indicate that regardless of participant group, participants would adapt their peak head velocity throughout the epochs as the target moved. Additionally, within-subjects contrasts revealed statistical significance at all epochs which would indicate that participants' peak head velocity was significantly different for all epochs when compared to the pre-adaptation block. However, no statistically significant between-group differences were observed between the SCNP and healthy control groups ($p = 0.465$, $\eta_p^2 = 0.023$). This also

indicates that any differences in VOR gain between the two groups would not be due to participant groups simply rotating their heads at different average velocities.

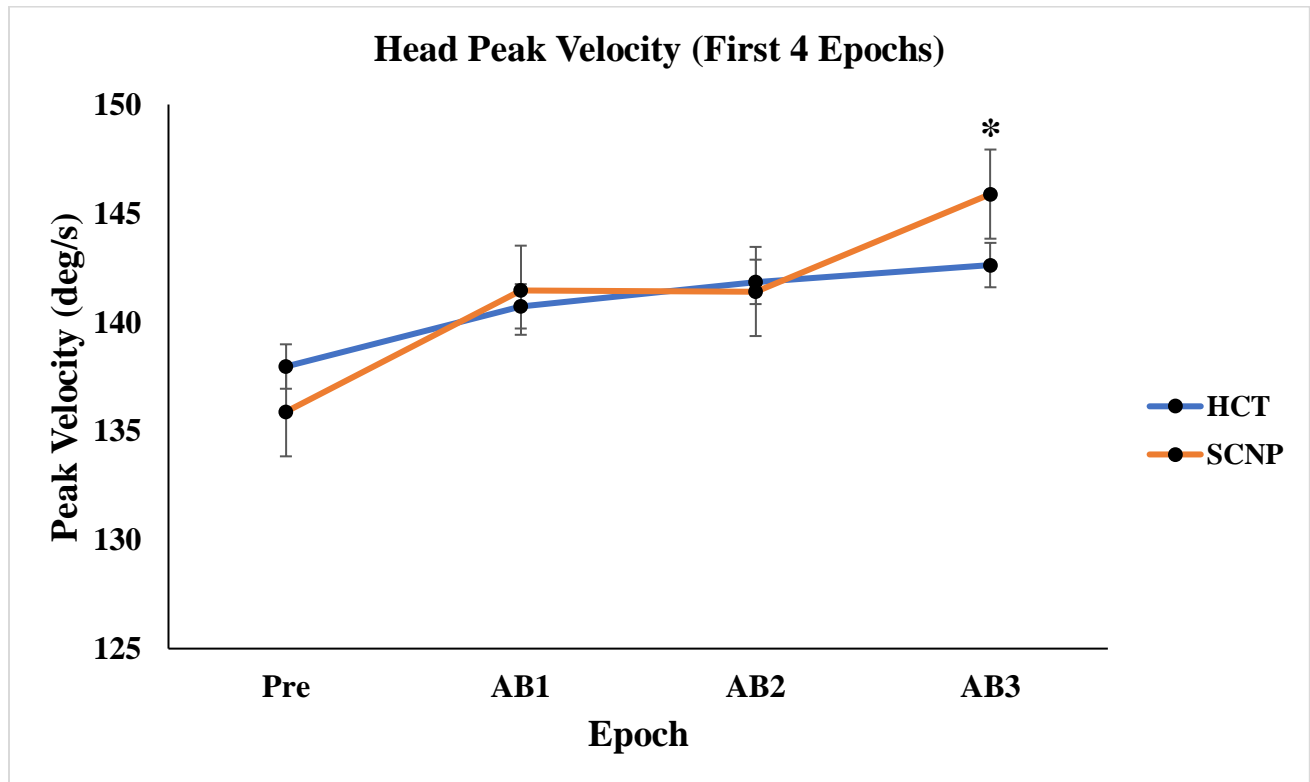


Figure 3.8. Trend in average head peak velocity over the first 4 epochs for the SCNP and healthy control groups. Asterisks denotes significant effect of time, with respect to the pre-adaptation block (i.e. baseline). * $p < 0.05$, ** $p < 0.01$.

Constant & Variable Error/

Statistically significant within-group differences were observed in CE ($p = 0.010$, $\eta_p^2 = 0.130$), while no significant within-group differences were observed in VE ($p = 0.144$, $\eta_p^2 = 0.064$). Additionally, no statistically significant between-group differences were observed between the SCNP and healthy control groups, for both CE ($p = 0.632$, $\eta_p^2 = 0.013$) and VE ($p = 0.629$, $\eta_p^2 = 0.024$).

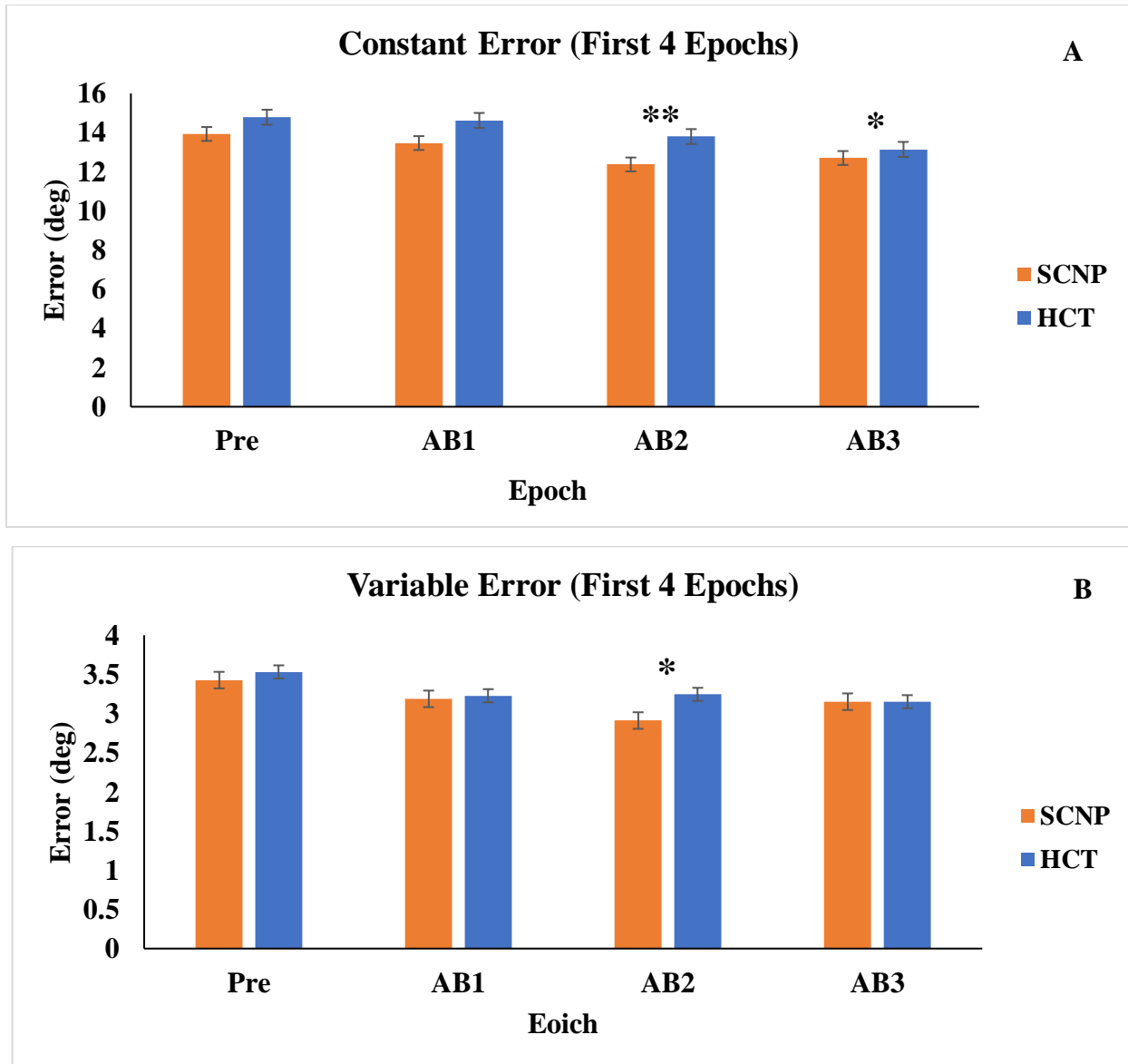


Figure 3.9. Trend in average (a) constant error and (b) variable error over the first 4 epochs for the SCNP and healthy control groups. Asterisks denotes significant effect of time, with respect to the pre-adaptation block (i.e. baseline). * $p < 0.05$, ** $p < 0.01$.

Correlation between COR Gain and VOR Gain

No statistical significance was observed for the correlation between COR gain and baseline VOR gain in either the SCNP or healthy control groups. There was no relationship between COR and VOR gain in the SCNP group SCNP: ($r = -0.038$, $p = 0.438$). A moderate

negative correlation was observed in the healthy control group between COR gain and baseline VOR gain ($r = -0.350, p = 0.088$), (Taylor, 1990).

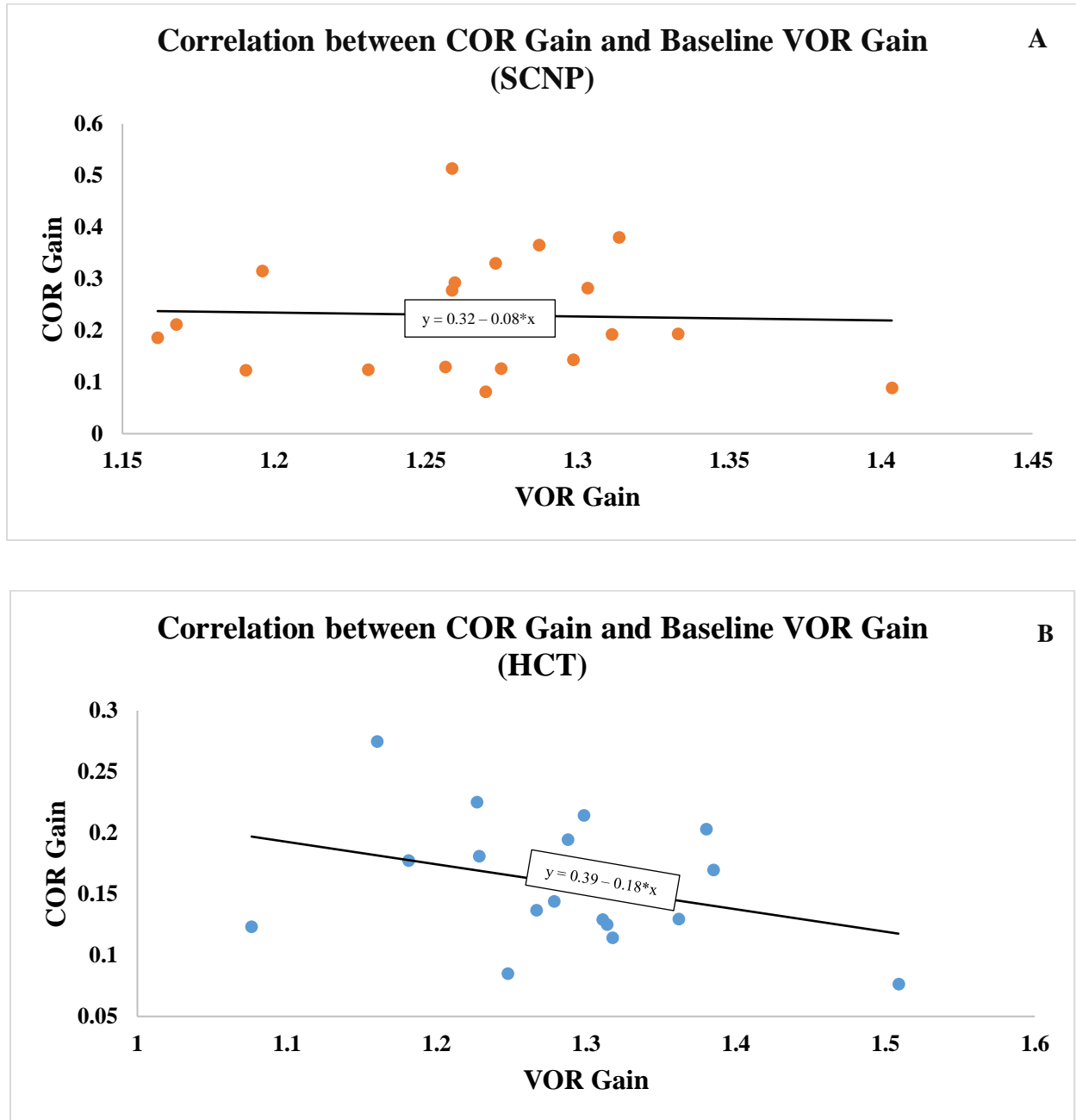


Figure 3.10. (a) Correlation between COR gain and baseline VOR gain in the SCNP ($r = -0.038, p = 0.438$) and (b) healthy control groups ($r = -0.350, p = 0.088$)

3.5 Discussion

This is the first study to examine changes within cerebellar processing, in a SCNP population, utilizing direct measures of the cerebellum. The methodology involved the analysis of differences within COR gain and VOR gain adaptation between a SCNP group and a healthy control group. In line with current literature, that has examined changes within the COR in individuals with various forms of neck pain (de Vries et al., 2016; Ischebeck et al., 2017; Kelders et al., 2005; Montfoort et al., 2008), the COR gain appeared to be higher within the SCNP compared to the healthy control group. This may be reflective of alterations in proprioceptive input towards the cerebellum. In contrast, both groups showed similar abilities to adapt their VOR in response to a distorted visual stimulus. However, the healthy control group did demonstrate higher VOR gain values for majority of the epochs, when compared to the SCNP group. This may suggest that because the SCNP has pain free days, the neuroplastic changes in the VOR have begun, but not progressed to the point of statistically significant differences in the VOR can be observed.

COR Gain

Prior literature suggested that the COR is heavily reliant upon input from the proprioceptive system (Gdowski et al., 2001). It has been suggested, that during trunk-on-head rotations, neck proprioceptors detect changes in neck velocity and transmit this information along the spinocerebellar tract (Röijezon et al., 2015). Some of this proprioceptive information enters the spinocerebellar division of the cerebellum while some of the information is transmitted to the central cervical nucleus (CCN) (Gdowski et al., 2001). Via mossy fibers, the CCN sends afferent input into the flocculus of the cerebellum (Gdowski et al., 2001). This may suggest that the alterations observed in COR gain may be due to altered proprioceptive input towards the

spinocerebellar division of the cerebellum. As demonstrated by Haavik and Murphy (2012), areas of joint/spinal dysfunction such as SCNP, represent areas of altered afferent input towards the CNS. Additionally, prior literature has demonstrated alterations in both head/neck, and upper limb, proprioception in individuals with SCNP (Paulus & Brumagne, 2008; Zabihhosseinian et al., 2017). Paulus and Brumagne (2008) suggest that recurrent neck pain may alter the discharge from muscle spindles, thus altering proprioceptive input towards the CNS. As demonstrated by Cooper and Daniel (1963), muscle spindle density is very high within the neck musculature, where spindle feedback plays a key role in integrating the position of the head and neck. Additionally, prior literature has also demonstrated that the muscle spindles located within the deep neck musculature relay proprioceptive information, essential for eye/head coordination (Bakker et al., 1984; Edney & Porter, 1986; Liu et al., 2003; Porter, 1986). This would suggest that alterations in muscle spindle activity, due to SCNP, may alter the coordination of eye movements such as those that occur during the COR response.

Additionally, these alterations in the COR response may be linked to disruptions in the ability of the cerebellum to formulate the body's internal model (i.e. body schema). Although subjective measures were not recorded, a portion of SCNP participants reported that they experienced the sensation of their head rotating throughout the protocol instead of their trunk rotating. Due to the COR and VOR sharing similar neural substrates, it has been suggested that one of these reflexes must be suppressed, during certain behavioural contexts, in order to ensure gaze stability is maintained by the active reflex (Gdowski et al., 2001). Literature suggest that the floccular Purkinje cells will send inhibitory input towards the vestibular nuclei; thus, the flocculonodular lobe able is to suppress the activity of the VOR while the COR is active (Belton & McCrea, 1999; Gdowski et al., 2001). However, if the afferent input towards the cerebellum is

disrupted, this could lead to alterations within the cerebellum's ability to update body schema in order to maintain accuracy (Baarbé et al., 2016). Therefore, it can be suggested that the altered proprioceptive input received from the neck may alter the ability of the cerebellum to update body schema, as proprioception has been demonstrated to play a key role in formulating body schema (Holmes & Spence, 2004). In turn, this altered proprioceptive feedback may cause the cerebellum to perceive that the head/neck is rotating while in actuality they are stable (i.e. altered body schema). Thus, this may lead to limited suppression of the VOR while the COR is active which, in turn, may cause an upregulation in COR gain as the VOR has been demonstrated to be the stronger of the two reflexes (Gdowski et al., 2001). This upregulation within the COR, that was observed within the SCNP group, would be indicative of a diminished VOR as consist with prior literature that has describe upregulations in the COR due to disruptions within the VOR (Bronstein et al., 1995; Kelders et al., 2003; Zamysłowska-Szmytke et al., 2019).

VOR Gain Adaptation

The VOR is a multisensory response that relies upon input from the proprioceptive, visual, and vestibular systems (Gdowski & McCrea, 2000; Gray, 2020b; Ito, 1998). However, the VOR seems to receive majority of its input from the vestibular system as demonstrated by disruptions, or the complete loss, of the reflex in individuals with vestibular system disturbances (Bronstein et al., 1995; Kelders et al., 2003; Zamysłowska-Szmytke et al., 2019). Montfort et al., (2008) suggests that the cerebellum will modify the either the COR or VOR in response to disruptions within the other reflex. This would suggest that the increases observed within the COR gain would indicate decreases within VOR gain within the SCNP group. However, this diminished VOR response was not observed in the SCNP group when compared to the healthy control group. Although these differences did not reach statistical significance, the SCNP group

did demonstrate lower VOR gain values for majority of the epochs while also demonstrating a lower VOR gain at baseline, when compared to the healthy control group. This may suggest that SCNP has a limited effect upon the vestibular input towards the cerebellum. Treleaven (2017) supports this as the researcher describes that vestibular disturbances are less likely with lower severity forms of neck pain. Prior studies that have examined changes within the COR and VOR, in individuals with various forms of neck pain, have also observed similar results (de Vries et al., 2016; Ischebeck et al., 2017; Kelders et al., 2005; Montfoort et al., 2008). As these same studies demonstrated an upregulation within COR gain without any significant differences in VOR gain; however, these non-changes within VOR gain may be due to technical challenges with the methodology utilized to elicit the VOR response. It is also possible that SCNP disrupts the relationship between VOR and COR. In line with previous literature, a negative correlation was observed between the two reflexes in the healthy group; where COR gain increased with decreases in VOR gain (Bronstein et al., 1995; Montfoort et al., 2008; Zamysłowska-Szmytko et al., 2019), while the SCNP had no relationship between VOR and COR gain. This uncoupling of the relationship between VOR and COR may be related to sensory mismatches between proprioceptive input from the neck and vestibular input in those with SCNP. The trend toward differences in VOR gain between the SCNP and healthy control group, may be due to the impact of SCNP on neck proprioceptors. As previously mentioned, the muscle spindles located within the deep neck musculature relay proprioceptive information, essential for eye/head coordination (Bakker et al., 1984; Edney & Porter, 1986; Liu et al., 2003; Porter, 1986). These muscle spindles will send proprioceptive signals towards the CCN and, in turn, the CCN will project these proprioceptive signals towards the vestibular nuclei as well as the flocculonodular lobe in order to modify the oculomotor reflexes (Gdowski & McCrea, 2000; Sato et al., 1997).

Furthermore, as suggested by Paulus and Brumagne (2008) recurrent neck pain may alter the discharge from the muscle spindles. Therefore, SCNP may alter the proprioceptive input towards the cerebellum via the CCN. Additionally, the spinocerebellar tract transmits unconscious proprioceptive information towards the spinocerebellum where it will synapse on the fastigial nucleus (Zhang et al., 2016). The fastigial nucleus then transmits this proprioceptive information towards the vestibular nuclei which utilize this information to modify the oculomotor reflexes (Zhang et al., 2016). Thus, it is reasonable to believe that the slight disruptions observed within the VOR may be due to the altered neck proprioceptive input (i.e. altered afferent input), towards the spinocerebellum via the spinocerebellar tract, that is present in individuals with joint/spinal dysfunction such as SCNP.

However, due to the modifications that had to be made within the Matlab script, due to the technical error that persisted throughout data collection, the results of this study may have been altered. Since it took ~2.5 minutes to transfer between the Matlab scripts, there is a possibility that the VOR gain adaptation process may have been disrupted and may have had a slight regression back towards baseline levels during that 2.5-minute transfer period. This can also be observed in figure 3.7 (a), as there seemed to be a trend in which VOR gain was steadily increasing, specifically within the healthy control group. However, as seen within figure 3.7 (c), there seemed to be a significant reduction in VOR gain from AB3 to AB4, during which the 2.5-minute transfer occurred. Therefore, it can be reasoned that if the protocol was allowed to run as intended statistically significant between group differences may have been observed; representing, maladaptive changes associated within SCNP.

The current study suggests that SCNP alters cerebellar processing as demonstrated by disruptions within the COR, but not the VOR, in a SCNP population. This would suggest that

SCNP has a greater impact upon the proprioceptive input towards the cerebellum and a lesser impact upon processing of vestibular input. However, due to the issues that were experienced within our VOR protocol, it can not be said with certainty if these results would be representative of a SCNP population. This study fills in the gaps in research regarding the use of a direct measure of cerebellar processing to assess changes within the cerebellum due to SCNP.

3.5.1 Limitations

Due to the weight of the eye-tracker neck fatigue and head discomfort commonly occurred when SCNP participants wore the device for long periods of time. Additionally, the prolonged use of the bandanas to restrict head movements, during the COR protocol, would sometimes re-aggravate symptoms in individuals with SCNP and thus, may have altered the proprioceptive input received from the neck proprioceptors. However, we addressed these limitations by using Borg's RPE scale to monitor the participants' perceived level of fatigue within their neck and to ensure pain was not a limiting factor. Additionally, the current study did not screen healthy control participants for vestibular disturbances such as motion sickness. Future studies should measure this and make motion sickness an exclusion criterion.

3.6 Conclusion

The results of the current study suggest that SCNP alters cerebellar processing as demonstrated by disruptions within the COR. Specifically, it is likely that SCNP alters the proprioceptive input directed towards the cerebellum but plays a limited role on the vestibular input. Future research could examine the relationship between severity of neck pain and its impact upon the VOR and cerebellar plasticity.

Link Between Study One and Two

Study one demonstrated that SCNP may alter the ability of the cerebellum to process proprioceptive information, as shown by the disruptions within the COR, but may have a limited impact on its ability to process vestibular information, as demonstrated by the minute alterations within the VOR. Study two focuses on the effects of spinal manipulation on cerebellar processing, within a SCNP population, by examining potential changes within COR gain and VOR gain adaptation, prior to, and following, a spinal manipulation intervention delivered over a period of eight weeks.

Chapter 4. Manuscript 2

The effects of spinal manipulation on cerebellar processing as measured by the cervico-ocular & vestibulo-ocular reflexes in a subclinical neck pain population

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4.1 Abstract

Background: Subclinical neck pain (SCNP) refers to untreated, recurrent episodes of mild-to-moderate neck pain with pain-free days. Prior literature has found that there are neurophysiological alterations in cerebellar processing in individuals with SCNP such as disruptions in sensorimotor integration (SMI), motor control processes, proprioception, and cerebellar inhibition (CBI). Literature has also demonstrated improvements within cerebellar processing, in a SCNP population, following a single session of spinal manipulation. However, these alterations and improvements have only been assessed indirectly. Cerebellar processing can be examined directly utilizing the cervico-ocular and vestibulo-ocular reflexes (COR & VOR). These two oculomotor reflexes act to keep images stable upon the retina during trunk and head movements. This study aims to investigate whether a course of manual treatment, delivered over an eight-week period, impacts COR gain and VOR gain adaptation in individuals with SCNP.

METHODS: 27 right-hand dominant participants with SCNP, aged 18 to 35 were randomized into two different experimental groups (15 SCNP treatment: 7M & 8F 12 SCNP controls: 6M & 6F). Each group completed two eye-tracking tasks. COR: participants were seated in a motorized chair and fitted with an eye-tracking device. They were instructed to stare at a visual target projected on a monitor 3 meters away from them. Once the target appeared on the screen, the motorized chair began a series of oscillations at a frequency of 0.04 Hz, with an amplitude of 5°, for 120 seconds. 10 trials were completed, with each trial lasting two minutes. VOR: participants were seated 90 cm away from a monitor and were instructed to make active head rotations while tracking a target projected on the screen in-front of them. Participants performed 390 trials divided into 13 blocks (pre-adaptation, 10 adaptation, & 2 post-adaptation blocks) in which the target would move at different speeds during each block.

Intervention: *SCNP treatment group:* 8-weeks of personalized high-velocity low amplitude (HVLA) spinal manipulation directed towards dysfunctional joints within the spine and pelvis and myofascial release of neck muscles as clinically indicated. *SCNP control group:* 8-weeks of continuing their regular activities of daily living, without receiving any form of manual therapy

RESULTS: The SCNP treatment group demonstrated significantly lower COR gain values than the SCNP control group following the 8-week intervention ($p = 0.011$, $\eta_p^2 = 0.242$) with no differences in VOR gain adaptation between the two groups, except for adaptation block 8, following the 8-week intervention ($p = 0.015$, $\eta_p^2 = 0.352$).

DISCUSSION: These results suggest that treatment of neck dysfunction may improve the ability of the cerebellum to process proprioceptive information, within a SCNP population as seen in the improved COR response. The minimal VOR change is likely because the vestibular system is less impacted by the altered neck input.

Keywords: Cerebellum, subclinical neck pain, cervico-ocular reflex, vestibulo-ocular reflex, vestibulo-ocular reflex adaptation, spinal manipulation, high-velocity low amplitude

4.2 Introduction

Work demands and routine activities of daily living are associated with greater reliance on technology. With this increased reliance there has been an equivalent rise in neck pain (Berolo et al., 2011; Green, 2008; Kim, 2015). Neck pain manifests in various forms, all of which are dependent upon the magnitude of injury/dysfunction on the mechanical and/or physiological structures within the neck musculature. However, it can be difficult to assess the impact of functional changes to the neck elucidating the various neural mechanisms underlying dysfunction as the associated pain has been demonstrated to alter these processes (Rossi et al., 2003; Strutton et al., 2005; Waberski et al., 2008). A subclinical neck pain (SCNP) population represents a window of opportunity to investigate the impact of chronic changes in neck sensory input on neural processing as this group can be tested on days where they have minimal pain, creating the opportunity to examine changes in the neural plasticity independent of the confounding impact of pain itself on movement patterns and neural pathways (Lee et al., 2005). SCNP is defined as recurrent episodes of mild-to-moderate neck pain that have not received treatment (Lee et al., 2005)

Previous studies that have examined alterations within the central nervous system (CNS) associated with SCNP have demonstrated alterations in both neck and upper limb proprioception (Haavik & Murphy, 2011; Lee et al., 2008; Zabihhosseinian et al., 2017). Alterations in shoulder and scapular kinematics, upper limb joint position sense, and head and neck movements have also been observed (Haavik & Murphy, 2011; Paulus & Brumagne, 2008; Zabihhosseinian et al., 2017). It has been suggested that areas of muscle and joint such as occurs in SCNP, represent areas of altered sensory feedback towards CNS (Haavik & Murphy, 2012), which would in turn lead to alterations in the ability of the CNS to appropriately process and filter sensory

information and adapt motor output appropriately. This neural process is known as sensorimotor integration (SMI) (Wolpert et al., 1995). Utilizing somatosensory evoked potentials (SEPs), prior studies have noted alterations in the processing of sensory information within the primary somatosensory cortex (S1), as reflected by alterations with the N20 SEP peak, associated with neck dysfunction (Haavik-Taylor & Murphy, 2007a). SEPs are electrical potentials that are generated within various regions within the brain, following the stimulation of afferent nerve fibers or their receptors in the periphery, and are recorded from the scalp as complex wave forms (Cruccu et al., 2008). Additionally, prior literature has noted disruptions within somatosensory processing, as reflected by alterations within the N30 SEP, in a SCNP population (Haavik-Taylor & Murphy, 2007a). Andrew and colleagues (2018), have built upon this by demonstrating alterations in both the N18 and N24 SEP peaks in response to motor skill acquisition in those with SCNP. These would suggest that SCNP alters the processing of sensory information projected towards the cerebellum, as well as somatosensory output projected from the cerebellum into S1, during SMI (Andrew et al., 2018). As such, it is reasonable to believe that SCNP alters cerebellar processing during SMI. Utilizing transcranial magnetic stimulation (TMS), prior literature has also demonstrated alterations in cerebellar processing within a SCNP population (Baarbé et al., 2018; Daligadu et al., 2013). When examining changes within cerebellar inhibition (CBI), Daligadu and colleagues (2013) were able to demonstrate increases in CBI within a SCNP population, which was improved when spinal manipulation was delivered prior to a motor skill acquisition task. CBI reflects the amount of inhibition the cerebellum is exerting upon the primary motor cortex (M1), during a motor task and is recorded as a motor evoked potential (MEP) within the distal hand musculature (Ugawa et al., 1995). Thus, this MEP reflects the connectivity between the M1 and the cerebellum (Daskalakis et al., 2004). Therefore,

the increases in CBI suggest that the altered afferent input from the cervical musculature and joints present in individuals with SCNP, disrupts the output from the cerebellar nuclei towards M1 (Daligadu et al., 2013). Similar results were produced by Baarbé and colleagues (2018), who were able to demonstrate increases in CBI, within a SCNP population, during a more complex motor skill acquisition task. The researchers suggested that SCNP may lead to neuroplastic changes within the cerebellum (i.e., altered cerebellar processing); thus, leading to altered movement patterns (i.e., altered motor output). Interestingly, prior literature has demonstrated that these neurophysiological changes associated with SCNP and other forms of joint dysfunction, may be improved following spinal manipulation

Spinal manipulation is a well-established technique in the treatment of SCNP (Baarbé et al., 2018). It commonly involves high velocity, low-amplitude (HVLA) thrusts to dysfunctional joints within the spine (Baarbé et al., 2018). Utilizing a joint repositioning task, Haavik and Murphy (2011), were able to demonstrate improvements in joint position sense (JPS) following an intervention consisting of spinal manipulation directed towards dysfunctional joints within the cervical spine, within a SCNP population (Haavik & Murphy, 2011). This may suggest that changes in proprioceptive input are a result of normalized afferent input from the cervical joints and musculature following HVLA adjustments to dysfunctional areas. Therefore, it can be rationalized that spinal manipulation may lead to improvements in SMI in a SCNP population. Utilizing SEPs, Haavik and Murphy (2007) outline this concept as the researchers demonstrated significant attenuation in both the N20 and N30 SEP peaks, following a single session of spinal manipulation. This decrease in amplitude of the N20 SEP peak would represent a decrease in processing within S1 which was initially higher due the SCNP (Haavik-Taylor & Murphy, 2007a). Additionally, the decrease in the N30 SEP peak may suggest a reduction in activity

within the cortical and subcortical loops that link with the basal ganglion, thalamus, pre-motor areas, and M1 (Haavik-Taylor & Murphy, 2007a). It was suggested that this change within the N30 SEP peak may be due to alterations within afferent input following spinal manipulation (Haavik-Taylor & Murphy, 2007a). Prior literature has demonstrated that primary afferents (Ia) act as the mediators for the central neural changes that occur following spinal manipulation (Bolton & Holland, 1996; Murphy et al., 1995; Pickar & Wheeler, 2001; Zhu et al., 2000; Zhu et al., 1993). It has also been demonstrated that the N30 SEP peak is sensitive to changes within the Ia afferents (Hoshiyama & Kakigi, 2000). Thus, it can be rationalized that HVLA manipulation may alter Ia afferent input towards the CNS; therefore, causing neuroplastic changes within SMI. Similar findings were observed in TMS studies that examined changes within CBI in a SCNP population (Baarbé et al., 2018; Daligadu et al., 2013). Daligadu, and colleagues (2013), were able to demonstrate significant reductions in CBI following cervical spinal manipulation. Similarly, Baarbé and colleagues (2018), were able to demonstrate decreases in CBI, as well as improvements in reaction time during a motor skill acquisition task (i.e. improved motor control), following a single session of spinal manipulation towards dysfunctional joints within the cervical spine. This may suggest that HVLA manipulation, directed towards dysfunctional joints, normalizes afferent feedback from the neck (Daligadu et al., 2013). This would then improve the ability of the cerebellum to create an accurate internal body schema with which to process somatosensory information (Daligadu et al., 2013). The issue with utilizing techniques such as SEPs and CBI-TMS, is that they are indirect measures of cerebellar processing, as they reflect the sensory input and motor output from the cerebellum, respectively, so cause and effect of altered neck input on cerebellar function cannot be directly established. To date, no direct measures of cerebellar processing have been utilized to assess changes in cerebellar processing,

following treatment within a SCNP population, and no studies have examined the impact of several weeks of treatment on cerebellar neuroplasticity.

Two direct measures of cerebellar function are the vestibulo-ocular reflex (VOR), and the cervico-ocular reflex (COR). The cerebellum, specifically the flocculonodular lobe, receives inputs from the proprioceptive, visual, and vestibular systems in order to modify and control the VOR and COR (Gdowski et al., 2001; Gdowski & McCrea, 2000; Gray, 2020c; Ito, 1998). The COR is a gaze stabilizing reflex that acts to stabilize images upon the retina by keeping the eyes fixated within the orbits during trunk-on-head rotations and can be quantified utilizing COR gain which is the ratio of peak eye velocity to peak trunk velocity (de Vries et al., 2016). The VOR is another oculomotor reflex that acts to stabilize gaze during head movements and can be quantified utilizing VOR gain, which is the ratio of peak eye velocity to peak head velocity (Ranjbaran & Galiana, 2015). Literature suggests that VOR gain will increase in response to a retinal image slip that can be elicited by utilizing a moving target (Shelhamer et al., 1994). This neurophysiological phenomenon is known as VOR gain adaptation (Shelhamer et al., 1994). Furthermore, has demonstrated a co-dependent, neurophysiological, relationship between the two oculomotor reflexes, in which one reflex will upregulate due to alterations within the other (Gdowski et al., 2001).

Prior literature has yet to demonstrate changes within the VOR in a neck pain population which may suggest that neck pain has a limited impact upon the vestibular system (de Vries et al., 2016; Ischebeck et al., 2017; Kelders et al., 2005; Montfoort et al., 2008). However, this may be due to issues in the methodology utilized within these studies. To assess VOR in past studies, participants were instructed to stare at a visual target while being passively rotated by a motorized chair, at a peak velocity of 5.03°/second (de Vries et al., 2016; Ischebeck et al., 2017;

Kelders et al., 2005; Montfoort et al., 2008). However, other literature suggest that the VOR is most prominent at high movement speeds and, thus, cannot be elicited at low movement frequencies (Tabak et al., 1997). Literature has also demonstrated that the VOR can only be elicited at speeds greater than 50°/second (Gray, 2020c). Therefore, these studies may not have utilized an appropriate methodology to elicit a proficient VOR response. Furthermore, these same studies have assessed differences in the COR response within a neck pain population; however, there may have also been issues in the methodology utilized to assess the COR (de Vries et al., 2016; Ischebeck et al., 2017; Kelders et al., 2005; Montfoort et al., 2008). To elicit the COR response, these studies instructed participants to stare at a target while being rotated within a motorized chair with their head fixated. To ensure the participants head was fixated within the center position during the chair rotations, participants were instructed to bite down on a bite board. However, biting down may lead to co-activation of the anterior and posterior neck muscles (Hellmann et al., 2012). Consequently, this may activate the muscle spindles and golgi tendon organs (GTO) within the cervical musculature as they are responsible for relaying proprioceptive information regarding the contraction and length of a muscle (Kandel et al., 2000). Therefore, the use of a bite board, to keep the head fixated, could alter the proprioceptive information received from the neck musculature thus altering the COR response.

Various studies have demonstrated that the COR and VOR have a negative correlation, in which decreases in one of the reflexes will cause an upregulation in the other (Bronstein et al., 1995; Kelders et al., 2003; Zamysłowska-Szmytke et al., 2019). This is commonly observed as upregulations in the COR due to disruptions within the VOR in various populations such as individuals with dizziness accompanied by asymmetric neck pathophysiology, individuals with bilateral vestibular labyrinth lesions, and in older populations (Bronstein et al., 1995; Kelders et

al., 2003; Zamysłowska-Szmytke et al., 2019). Montfoort et al., (2008), suggests that the cerebellum will modify the either the VOR or COR in response to disruptions/alterations within the other reflex. Literature has also demonstrated upregulations within the COR in individuals with various forms of neck pain (de Vries et al., 2016; Ischebeck et al., 2017; Kelders et al., 2005; Montfoort et al., 2008). Conversely, these same studies were not able to demonstrate alterations within the VOR; however, this may have been due to the methodology utilized or the fact that these individuals had chronic pain which impacted neck movements. Unlike individuals with SCNP, a chronic neck pain population does not experience pain free days and, thus, the presence of pain may have altered movement patterns, leading to inaccurate measurement of the COR and VOR.

Thus, the current study seeks to address the gaps in the literature related to a lack of direct measures of alterations in cerebellar processing in SCNP populations, by utilizing the COR and VOR to directly assess the effects of SCNP on cerebellar processing. The current study will also address the potential limitations of previous studies which measured changes within the COR and VOR responses by monitoring neck movement speed for the VOR, and eliminating the bite board when measuring the COR. It is hypothesized that individuals with SCNP will have an increased COR gain and a diminished ability to adapt their VOR response, representing alterations in cerebellar processing.

4.3 Methodology

4.3.1 Participants

27 right-hand dominant participants, with and without SCNP, were recruited from the Ontario Tech University student population and were all between the ages of 18 – 35 years old.

15 participants (7M & 8F; 21.80 ± 2.11 years) were randomly allocated to the SCNP group, while 12 participants (6M & 6F; 22.00 ± 3.10 years) were allocated to the SCNP control group which did not receive treatment.

To be deemed eligible for the study, participants completed a set of pre-screening questionnaires consisting of: the neck disability index (NDI), Edinburgh Handedness Inventory (EHI), electroencephalography (EEG) safety screening checklist, chiropractic adjustment safety checklist (CASC). The NDI was utilized to determine the presence or absence of reoccurring neck pain, within the previous three months. NDI is an objective measure for the assessment of neck disability in both clinical and research settings (Vernon, 2008). EHQ was utilized to confirm right-hand dominance for each participant (Oldfield, 1971). Participants had to have a score greater than 40 to be considered right-hand dominant (Oldfield, 1971). On the day of data collection, participants completed the visual analog scale (VAS) which is a continuous 10 cm line that is commonly used for the assessment of chronic pain (Bijur et al., 2001). Furthermore, research has demonstrated that the VAS is an effective tool for the assessment of acute pain as well (Bijur et al., 2001). Participants were required to have a score of 3 cm, or lower, on the 10 cm VAS, which would indicate the presence of little-to-no pain at the time of study (Bijur et al., 2001; Tashjian et al., 2009). This was to minimize the effect of pain on movement patterns and neural pathways during data collection. To determine if the participants utilized medication that altered their balance or alertness, had been diagnosed with attention deficit hyperactive disorder (ADHD), or had a history of neurological disorders or visual problems, the EEG safety checklist was incorporated. If participants had received treatment for their neck in the past six months, they were excluded from the study. Additionally, participants within the treatment group completed the CASC was to ensure that they had no contraindications that may have prevented

them from receiving treatment. To assess level of fatigue within the head, neck, eyes and low back, Borg's 10-point rating of perceived exertion (RPE) scale was utilized at different timepoints during both protocols to ensure that participants were not becoming uncomfortable (Borg, 1982).

4.3.2 Instrumentation and Data Acquisition

An Eye-Link-II eye-tracker (SR-Research, Ottawa, Canada) was utilized to record eye movements during both the COR and VOR protocols. Monocular, left, eye movements were recorded during the COR protocol utilizing a sampling frequency of 250 frequency, consistent with previous literature (de Vries et al., 2016; Ischebeck et al., 2017). Binocular eye movements were recorded during the VOR protocol with a sampling frequency of 500 Hz. Pilot trials demonstrated that the Eye-Link-II eye-tracker was incapable of maintaining the corneal reflection (CR) signal on the left eye during right head turns and vice versa for the right eye during left head turns. As a result, binocular eye movement was recorded. The ipsilateral eye with respect to the head movement was then analyzed (i.e., left eye data for left head turns and right eye data for right head turns).

A custom-built motorized chair was utilized during the COR protocol to stimulate the COR response by rotating the individual's trunk. To record the degree of chair rotation and angular velocity during the protocol, the chair was fitted with three infrared markers, with a marker power frequency of 1000 Hz. During the VOR protocol the eye-tracking device was also fitted with three infrared markers, each with a marker power frequency of 1000 Hz. These were utilized to record the degree of head rotation and angular velocity for each trial. Two *Northern Digital Incorporated* Optotrak cameras were utilized to record trunk rotation data, during the COR protocol, and head rotation data, during the VOR protocol. For the COR and VOR

protocols, the cameras were placed, 275 cm and 255 cm away from the participant, respectively, and sampled at a frequency of 50 Hz. Analog trunk and head rotation signals were recorded as digital trunk and head displacement signal and stored as a Matlab files for further analysis.

4.3.3 COR Protocol

Participants were seated 3 meters away from a 50-inch monitor, within a custom-built motorized chair and were, subsequently, fitted with an Eye-Link-II eye-tracker. To ensure the participants head stayed fixated within the center position during the protocol, the participant's head was secured to a headrest behind the chair, utilizing two bandanas (FIG 4.1), after they had been fitted with the eye-tracker. Following eye-tracker setup, eye position was calibrated utilizing a built-in 9-point calibration system. Once calibration was completed, participants were instructed to fixate their eyes on a fixation target that was projected on the screen. This was utilized to ensure the position of the participant's eye was accurately fixated before the trial began. Once eye position was fixated, a circular target appeared on the screen and then disappeared, after three seconds. Participants were instructed to stare at this target, and where they last saw the target after it disappeared, for the duration of the trial. Literature suggests that the COR seems to be enhanced in the absence of a visual stimuli (Gdowski et al., 2001). Therefore, by having the target disappear, a stronger COR response can be elicited. Once the target appeared on the screen, the motorized chair also began to rotate the participant's trunk for five full oscillations. The chair rotated for, approximately, 120 seconds, at a frequency of 0.04 Hz, and to an amplitude of 5°. This led to a peak trunk velocity (i.e., stimulus velocity) of ~1.5°/second. This occurred when the chair reached its center position which was the instance when the head and trunk were in-line with one another. 10 trials were completed in which one trial lasted ~120 seconds and consisted of 5 full oscillations. Once each trial was completed,

participants were instructed to report their RPE for their head, neck, eyes, and lower back. Participants were also offered a break after the completion of each trial; however, if the participant decided not to take the break, the next trial began. To ensure participants did not experience acute neck pain during the protocol, participants were given a mandatory break if their RPE was reported to be 4 or more in either their head, neck, or lower back, following two consecutive trials. After completion of the 5th trial, participants were also given a mandatory break. During these breaks, both the eye-tracker and bandanas were removed and the next trial didn't begin until the participant was ready to continue. Once RPE was recorded, the fixation target re-appeared on the screen which indicated that the next trial could begin.



Figure 4.1. Participants head secured into the head rest utilizing bandannas

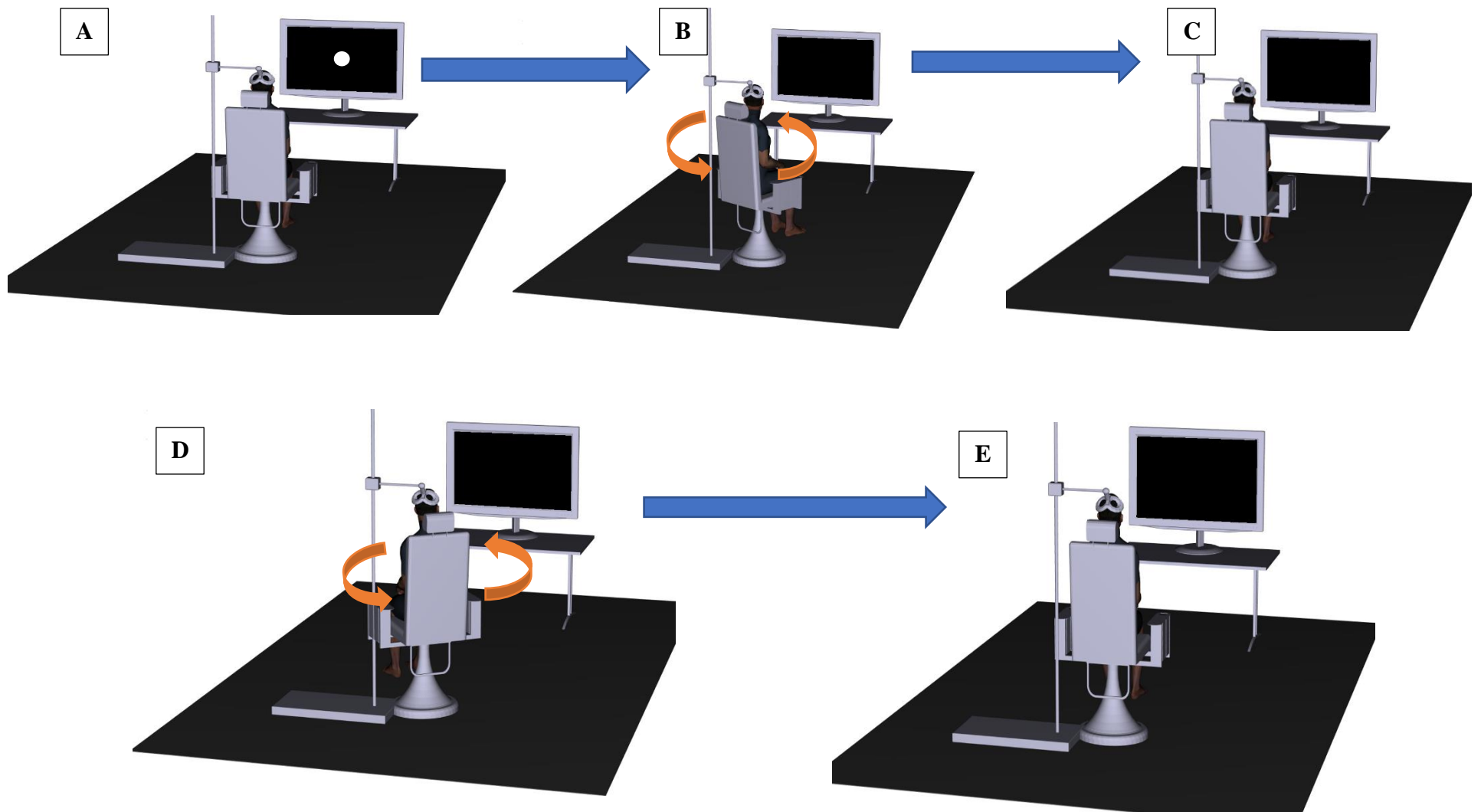


Figure 4.2. Illustration of COR Protocol: (a) Starting position of the chair with target projected on the screen for 3 seconds, (b) Chair rotating to 5° in the clockwise direction, (c) Chair rotating 5° back towards the center position, (d) Chair rotating 5° in the counter-clockwise direction, & (e) Chair rotating 5° back towards the center position

4.3.4 VOR Protocol

Seated 90 cm away from a 26-inch monitor, participants were fitted with the Eye-Link-II eye-tracker. Following eye-tracker setup, binocular eye position was calibrated utilizing a built-in 3-point calibration system. To accurately fixate the position of both eyes, before the trial commenced, participants were instructed to stare at a fixation target that was projected on the screen. Following the fixation of eye position, a circular target was projected on the screen and participants were instructed to rotate their head to either the right or left, by 15° from the center position, while also keeping their eyes fixated on where they last observed the target. Previous studies have utilized an end range of 25° (Schubert et al., 2008); however, pilot results demonstrated that participants tended to end the rotation between a range of 30° – 35°. This suggested that participants were overshooting the end angle by 5° – 10°. Thus, to compensate for this overshoot, the end angle was reduced. To indicate to the participant that they have reached the end range of their rotation, a grey screen appeared on the monitor once participants reached the 15° mark of head rotation. Upon seeing this grey screen, participants were instructed to pause the rotation of their head until the grey screen disappeared on its own, after a three second period, and then return their head back towards the center position. Once the participant had returned their head to the center position, the fixation target reappeared and the next trial commenced once the circular target was displayed on the screen again. Participants were instructed to alternate their head movements between each trial (i.e. left then right head turn or right then left head turn), in which each trial lasted ~5 seconds.

Participants completed 390 trials, that were evenly divided over 13 epochs (i.e. 30 trials per epoch). During epoch 1, the target remained in the center of the screen, during the first $\pm 2^\circ$ of head rotation. This was utilized to determine the participants' baseline VOR gain and was

referred to as the pre-adaptation block. In epochs 2-11 the target moved in the opposite direction of the participant's head rotation and were referred to as the adaptation blocks. In each subsequent adaptation block, the target increased in velocity by increments of 10% of the participant's head angular velocity. For example, the target moved at 10% of the participants head angular velocity in adaptation block 1, while in adaptation block 4, the target moved at 40% of the participants head angular velocity. These epochs elicited a retinal slip on the participants retina and thus, were used to assess the participants ability to adapt their VOR response (i.e., VOR gain adaptation). During epochs 12-13, the target remained in the center of the screen, during the first $\pm 2^\circ$ of head rotation. These final epochs were referred as post-adaptation blocks 1 and 2, as they were utilized to assess the participants ability to re-adapt their VOR back to baseline levels. During each trial, participants received feedback, in regards to their peak angular velocity of their head rotation, in the form of audible beeps. Participant's received two low pitched beeps, if their peak head rotation angular velocity was below $140^\circ/\text{second}$ (i.e., too slow), two high pitched beeps if their peak head rotation angular velocity was above $170^\circ/\text{second}$ (i.e., too fast), and one medium pitched beep if their peak head rotation angular velocity was between $140^\circ/\text{second} - 170^\circ/\text{second}$ (i.e., a good speed). Participants received a 45 second break, at the end of each epoch, to rest their eyes and ensure neck fatigue did not accumulate. During these breaks the participants were instructed to report their RPE within their head, neck, and eyes. If participants reported a RPE of 4 or more in either their head or neck following two consecutive epochs, the eye-tracker was loosened for 30 seconds. This was implemented to ensure that acute neck pain did not occur during the protocol.

To familiarize themselves with the task, participants completed 25 practice trials, prior to commencing the protocol. The structure for the first 20 trials of the practice was the exact same

as the pre-adaptation block, while the structure for the last five trials of the practice was the exact same as adaptation block 1. Only five adaptation trials were utilized to ensure the participant did not adapt prior to beginning the experimental protocol.

An uncontrollable technical error was also experienced at random times throughout the data collection process for the VOR protocol. This error was assumed to be the result of an interruption in the connection between the Matlab script, utilized to run the protocol, and the Optotrak cameras. This caused the visual target to no longer respond to the participants head rotation, the grey screen to no longer appear when the participant reached the end range of rotation, and the audible beeps to no longer be elicited. This error led to a loss of data in the following trials as the Optotrak cameras were no longer able to record head rotational data and there was no change in the visual stimulus to elicit VOR gain adaptation. In an attempt to minimize this loss of data, the Matlab script was divided into three separate scripts where the first script contained trials 1 – 120 (i.e., Pre-adaption – AB3), the second script contained trials 121 - 240 (i.e., AB4 – AB7), and the third script contained trials 241 – 390 (AB9 – Post-adaptation 2). However, it took ~2.5 minutes to transition between scripts.

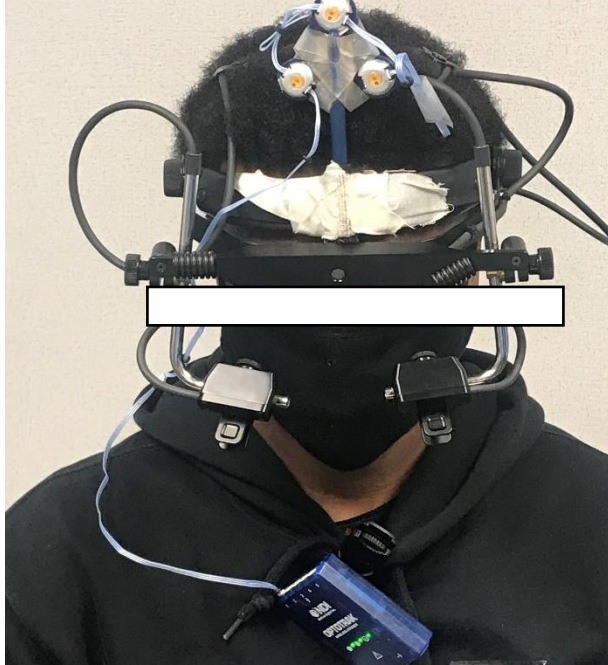


Figure 4.3. Eye tracker setup for VOR protocol

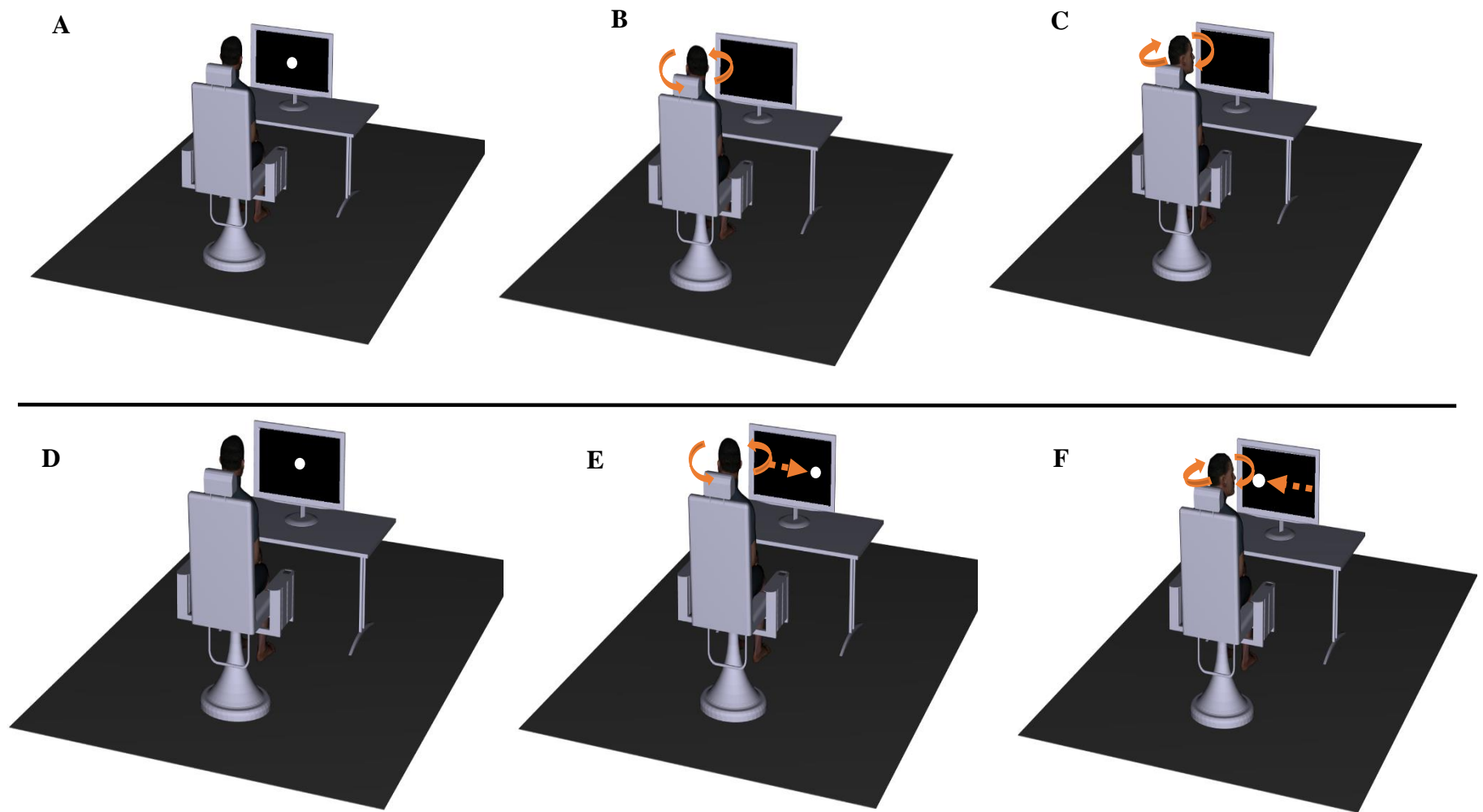


Figure 4.4. Illustration of VOR Protocol for **Pre-/Post-adaption blocks**: (a) Target in the starting position with head in center position, (b) Left head turn with target disappearing at -2° of head rotation, & (c) right head turn with target disappearing at $+2^\circ$ of head rotation; **Adaptation blocks**: (d) Target in the starting position with head in center position, (e) Left head turn with target moving towards the right at set percentage of head velocity, & (f) Right head turn with target moving towards the left at set percentage of head velocity

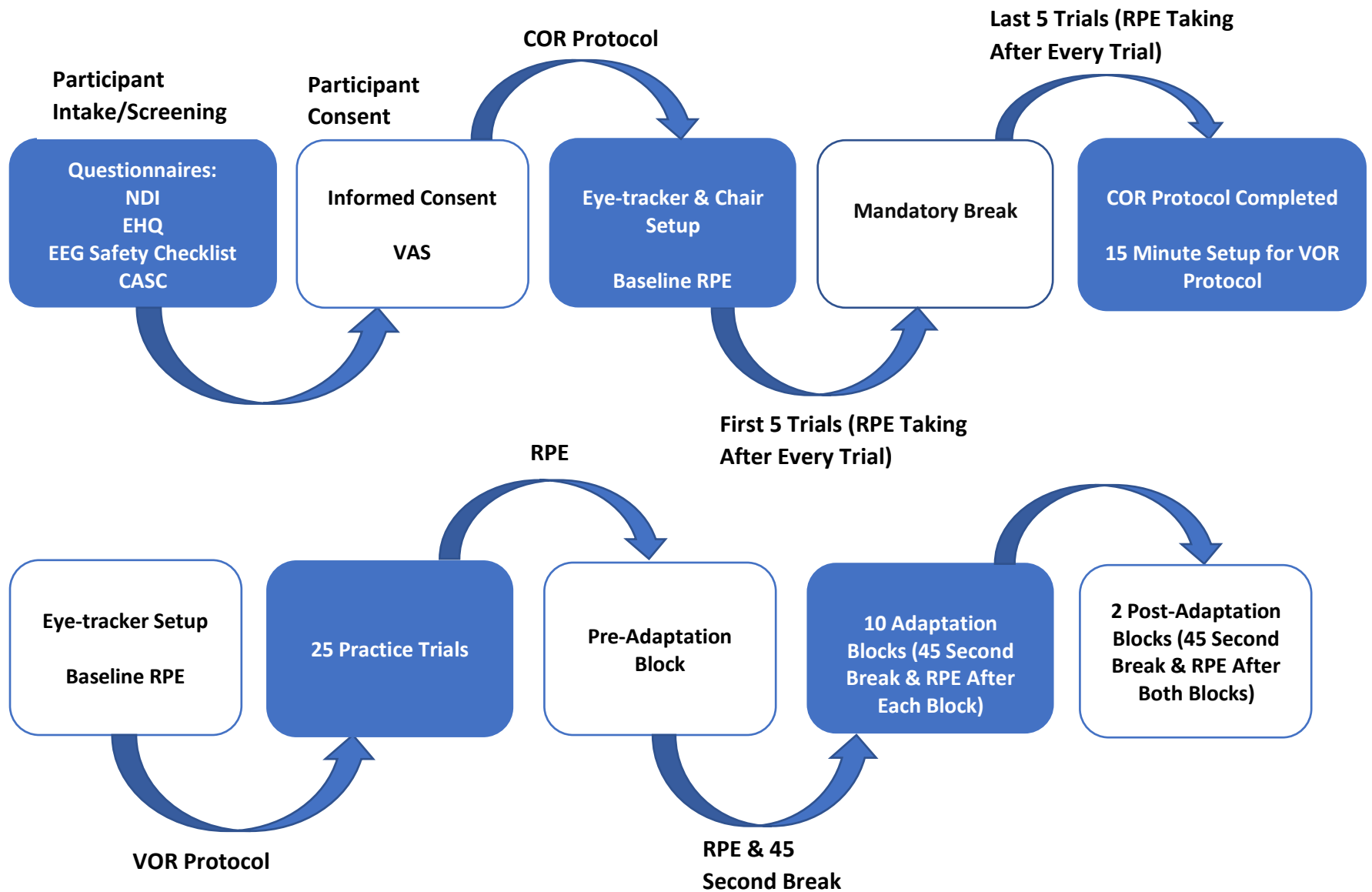


Figure 4.5. Flow of COR and VOR Protocols During Study Two

4.3.5 Interventions

4.3.5.1 Spinal Manipulation Intervention

Participants within the SCNP treatment group received 8-weeks of, individualized manual therapy which consisted of high-velocity low amplitude thrusts directed to areas of dysfunction in the spine or pelvic joints, and soft tissue myofascial release of the scalene and sternocleidomastoid muscles if clinically indicated by the presence of myofascial trigger points. An 8-week period was chosen as previous works suggests that 6 to 8 weeks are required to see neuro-plastic changes in response to treatment (Karellas, 2020).

Treatment sessions were performed twice per week with treatments tapering off towards the end of the 8-week intervention, if clinically indicated. Prior to, and following each session, participants were manually palpated to assess for tenderness over relevant joints, restricted ranges of motion, asymmetrical muscle tension, and any abnormal or blocked joint play, as well as the presence of myofascial trigger points. The first treatment session was ~30 – 60 minutes, in order to take a patient history, obtain informed consent, and perform a physical examination, including determining dysfunctional joints/regions within the spine for each participant, through the use of manual palpation. Following this, each treatment session was ~15 – 30 minutes.

4.3.5.2 Control Intervention

Participants within the SCNP control group were instructed to continue their regular activities of daily living during the 8-week intervention period. However, they were instructed to avoid receiving any form of manual therapy.

4.3.6 Data Analysis

All data was analyzed utilizing customized MATLAB R2021a codes (The MathWorks Inc., Natick, MA).

COR Analysis

A low-pass, second-order Butterworth filtered with a cut-off frequency of 0.5 Hz was utilized to filter the raw chair angular velocity data. Chair angular velocity was then smoothed utilizing a moving average. The maximum chair velocity was then outputted for each trial. A custom written Matlab script was then utilized to identify and, subsequently, remove blinks, saccades, and fast-phases. The slope of these missing eye angular velocity data points was interpolated and filled utilizing a piecewise cubic hermite interpolating polynomial (PCHIP). A low-pass, second-order Butterworth filtered with a cut-off frequency of 0.25 Hz was utilized to filter the raw eye angular velocity data. A sinusoidal wave was then fit through the filtered eye angular velocity data and the amplitude of this sine fit was then outputted for each trial. An open source Matlab script, provided by Seibold (2022), was utilized to create this sinusoidal wave. COR gain was calculated for each trial by dividing the amplitude of the sine fit by the peak chair angular velocity and was then averaged out for all ten trials.

$$\text{COR Gain} = \frac{\text{Amplitude of sine fit}}{\text{Peak chair angular velocity}}$$

VOR Analysis

A low-pass, second-order Butterworth filtered with a cut-off frequency of 10 Hz was utilized to filter head displacement and angular velocity signals. A cubic spline was also utilized to interpolate any missing head angular velocity data points. A custom written Matlab script was then utilized to identify and, subsequently, remove blinks, saccades, and fast-phases. The slope of these missing eye angular velocity data points was interpolated and filled utilizing a PCHIP. A

low-pass, second-order Butterworth filtered with a cut-off frequency of 6 Hz was utilized to filter the raw eye displacement and angular velocity signals. VOR gain was calculated for each trial by taking the ratio of average eye angular velocity to average head velocity during the 120ms before and following, peak head velocity. Previous studies has calculated VOR gain by taking the ratio of eye velocity to head velocity during the 30ms prior to peak head velocity (Schubert et al., 2008). However, pilot data demonstrated that this window was too small and, occasionally, did not capture the point at which peak eye velocity occurred at. Trials were also removed from individual participants' data set if the following occurred during the trial: participants changed head rotation direction mid trial, participant did not reach the 15° mark for head rotation, or loss of corneal reflection signal during the 120ms window utilized to calculate VOR gain. On average, 10.2% (~40/390 trials) and 13.3% (~52/390 trials) of trials were removed in the SCNP treatment group at baseline and post-intervention, respectively. In the SCNP control group, on average, 15.93% (~62/390 trials) and 14.65% (~57/390 trials) of trials were removed at baseline and post-intervention, respectively. Similar to study 1, since each epoch contained 30 trials, the missing trials were relatively distributed amongst the 13 blocks and, therefore, were robust against bias or type II errors. VOR gain was calculated for each trial and then averaged out for each epoch.

$$\text{VOR Gain} = \frac{\text{Average eye velocity 120 ms prior to \& following peak head velocity}}{\text{Average head velocity 120 ms prior to \& following peak head velocity}}$$

4.3.7 Statistical Analysis

Descriptive Statistics

A sample size calculation, performed on G*Power 3.1.9.7 statistical software, established that to achieve a large effect size (0.40), an alpha (α) of 0.05, and a power ($1 - \beta$) of 0.95 a

sample size of 15 individuals per group was required. All statistical tests were completed utilizing SPSS version 26 (IBM Corp., Armonk, NY, USA). All statistical analyses were run assuming a p value of 0.05. Normal distribution was tested using the Shapiro-Wilk test; however, for data sets that were violated a log transformation was applied. Levene's test of homogeneity was also run for all variables. Effect size was reported utilizing partial eta squared, where 0.0099 is consider a small effect size, 0.0588 is considered a medium effect size, and 0.1379 is considered a large effect size (Richardson, 2011).

NDI & VAS

Levene's Test of Homogeneity revealed that there was equal variance in both the NDI and VAS values between the SCNP control and treatment groups and both data sets were normally distributed. Two 2 X 2 repeated measures analysis of variance (ANOVA), with pre-planned contrast to baseline, were utilized. The between-subjects' factor was set to the two groups (SCNP control vs SCNP treatment), while the within-subject factor was set to time which represented the two data collection timepoints (baseline and post-intervention).

COR Gain

Levene's Test of Homogeneity revealed that there was equal variance in COR gain values between the SCNP control and treatment groups, and the data was normally distributed., A 2 X 2 repeated measures ANOVA, with pre-planned contrast to baseline, was utilized. The between-subjects' factor was set to the two groups (SCNP control vs SCNP treatment), while the within-subject factor was set to time which represented the two data collection timepoints (baseline and post-intervention). Additionally, an independent samples t-tests was utilized to compare the differences in COR gain, at baseline, between the two groups. Effect size was

reported utilizing Cohen's D, where 0.2 is considered a small effect size, 0.5 is considered a medium effect size, and 0.8 is considered a large effect size (Cohen, 2013). Outliers were removed from the data set if a participant's COR gain value was 2 standard deviations away from the interquartile range (IQR), plus or minus the 75th or 25th percentile range, at baseline and post-intervention.

VOR Gain & Head Peak Velocity

Similar to study 1, due to the uncontrollable Matlab error that led to the adaptation of the Matlab script into three different scripts, only the first four blocks were included in the statistical analyses for VOR gain and head peak velocity. As it was noted that the 2.5-minute breaks to transfer between scripts, which occurred at the end of AB3 and AB7, may have led to a loss of the VOR adaptation response. Thus, the data following this 2.5-minute break is most likely representative of participants attempting to regain the adaptation response and may not be a true representative of a VOR adaptation profile.

Levene's Test of Homogeneity revealed that there was equal variance in both VOR gain and head peak velocity values at all 4 epochs. Shapiro-Wilk's test revealed the data for VOR gain was normally distributed, while the data for head peak velocity was not normally distributed in the pre-adaptation block and adaptation block 2 at the post-intervention timepoint only. Two 2 X 2 repeated measures ANOVA's, with pre-planned contrast to baseline, were utilized to assess the group differences in VOR gain and head peak velocity, respectively. For each ANOVA, the between-subjects' factor was set to the two groups (SCNP treatment vs SCNP control), while the within-subject factor was set to time which represented the first 4 epochs at the two data collection timepoints (baseline and post-intervention). Effect size was also reported utilizing partial eta squared. Outliers were removed from the data set if their VOR gain value was 2

standard deviations away from the IQR, plus or minus the 75th or 25th percentile value, respectively. These outliers also had to be present in 3 or more epochs to be removed, as they would indicate that the participant was not completing the task as requested and their measurements would not be valid. Additionally, a 2 x 4 repeated measures ANOVA, with pre-planned contrasts to baseline was utilized to compare baseline differences in VOR gain between the two groups. Shapiro Wilk's test revealed that this data set was normally distributed. According to Mauchly's test, sphericity was also assumed ($p = 0.336$). The between subjects' factor was set to the two groups, while the within group factor was set to the average VOR gain for each of the first 4 epochs.

4.4 Results

Demographic

26 participants were included in the analysis of COR gain: 15 SCNP treatment (7M & 8F, 21.80 ± 2.11 years) and 11 SCNP control (6M & 5F, 22.09 ± 3.24 years). 15 participants were included in the analysis of VOR gain and head peak velocity: 8 SCNP treatment (5M & 3F, 22.00 ± 2.27 years) and 8 SCNP control (5M & 3F, 21.57 ± 2.99 years). One female SCNP control participant was removed from the analysis of COR gain as their COR gain value was over 2 standard deviations away from the IQR, plus the 75th percentile value at baseline and post-intervention. Therefore, they were considered an outlier. Additionally, one female SCNP control participant was removed from the analysis of VOR gain as their VOR gain value was greater than 2 standard deviations away from the IQR minus the 25th percentile value, for 3 epochs.

As previously mentioned, when running the VOR protocol, an unforeseen technical issue would occur at random times that would cause the protocol to stop running and a loss of data to

occur. Additionally, the eye-tracker had difficulty recording eye movements for certain participants during the VOR protocol. This was most likely due to certain biological differences within these participants eyes and occurred within 4 participants (3 SCNPs treatments & 1 SCNPs control). Also, two SCNPs control participants did not return to complete the follow-up sessions for the VOR protocols. Due to technical issues, the VOR could not be completed on the same day as the COR and the participants were unwilling to return on a second day to complete the VOR protocol.

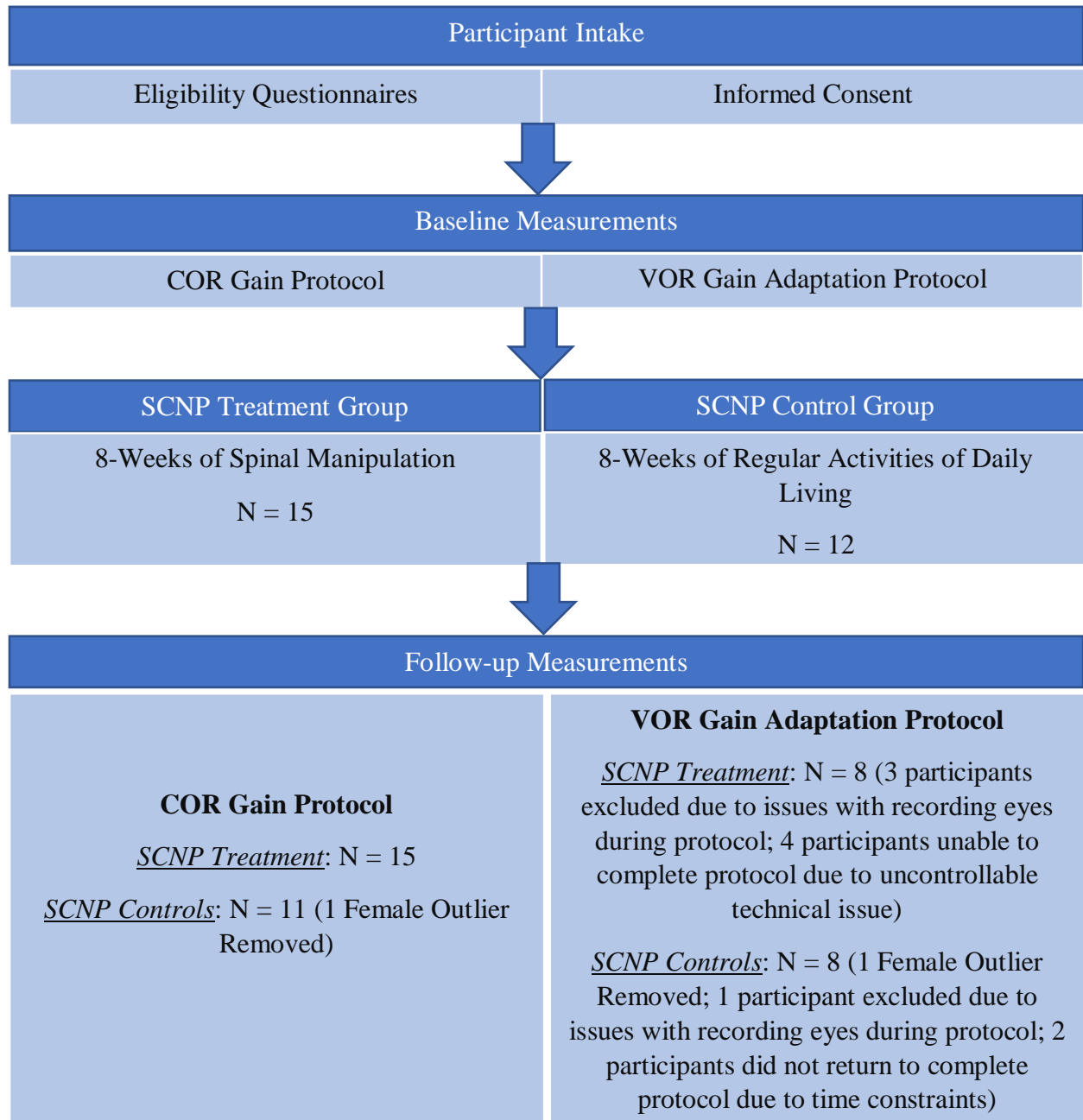


Figure 4.6. Flow chart detailing participant intake, randomization, and follow-up throughout the study

NDI & VAS

A significant time x group effect was observed for the NDI scores, between the two groups ($p = 0.027$, $\eta_p^2 = 0.188$). This would indicate that the SCNP treatment group ($\bar{X} = 6.27 \pm 4.22$) had significantly lower NDI scores than the SCNP control group ($\bar{X} = 7.17 \pm 6.22$), following the 8-week intervention. This would also suggest that spinal manipulation may have lessened the impact of neck pain upon these individuals' activities of daily living. No significant group x time differences were observed in VAS scores between the two groups ($p = 0.109$, $\eta_p^2 = 0.103$). This would indicate that the SCNP treatment group ($\bar{X} = 1.47 \pm 0.73$ cm) demonstrated similar VAS scores to the SCNP control group ($\bar{X} = 1.88 \pm 1.09$ cm). This would also suggest that both groups were experiencing similar levels of pain during the time of data collection.

COR Gain

There were no significant differences in COR gain between the two groups at baseline; however, a small effect size was observed ($p = 0.0216$, $D = 0.317$). This would indicate that, prior to the 8-week intervention, the SCNP treatment ($\bar{X} = 0.241 \pm 0.103$) and SCNP control groups ($\bar{X} = 0.209 \pm 0.128$), demonstrated similar COR gain values. A significant time x group effect, with a large effect size, was observed ($p = 0.011$, $\eta_p^2 = 0.242$). This would indicate that, following the 8-week intervention, there were significant differences in COR gain between the two groups. This can be observed in figure 4.7, as the SCNP treatment group ($\bar{X} = 0.182 \pm 0.075$) has significantly lower COR gain values than the SCNP control group ($\bar{X} = 0.255 \pm 0.098$), following the 8-week intervention.

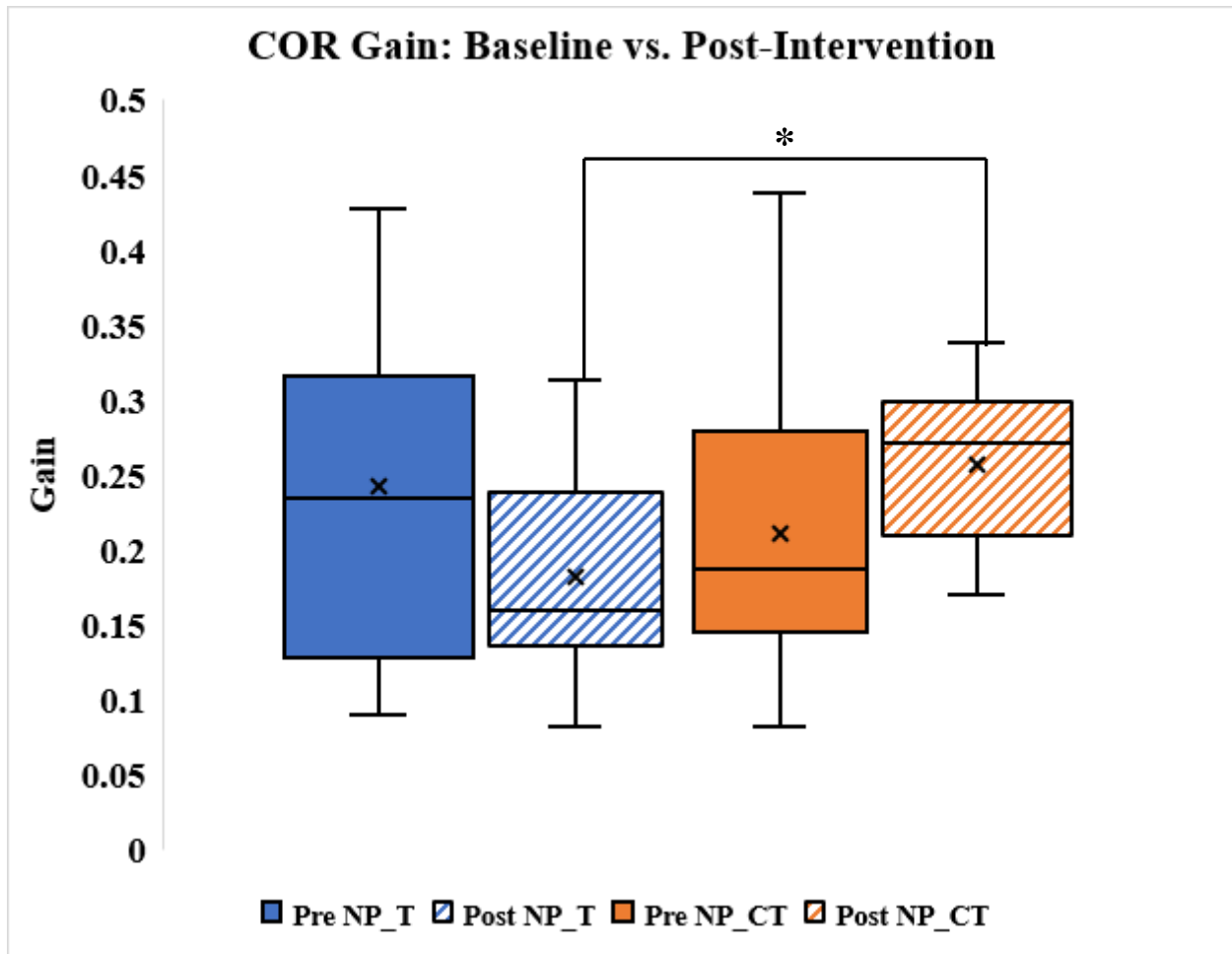
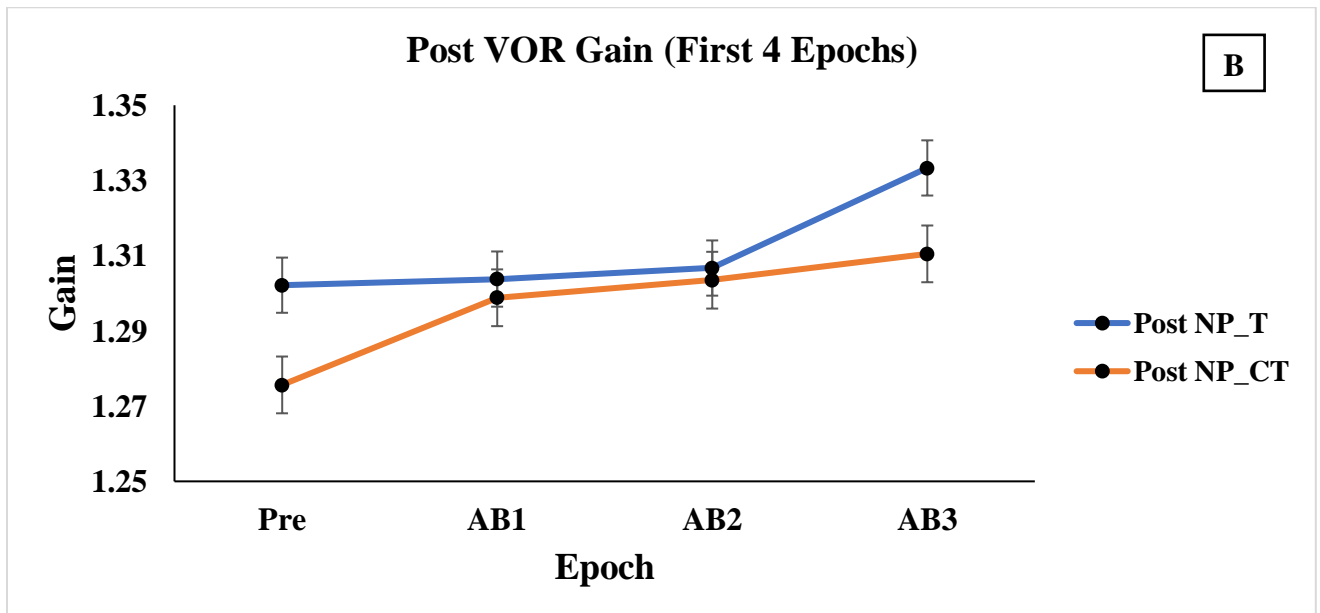
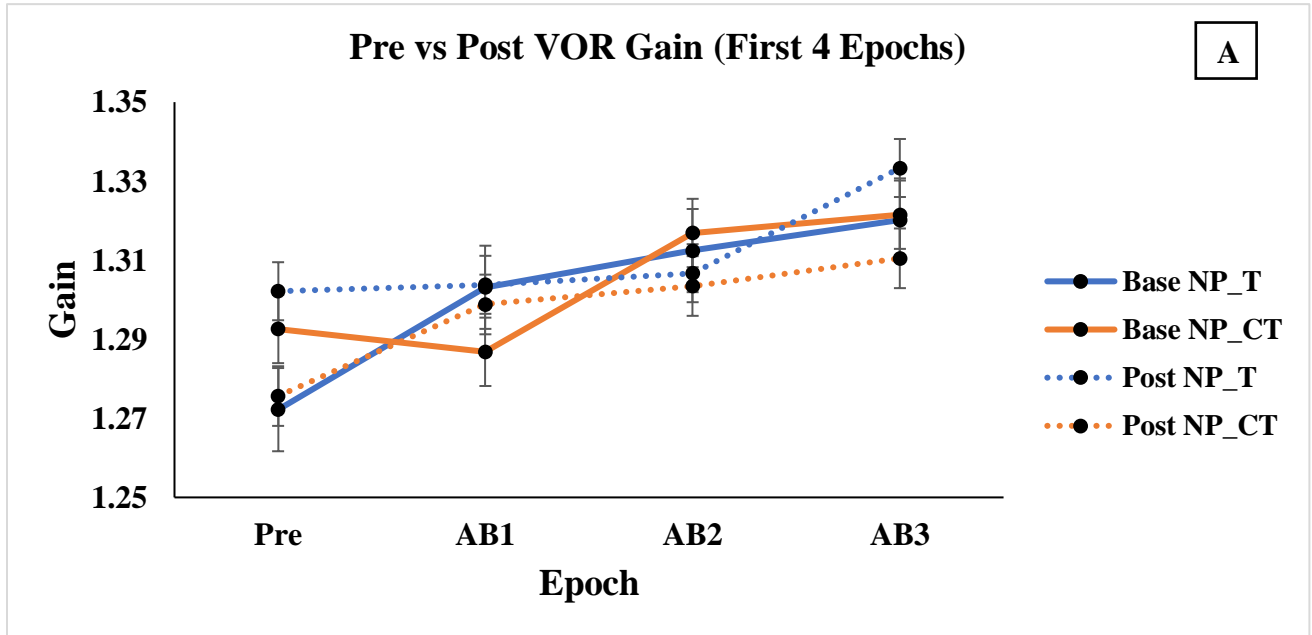


Figure 4.7. Average COR gain of SCNP treatment (NP_T) and SCNP control (NP_CT) groups at baseline and following the 8-week intervention (NP = Neck Pain). Asterisks and bars denote significant effect of group x time. * $p < 0.05$, ** $p < 0.01$

VOR Gain

No significant differences were observed in VOR gain, between the two groups at baseline ($p = 0.524$, $\eta_p^2 = 0.051$). This would indicate that, prior to the 8-week intervention, the SCNP treatment and SCNP control groups, demonstrated similar VOR gain values at baseline (FIG. 4.8.C). No significant time x group effects were observed; however, a trend was observed

in the SCNP treatment group in which they seemed to be steadily increasing VOR gain, following the 8-week intervention (FIG. 4.8 A & B).



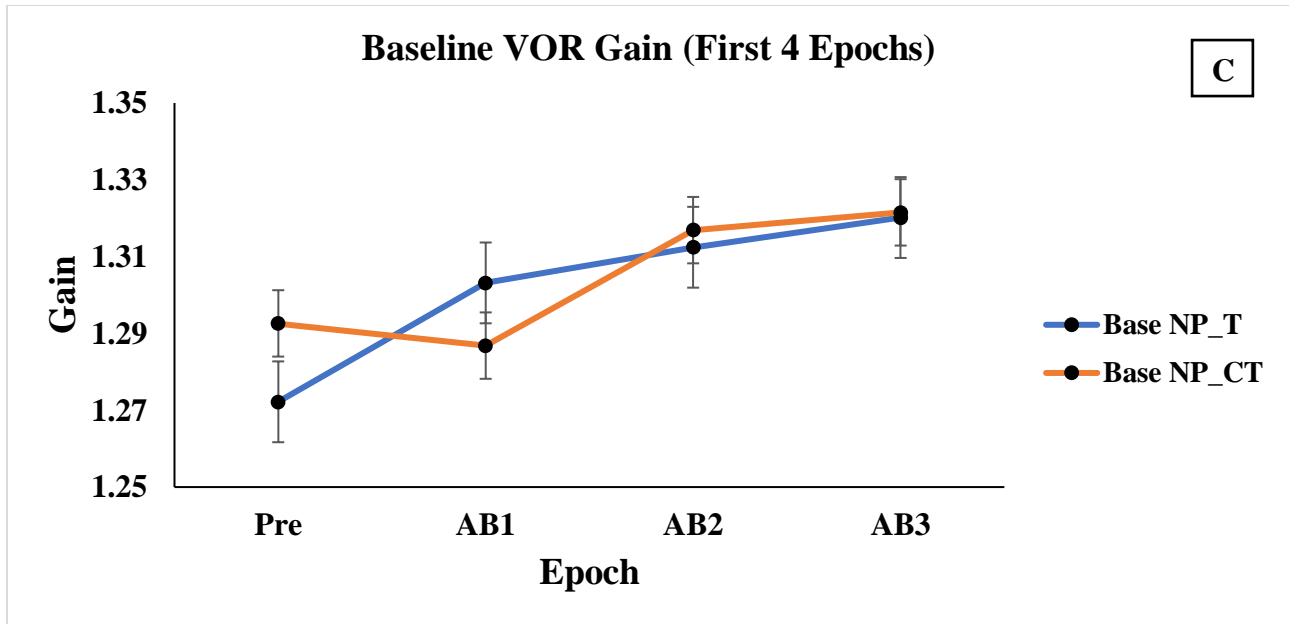


Figure 4.8. Trend in average VOR gain for the SCNP treatment and SCNP control groups at: (A) baseline vs post-intervention, (B) post-intervention, and (C) baseline.

Head Peak Velocity

No significant time x group differences were observed in head peak velocity between the two groups, at any of the 4 epochs ($p = 0.094$, $\eta_p^2 = 0.486$). This would indicate that regardless of the group, participants were rotating their heads at similar peak velocities, both at baseline and following the 8-week intervention. This would also suggest that any differences that were observed in VOR gain between the two groups was not due to one group rotating their head slower than the other and was due to an underlying neurophysiological change associated with SCNP and/or spinal manipulation.

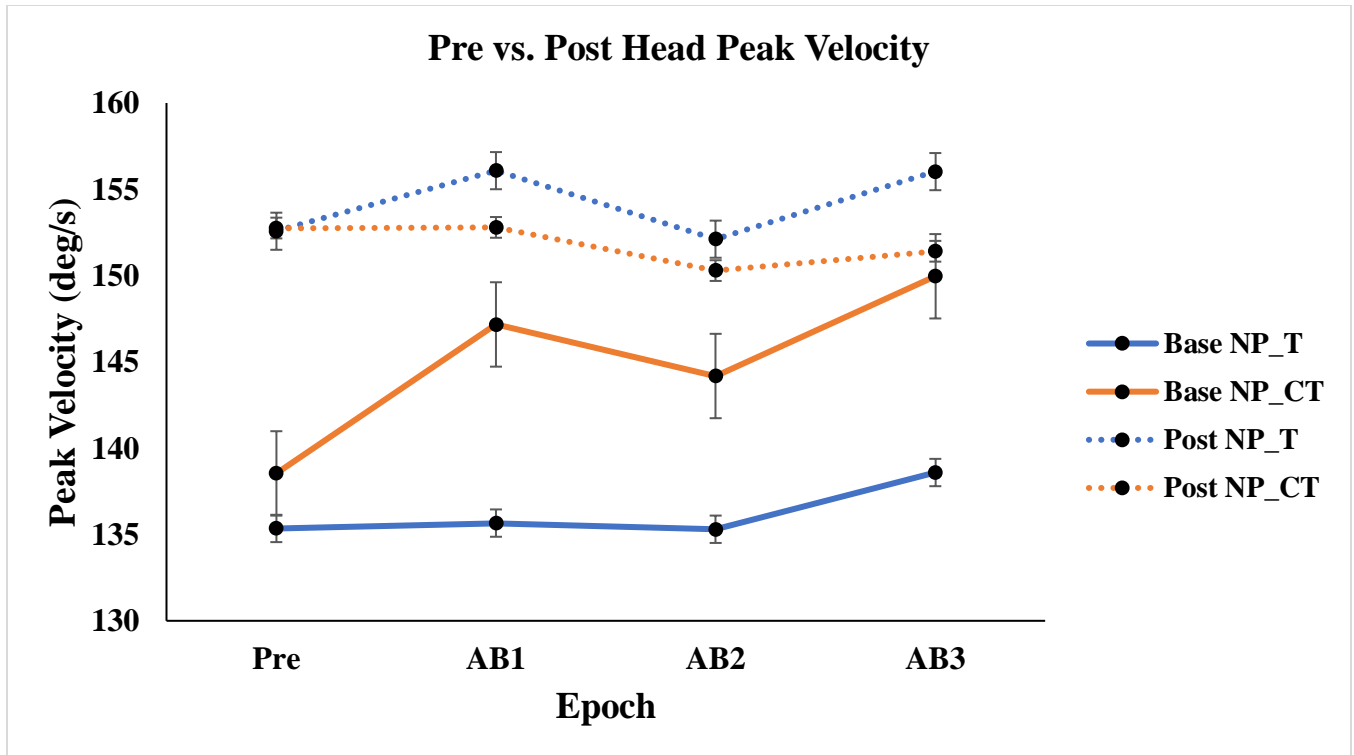


Figure 4.9. Trend in average head peak velocity for the SCNP treatment and SCNP control groups at baseline and following the 8-week intervention

4.5 Discussion

This is the first study to examine changes within cerebellar processing, following spinal manipulation within a SCNP population, utilizing direct measures of the cerebellum. The methodology involved the analysis of differences within COR gain and VOR gain adaptation between a SCNP treatment group and a SCNP control group. The results of this current study are in line with prior literature, that has demonstrated improvements within cerebellar processing, in a SCNP population, following spinal manipulation (Baarbé et al., 2018; Daligadu et al., 2013). The improvement in COR gain within the treatment group, when compared to the control group, may be reflective of improved processing of proprioceptive information within the cerebellum as the COR is reliant upon proprioceptive input from the neck muscles and joints. In contrast,

significant differences within the VOR were only observed with adaptation block 8. However, the SCNP treatment group did demonstrate higher VOR gain values for majority of the epochs at the 8 weeks post treatment; specifically, the later epochs (i.e. AB8 – Post 2) where VOR gain adaptation should be most prominent. This may suggest that spinal manipulation has a greater effect upon the VOR adaptation during greater visual disturbances. A larger sample size may yield more significant results.

COR

Literature suggests that the COR is heavily reliant upon input from proprioceptive signals within the neck muscles and joints (Gdowski et al., 2001). During trunk-on-head rotations, neck proprioceptors detect changes in neck velocity and transmit this information along the spinocerebellar tract (Röijezon et al., 2015). Some of this proprioceptive information enters the cerebellum while some of the information is transmitted to the central cervical nucleus (CCN) (Gdowski et al., 2001). Utilizing mossy fibers, the CCN projects afferent input into the flocculus of the cerebellum (Gdowski et al., 2001). This may suggest that the alterations observed in COR gain may be due to altered proprioceptive input toward the cerebellum. Haavik and Murphy (2012), also suggest that areas of joint/spinal dysfunction such as what occurs with SCNP, represent areas of altered afferent input towards the CNS. Building upon this concept, prior literature has demonstrated alterations in both head/neck and upper limb proprioception in individuals with SCNP (Paulus & Brumagne, 2008; Zabihhosseinian et al., 2017).

Therefore, the significant difference observed between the SCNP treatment and control groups, following the 8-week intervention, may indicate a normalization of the afferent input (i.e. proprioceptive input) towards the cerebellum. Research by Haavik and Murphy (2011) supports this, as the researchers demonstrated improvements in upper limb JPS following spinal

manipulation directed towards dysfunctional joints. It was suggested that these improvements in JPS are indicative of normalized afferent input (proprioceptive input) from the cervical spine following HVLA adjustments to dysfunctional areas within the cervical spine. Furthermore, these improvements in COR gain, within the treatment group, may be due to improvements in neck muscle spindle discharge associated with spinal manipulation. Research by Cooper and Daniel (1963), has also demonstrated that muscle spindle density is very high within the neck musculature, where spindle feedback plays a key role in integrating the position of the head and neck. Additionally, literature has demonstrated that the muscle spindles located within the deep neck musculature relay proprioceptive information, essential for eye/head coordination (Bakker et al., 1984; Edney & Porter, 1986; Liu et al., 2003; Porter, 1986). However, research by Paulus and Brumagne (2008) has demonstrated that recurrent neck pain may alter the discharge from the muscle spindles (Paulus & Brumagne, 2008). Thus, this may alter the proprioceptive input towards the CNS. Additionally, animal studies have examined changes in muscle spindle discharge following spinal manipulation, and found a transient normalization of muscle spindle firing rates (Cao & Pickar, 2014; Ge et al., 2005). Thus, this improvement in COR gain within the treatment group may reflect improvements in the ability of the cerebellum to process proprioceptive information from the cervical musculature, following improvement in the muscle spindles discharge associated with spinal manipulation. Prior literature has also demonstrated that the cerebellum will upregulate either the COR or VOR in response to disruptions within the other reflex (Gdowski et al., 2001). Therefore, this reduction in COR gain within the treatment group, which trended towards healthy levels that was observed within study one, should be reflective of an increase in VOR gain. However, this increase in VOR gain was not observed, possibly because these participants only had mild recurrent neck pain, which had not persisted

long enough to lead to up-regulation of the VOR in the face of a lessened COR. Additionally, as observed in study one, VOR gain in those with SCNP was not significantly different than healthy controls suggesting that the CNS would not need to adapt a response that was not “broken”.

VOR Gain Adaptation

The VOR is a multisensory response that relies upon the vestibular, proprioceptive, and visual systems in order to modify the reflex (Gdowski & McCrea, 2000; Gray, 2020b; Ito, 1998). However, prior literature has demonstrated disruptions, or the complete loss, of the reflex in individuals with vestibular system disturbances which would indicate that the VOR seems to receive majority of its input from the vestibular system (Bronstein et al., 1995; Kelders et al., 2003; Zamysłowska-Szmytko et al., 2019). Montfort et al., (2008) also suggests that the cerebellum will modify either the COR or VOR in response to disruptions within the other reflex. This would suggest that the decrease in COR gain which was observed within the treatment group, following the 8-week intervention, would be associated with increases in VOR gain, following treatment. However, this improved VOR response was not observed during the first four epochs. Although these differences did not reach statistical significance, the SCNP treatment group did demonstrate a greater, but slight, upward trend in their VOR gain adaptation when compared to the SCNP control group, following the 8-week intervention. As noted by Treleaven (2017), vestibular disturbances are less likely with lower severity forms of neck pain such as SCNP. Thus, the minimal improvements observed within the treatment group may be due to the slight normalization of the abnormal neuroplastic changes that may have occurred within the vestibular input towards the cerebellum, but did not progress to the point of statistical significance. Additionally, the slight improvements observed within VOR gain,

following the spinal manipulation intervention, may be due to the impact of SCNP on neck proprioceptors.

As previously mentioned, the muscle spindles located within the deep neck musculature relay proprioceptive information, essential for eye/head coordination (Bakker et al., 1984; Edney & Porter, 1986; Liu et al., 2003; Porter, 1986). The muscle spindles relay proprioceptive signals towards the CCN and, in turn, the CCN will project these proprioceptive signals towards the vestibular nuclei as well as the flocculus of the cerebellum in order to modify the oculomotor reflexes (Gdowski & McCrea, 2000; Sato et al., 1997). It has also been suggested that recurrent neck pain may alter the discharge from the muscle spindles (Paulus & Brumagne, 2008). Thus, SCNP may alter the proprioceptive input towards the cerebellum via the CCN. However, prior literature that has examined changes within muscle spindle discharge within anaesthetized cats, has demonstrated temporal normalization of the paraspinal muscle spindles following spinal manipulation (Cao & Pickar, 2014; Ge et al., 2005). Cao and Pickar (2014), suggest that these improvements in muscle spindle discharge may also lead to reduced proprioceptive errors. Therefore, the minimal improvements observed within the treatment group, following the 8-week intervention, may be due to improved proprioceptive input from the cervical muscle spindles. Additionally, Haavik and Murphy (2011) have demonstrated that spinal manipulation directed towards dysfunctional joints may normalize the afferent input (proprioceptive input) from the cervical region towards the CNS. Furthermore, the cuneocerebellar division of the spinocerebellar tract transmits unconscious proprioceptive information from muscle spindles and joint receptors within the upper limb towards the fastigial nucleus (i.e. one of the deep cerebellar nuclei) (Röijezon et al., 2015). The fastigial nucleus then transmits this proprioceptive information towards the vestibular nuclei which utilize this information to modify the

oculomotor reflexes (Zhang et al., 2016). Thus, it is reasonable to believe that the slight improvements observed within the VOR may be due to improvements in neck proprioceptive input (i.e. afferent input), towards the spinocerebellum via the spinocerebellar tract.

Similar to study 1, it is possible that the modifications that had to be made within the Matlab script, due to the technical error, may have influenced the results of this study. The 2.5-minute transfer period between Matlab scripts may have disrupted the process of VOR gain adaptation which may have had a slight reduction in VOR gain towards baseline levels during. Additionally, it is possible that a type II error may have accounted for the limited significant time by group differences, as a power calculation determined the minimal sample size required to confirm these results was 15. Thus, if the protocol was allowed to run as intended, and a sufficient sample size was utilized, significant differences in VOR gain adaptation profiles may have been observed between the two groups. Specifically, during the later epochs such as AB8 – AB10, where VOR gain should be its most prominent.

An interesting point is that a longer period of treatment may have been required to see changes in the VOR. Prior literature describes that altered postural adaptation associated with an altered body schema persisted for several months following plastic surgery (either breast augmentation or reduction) which altered body schema and required postural adaptations (Iodice et al., 2015) This may suggest that longer periods of treatment may be necessary to see significant changes within body schema (Iodice et al., 2015), which may also impact COR and VOR. It took 4 to 12 months for internal modeling mechanisms to re-adapt after the body has formed new dynamic equilibriums following the surgical intervention (Iodice et al., 2015). Although, these changes were observed following surgery, this study suggests that the formation of a new body schema requires a longer period in order for the internal model to re-adapt.

Overall, this current study suggests that spinal manipulation may be able to improve cerebellar processing in individuals with SCNP, as demonstrated by the improvements within the COR, but not the VOR. This would suggest that SCNP has a greater impact upon the proprioceptive input towards the cerebellum and minimal impact upon processing of vestibular input. Thus, spinal manipulation may have a greater impact upon normalizing proprioceptive input towards the cerebellum, and a minimal impact upon normalizing the vestibular input towards the cerebellum, within a SCNP population. However, due to the issues experienced during the VOR protocol as well as the small sample size for the protocol, it is not conclusive as to whether these results may be reflective of a SCNP population. This study fills in the gaps in research regarding the use of a direct measure of cerebellar processing to assess improvements within the cerebellar processing, following spinal manipulation, in individuals with SCNP.

4.5.1 Limitations

Similar to study one, the main limitations within this study are a product of the instrumentation utilized. The weight of the eye-tracker commonly induced neck fatigue and head discomfort within the SCNP participants, when worn for a prolonged period. Additionally, the sustained use of the bandanas during the COR protocol, to restrict the participants head movements, would sometimes re-aggravate symptoms of SCNP and thus, may have altered the proprioceptive input received from the neck proprioceptors. However, these limitations were addressed by incorporating Borg's RPE scale to monitor the participants' perceived level of fatigue within their neck and to ensure pain was not a limiting factor. Furthermore, the results for the VOR adaptation protocol may have been limited due to a small sample size; thus, a larger sample size may have yielded different results.

4.7 Conclusion

The results of the current study suggest that spinal manipulation may be able to normalize cerebellar processing in individuals with SCNP as demonstrated by the improvements within the COR. Specifically, it is likely that spinal manipulation normalizes the proprioceptive input directed towards the cerebellum and has a minimal impact upon the vestibular input as it is likely to not be disrupted in individuals with SCNP, though a larger sample may have produced different results. Future research could examine the effects of treatment on more severe forms of neck pain, and its impact upon the VOR and cerebellar plasticity.

Chapter 5. Thesis Summary

Subclinical neck pain (SCNP) alters various neurophysiological functions associated with the cerebellum such as sensory motor integration (SMI), motor control, and cerebellar inhibition (CBI) (Andrew et al., 2018; Baarbé et al., 2018; Daligadu et al., 2013). It has been suggested that these alterations are due to altered afferent input from areas of joint/spinal dysfunction associated with SCNP (Haavik & Murphy, 2012). These alterations within cerebellar processing have also been shown to improve following spinal manipulation as it involves high-velocity low amplitude (HVLA) thrusts directed towards dysfunctional joints within the spine and, thus, normalize the afferent input from these joints (Baarbé et al., 2018; Daligadu et al., 2013; Haavik & Murphy, 2011). However, these alterations and improvements have only been examined utilizing indirect measures of the cerebellum such as transcranial magnetic stimulation (TMS) and somatosensory evoked potentials (SEP). To this date no direct measures have been utilized to directly assess changes within the cerebellum in an SCNP population. The cervico-ocular and vestibulo-ocular reflexes (COR & VOR) are two direct measures that may be utilized to assess these changes as they are directly controlled by the cerebellum (Gdowski et al., 2001; Montfoort et al., 2008).

Manuscript one sought to address this deficiency by comparing differences within COR gain and VOR gain adaptation between a healthy control and SCNP group. The findings of this study suggest that SCNP alters the ability of the cerebellum to process proprioceptive input as demonstrated by the upregulation (i.e. alterations) within COR gain in the SCNP group when compared to the healthy control group. These alterations within the COR gain are most likely due to disrupted afferent input from the muscle spindles located within the neck which conveys proprioceptive input, essential for eye/head coordination, towards the CNS (Bakker et al., 1984; Edney & Porter, 1986; Liu et al., 2003; Porter, 1986). The COR and VOR have been demonstrated to have a compensatory relationship in which an increase in one of the reflexes

may indicate alterations within the other reflex (Gdowski et al., 2001). This is commonly observed as upregulations within the COR gain due to disruptions within the VOR (Zamysłowska-Szmytke et al., 2019). However, these disruptions within VOR gain were not observed within the SCNP group, which suggests that SCNP may have a limited impact upon the ability of the cerebellum to process vestibular information. This is in-line with current literature that suggests that vestibular disturbances are uncommon in less severe forms of neck pain such as SCNP (Treleaven, 2017).

Manuscript two furthered these findings by investigating changes in COR gain and VOR gain adaptation prior to and following, either, an 8-week manual treatment intervention or 8-weeks of regular activities of daily living. Preliminary findings suggest that treatment of areas of joint and muscle dysfunction may be able to improve the ability of the cerebellum to process proprioceptive information as demonstrated by the improvements in COR gain within the SCNP treatment group. These improvements within COR gain are most likely due to normalization of the firing of muscle spindles located within the deep neck musculature. Prior literature has demonstrated that spinal manipulation may lead to transient normalization of muscle spindle discharge, resulting in reduced proprioceptive errors (Cao & Pickar, 2014). In contrast, no significant improvements were observed within VOR gain adaptation which would suggest that spinal manipulation has a limited impact on cerebellar processing of vestibular information. However, study one showed no differences in VOR gain between those with SCNP and healthy controls, suggesting that the lack of change may have been simply because the VOR response was not maladaptive in those with SCNP and thus did not need to be “fixed”. Alternately, the lack of change could be a type II error, as a power calculation suggested that a larger sample size of 15 participants per group would be required to confirm these results. Furthermore, the SCNP

treatment group did demonstrate higher VOR gain values during the later epochs of the VOR adaptation protocol, during which VOR adaptation should be most prevalent, and , statistically significant differences were observed between the two groups at adaptation block 8, following the 8-week intervention. This may suggest that spinal manipulation may be able to improve VOR gain adaptation and cerebellar plasticity, within a SCNP population, and may be observed with a larger sample size, or a neck pain group with worse pain and/ or longer symptom duration.

Overall the findings of these studies suggest that SCNP may alter the ability of the cerebellum to process proprioceptive information, and these alterations may be normalized following 8-weeks of manipulation based treatment, as demonstrated by the alterations and improvements within COR gain. It is also likely that SCNP has a limited impact upon the cerebellum's ability to process vestibular information and, thus, significant differences are unlikely to be observed within VOR gain adaption following an 8-week spinal manipulation intervention. However, a larger sample size is required to confirm these findings.

Appendices

Appendix A – Informed Consent

COVID-19 UPDATED VERSION

All aspects of this study have been revised to include all possible risk mitigation strategies against COVID-19. Please see appended document at the end of this consent form for specific procedures and protocols regarding COVID-19

Title of Research Study: Impact of subclinical neck pain on visuomotor plasticity and motor control

You are invited to participate in a research study entitled “Impact of subclinical neck pain on visuomotor plasticity and motor control”. This study has been reviewed by the University of Ontario Institute of Technology Research Ethics Board [REB # 14991] and originally approved on October 28, 2018.

If you feel that you are in a vulnerable group with respect to COVID-19 effects (e.g. senior, immunocompromised, living with individuals that may be susceptible to COVID-19), it may be best that you do not participate in the study.

Please read this consent form carefully, and feel free to ask the Researcher any questions that you might have about the study. If you have any questions about your rights as a participant in this study, please contact the Research Ethics Coordinator at 905 721 8668 ext. 3693 or researchethics@ontariotechu.ca.

Researcher(s): Dr. Bernadette Murphy, Dr. Paul Yielder, Dr. Mahboobeh Zabihhosseinian, Praveen Sanmuganathan, Dr. Jim Burkitt, Navika Cheema (Master’s student), and Devonte Campbell (Master’s student). All researchers involved have signed confidentiality agreements and have completed the TCSP II tutorial on research ethical concerns.

Departmental and institutional affiliation(s): Faculty of Health Sciences at the University of Ontario Institute of Technology (UOIT)

Phone number: 905-721-8668 x 2778 – Dr. Bernadette Murphy (office)

Contact emails: Bernadette.Murphy@ontariotechu.ca ; Paul.Yielder@ontariotechu.ca ; mahboobeh.zabihhosseinian@ontariotechu.net ; Praveen.Sanmuganathan@ontariotechu.net

External Funders: Australian Spinal Research Foundation, NCMIC, and Natural Sciences and Engineering Research Council of Canada

Purpose of the Study: Research shows that neck pain is a significant burden that affects 30-50% of the population every year. Research is also showing that neck pain affects the way people perform movements and perceive their body positions in space. In past studies, our lab group has shown that these effects can be attributed to differences in how individuals with neck pain process sensory information. The current study will examine whether there are differences in how individuals with and without neck pain perform rapid eye and upper limb movements. These movements are of interest because their control relies on sensory processing in distinct brain regions, and any differences in control may highlight impacted brain regions in those experiencing

neck pain. We also want to examine whether chiropractic treatment restores eye and upper limb movement performance and thus, restores brain activity to more typical levels in these individuals.

Participants: For this study, we are seeking right-handed people aged 18-35 years who either experience no neck problems or have had a history of moderate neck pain in the past six months and have not received treatment in the past 4 weeks. To participate in this study you will complete an eligibility checklist with one of the researchers. You will also be examined by a registered chiropractor to identify the presence and extent of neck pain. You will be given a chance to review the study details and ask any questions in advance of your participation.

Please refer to the Appendix at the end of this consent form for additional information on COVID-19 risk mitigation pertaining to this study. Specific protocols exist for entering and exiting the building, maintaining physical distancing, wearing non-medical face masks at all times and pre-screening for COVID-19 symptoms. Please review this document (Appendix A) carefully before also considering the following procedures that are specific to this experimental study.

Procedure:

The research examines how the brain responds to neck pain. If you volunteer to participate in the study, you will experience two data collection sessions at the start and two identical sessions at the end of the study, eight weeks later. At both baseline and 8 weeks, you will be asked to complete questionnaires that provide information about your current functional capacity, level of neck pain (if any), and general well being.

You will also perform a series of eye, upper limb, neck, and passive body rotation movements during these data collection sessions using the following protocols:

- 1) **Upper Limb Aiming/Eyetracking:** You will direct these movements to targets presented on a vertically mounted computer screen using two differently weighted styli while wearing an eye tracking device and/or a fingertip infrared light emitting diode.
- 2) **Elbow Proprioception:** You will be fitted with rigid bodies on your torso, head (attached to a headband), upper arm, and wrist in order to calculate the location of your upper limb in 3-D space. You will also have a small device called an electrogoniometer placed on the outside of your elbow joint, in order to measure your elbow joint angles during the task. In this task, you will be wearing opaque goggles (so that you can't see your arm) and the experimenter will move your upper limb to a position and then ask you to recreate the position of your limb.
- 3) **Accuracy of your awareness of the position of your head and neck:** this will be measured via a cervical range of motion (C-ROM) device (this device has 3 inclinometers attached to it to measure your range of movement in all three

planes of motion).) This is worn on your head with a strap fastened at the back of the head. You will be blindfolded and the accuracy of your ability to reproduce different head positions will be measured by reading the dial on the inclinometer and writing down the measurement. You will wear the C-ROM device for approximately 10 minutes.

- 4) **Vestibular-ocular reflex (VOR)/Cervico-ocular reflex (COR):** You will sit in a special gaming chair, which will rotate very slowly (e.g. roughly 1.5 degrees per second), while the eye tracking device measures your eye movements in relation to the chair movements. In addition to this, you will perform a rapid head movement whilst wearing the eye tracking device to measure eye movements. Rest will be regularly scheduled during the experiment and offered anytime at your request.

You will be given a chance to ask questions and will be verbally debriefed at the completion of the eight-week sessions about some of the more specific experimental purposes and hypotheses. Each data collection session will take approximately 2 hours to complete, and there will be two sessions at baseline and two follow-up data collection sessions after 8 weeks (up to 8 hours total for the study). The baseline and follow-up sessions are separated into two sections to prevent you from getting bored or fatigued.

If you have neck pain, and you are randomized to the experimental group, you will receive chiropractic treatment 2 times per week for 8 weeks between the experimental sessions. This chiropractic treatment will involve high velocity-low amplitude spinal joint manipulations to the affected area of the neck and soft tissue therapy for muscles, if needed. If you are in this group, one of the researchers will complete an eligibility questionnaire with you to ensure that you are a suitable candidate to receive spinal manipulation. If for any reason you are not an appropriate candidate for this study, we will withdraw you from the study. This will not impact your eligibility for compensation. If you are receiving chiropractic care as a component of this study, you will need to attend chiropractic sessions with Dr. Bernadette Murphy or Dr. Nicholas Antony in addition to the two experimental sessions. There is no cost for this treatment. If you are not receiving chiropractic care as a component of this study, you will only need to attend the two experimental sessions. If you are not randomized to the treatment intervention, you will be offered a complementary assessment (to determine if you would benefit from chiropractic care) and free treatment at the end of the study. **NOTE:** *Dr. Bernadette Murphy is both a registered chiropractor and the principal investigator on this research project. While she will be performing most of the chiropractic treatments and many of the research activities involved with this project, the information presented in the treatment sessions will remain independent of the research process and will remain confidential. The only treatment information that may be released with the study findings will involve the spinal joint areas receiving high-velocity low-amplitude manipulations and soft tissue therapy. This serves the purpose of allowing future researchers to replicate our findings. You will not be identified in the release of these data (see Confidentiality section below).*

Chiropractic care: Dr. Bernadette Murphy and Dr. Nicholas Antony are registered chiropractors. They will take a detailed case history and make assessments to ensure that you are a suitable candidate to receive care. The treatment frequency will be individualized but will likely involve two sessions per week initially, tapering off to one session per week as the study progresses. The initial session will take 30 to 60 minutes and subsequent sessions will take 15-30 minutes. Only safe conventional high velocity-low amplitude spinal manipulation techniques will be employed in this study. These treatments have been used in previous studies employed by the lab group, and most participants have shown improvements in their outcome measures. You may experience soreness the day after the first treatment. This soreness should only be temporary, as this is the first stage of the treatment and healing process. If you experience prolonged soreness or unexpected worsening of your neck pain, you are encouraged to speak to Dr. Murphy for further advice. Consent with respect to any chiropractic sessions is separate from this consent and will be covered/explained within the scope of the chiropractic sessions themselves.

Payment or Reimbursement: If you are a student enrolled in approved Kinesiology courses you have the opportunity to earn up to 4% extra credit toward your final grade (2% for completing the experiments at each of the baseline and 8-week time periods). If you are interested in this option, the investigator will provide you with additional information. If you opt for extra course credit as compensation, Dr. Jim Burkitt will handle this information confidentially and your instructor will not be informed of your extra credit until your course is already complete. If you are not interested in this option or are not enrolled in any of the eligible courses, you will be compensated with two \$10 Tim Hortons gift cards.

Potential Benefits: If you are in the neck pain group, you may be randomized to receive chiropractic care, and you may benefit from the free treatment sessions and may also experience improvement in your pain levels. If you have neck pain and you are randomized to the non-treatment group, you will be provided with a free assessment and treatment at the conclusion of the study. For healthy participants who do not have neck pain, while you will not benefit directly from this research, this experiment is a part of a series of studies that will help determine how neck pain contributes to sensory processing and movement control, so you will enhance your knowledge of these areas.

Potential Risks or Discomforts: Potential risks associated with participation in this study are mental fatigue, physical fatigue, and boredom. To mitigate these risks, rest periods will be frequently provided and offered anytime upon your request. Wearing the eye tracker for extended periods of time may also become uncomfortable. To mitigate this discomfort, we attempted to limit the length of time it will be worn during the data collection sessions to approximately 1 hour (or less). If at any time you need the eye tracker removed, please let us know and we will remove it. If you receive chiropractic treatment, you may experience soreness the day after the first treatment. Since this is the first stage of the treatment and healing process, the soreness should be temporary. If you experience soreness beyond 24 hours post-treatment or unexpected worsening of your neck pain, please speak to Dr. Murphy for further advice (see below for contact

information). You do not have to provide answers to any of the questions or questionnaires involved in this study if they make you feel uncomfortable.

Participation and Withdrawal: Your participation in this study is entirely voluntary and you are free to decline in taking part. You may also withdraw from the study at any time following the start. This will in no way affect your compensation for the study, your academic progress, or your relationship with your TAs or instructors. If you decide to withdraw, your data will be destroyed unless you indicate otherwise. If you decide to withdraw following the completion of the study, it may not be possible to destroy your data because it may have already been recoded to remain anonymized. Any questions regarding your rights as a participant, complaints, or adverse events may be addressed to Research Ethics Board through the Research Ethics Coordinator – researchethics@uoit.ca or 905.721.8668 x. 3693.

Confidentiality: The cameras used to measure your eye movements will only capture images of the immediate areas surrounding your eyes (and possibly eye brows) and will only be displayed to the researcher during the experimental sessions. These images will not be saved. The optoelectric cameras used to measure your upper limb movements do not capture visual images, and the data they store is in the form of number sequences from which you cannot be identified. All of your data files will be coded so that they can be kept in confidence and not directly linked to you. Your personal information will not be disseminated. All questionnaire data will be locked and stored in the Human Neurophysiology and Rehabilitation laboratory that only the research team will have access to. All electronic files will be encrypted and stored on a computer that is locked in the Human Neurophysiology and Rehabilitation laboratory. While other lab group members will have access to this computer, your data: a) will only consist of number series' from which you cannot be identified, and b) will be recoded and removed of personal identifiers. Only frequency counts, means, and standard deviations calculated over many participants will be published. In the odd event that a graphical representation of one of your eye or upper limb movements is presented in publication, it will only be formatted as a sequence of numbers from which you cannot be identified. The only information from the chiropractic treatment sessions that may potentially be released with the study findings are your body regions treated with high-velocity low-amplitude spinal manipulation and soft tissue therapy. This information will be void of identifiers and thus, will not be specifically linked to you. Releasing this information serves the purpose of allowing future researchers to fully replicate our methods.

Results Dissemination: The data from this research will be submitted to scientific conferences and peer reviewed journals. All published data will be coded so that you are not identifiable.

Secondary Use of Data: There is potential for your data from this study to be used as secondary data in a future research project. As such, we are providing you the option (see below) to tick a box indicating that you give consent to use these data in future research. You are free to select “no” to this option without any negative consequences.

Data for secondary use will be stored in a locked area at UOIT for ten years from the completion of this study after which it will be destroyed.

RIGHTS OF RESEARCH PARTICIPANTS: You may withdraw your consent at any time and discontinue participation without penalty. If you have any questions concerning the research study or experience any discomfort related to the study, please contact the researchers Praveen Sanmuganathan at Praveen.Sanmuganathan@ontariotechu.net, Dr. Mahboobeh Zabihhosseinian at mahboobeh.zabihhosseinian@ontariotechu.net, Dr. Bernadette Murphy at Bernadette.Murphy@ontariotechu.ca, or Dr. Paul Yelder at Paul.Yelder@ontariotechu.ca. Any questions regarding your rights as a participant, complaints or adverse events may be addressed to Research Ethics Board through the Research Ethics Coordinator – researchethics@ontariotechu.ca or 905.721.8668 x. 3693. By consenting, you do not waive any rights to legal recourse in the event of research-related harm.

Thank you very much for your time. If you have any questions please contact:

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Email: Paul.Yelder@ontariotechu.ca

Please read the following before signing the consent form and remember to keep a copy for your own records.

- I understand that taking part in this study is voluntary and that I am free to withdraw from the study at any time. My withdrawal will in no way affect my academic progress.
- This consent form will be kept in a locked area in the Neurophysiology and Rehabilitation Research Laboratory at UOIT, Oshawa, Ontario for a maximum period of seven years before being destroyed.
- The data collected in this study will be coded so that it is confidential and remains independent from the letter of informed consent. All data will be stored in a locked area at UOIT, Oshawa, Ontario for a maximum period of seven years before being destroyed.
- I have read and understand the information provided to me about this study. I have had the opportunity to discuss this study with the experimenters and am satisfied with the answers I have been given.
- I have completed an eligibility checklist to ensure that I am eligible to participate in this research.
- I understand that I can withdraw my data from this experiment. I also understand that it may not be possible to withdrawal my data following completion of the experiment if my data has already been recoded.
- I understand that my participation in this study is confidential and that I will not be personally identified in any of the reports on this study.
- I have had sufficient time to consider whether to take part.
- I know whom to contact if I experience any side effects to the study.
- I give consent for the data from this study to be used in future research as long as there is no way that I can be identified in this research (tick one): **YES** **NO**
- I give consent for these data to be used as secondary data in another project (tick one): **YES** **NO**
- I would like to receive a report about the results of this study (tick one): **YES** **NO**
- There may be additional risks to participating in this research during the COVID-19 pandemic that are currently unforeseen and, therefore, not listed in this consent form.

If you should develop any symptoms of COVID-19 after completion of this study, please contact to the study, please contact the researchers:

Mahboobeh.zabihhosseinian@ontariotechu.net or Praveen.Sanmuganathan@ontariotechu.net at your earliest convenience

I consent to participate in the following studies:

- | | | |
|-------------------------------|----------------------------------|---------------------------------|
| Upper Limb Aiming/Eyetracking | YES <input type="radio"/> | NO <input type="radio"/> |
| Neck and Elbow Proprioception | YES <input type="radio"/> | NO <input type="radio"/> |

Vestibular-ocular reflex (VOR)/Cervico-ocular reflex (COR)

YES NO

Consent to Participate:

1. I have read the consent form and understand the study being described;
2. I have had an opportunity to ask questions and my questions have been answered. I am free to ask questions about the study in the future;
3. I freely consent to participate in the research study, understanding that I may discontinue participation at any time without penalty. A copy of this Consent Form has been made available to me.

(Name of Participant) (Date)

(Signature of Participant)/ (Signature of Researcher)

Appendix B – Neck Disability Index

The Neck Disability Index

This questionnaire has been designed to give your therapist information as to how your neck pain has affected your ability to manage in everyday life. Please answer every question by placing a mark in the **ONE** box that applies to you. We realize that 2 of the statements may describe your condition, but please mark only the **ONE** box that most closely describes your current condition.

Neck Pain Intensity

- I have no pain at the moment.
- The pain is very mild at the moment.
- The pain is moderate at the moment.
- The pain is fairly severe at the moment.
- The pain is very severe at the moment.
- The pain is the worst imaginable at the moment.

Concentration

- I can concentrate fully when I want to with no difficulty.
- I can concentrate fully when I want with slight difficulty.
- I have a fair degree of difficulty in concentrating when I want to.
- I have a lot of difficulty in concentrating when I want to.
- I have a great, great deal of difficulty in concentrating when I want to.
- I cannot concentrate at all.

Personal Care (eg washing, dressing)

- I can look after myself normally without causing extra pain.
- I can look after myself normally but it causes extra pain.
- It is painful to look after myself, and I am slow and careful
- I need some help, but manage most of my personal care.
- I need help every day in most aspects of self-care.
- I do not get dressed, I wash with difficulty, and stay in bed

Work

- I can do as much work as I want too.
- I can only do my usual work, but no more.
- I can do most of my usual work, but no more.
- I cannot do my usual work.
- I can hardly do any work at all.
- I cannot do any work at all.

Lifting

- I can lift heavy weights without extra neck pain
- I can lift heavy weights, but it gives extra neck pain
- Neck pain prevents me from lifting heavy weights off the floor, but I can manage if they are conveniently positioned, for example on a table
- Neck pain prevents me from lifting heavy weights, but I can manage light to medium weights if they are conveniently positioned
- I can lift only very light weights
- I cannot lift or carry anything

Driving

- I can drive my car without any neck pain at all.
- I can drive my car as long as I want, with slight pain in my neck.
- I can drive my car as long as I want, with moderate pain in my neck.
- I cannot drive my car as long as I want, because of moderate pain in my neck.
- I can hardly drive at all because of severe pain in my neck.
- I cannot drive my car at all because of the pain in my neck.

Reading

- I can read as much as I want, with no pain in my neck.
- I can read as much as I want, with slight pain in my neck.
- I can read as much as I want, with moderate pain in my neck.
- I cannot read as much as I want, because of moderate pain in my neck.
- I can hardly read at all because of severe pain in my neck.
- I cannot read at all because of pain in my neck.

Sleeping

- I have no trouble sleeping.
- My sleep is barely disturbed (sleepless less than 1 hr).
- My sleep is mildly disturbed (sleepless 1-2 hrs).
- My sleep is moderately disturbed (sleepless 2-3 hrs).
- My sleep is greatly disturbed (sleepless 3-5 hrs).
- My sleep is completely disturbed (sleepless 5-7 hrs).

Headaches

-
- I have no headaches at all.
- I have slight headaches that come infrequently.
- I have moderate headaches that come infrequently.
- I have moderate headaches that come frequently.
- I have severe headaches that come frequently.
- I have headaches almost all the time.

Recreation

- I am able to engage in all my recreational activities, with no neck pain at all.
- I am able to engage in all my recreational activities, with some pain in my neck.
- I am able to engage in most, but not all of my usual recreational activities, because of pain in my neck.
- I am able to engage in few of my usual recreational activities, because of pain in my neck.
- I can hardly engage in any recreational activities because of pain in my neck.
- I cannot engage in any recreational activities at all because of pain in my neck.

Vernon, H. and S. Mior, *The Neck Disability Index: A Study of Reliability and Validity*. Journal of Manipulative and Physiological Therapeutics, 1991. 14(7): p. 409-415.

Appendix C – Edinburgh Handedness Inventory

Edinburgh Handedness Inventory

Please indicate your preferences in the use of hands in the following activities *by putting a check in the appropriate column. Where the preference is so strong that you would never try to use the other hand, unless absolutely forced to, put 2 checks.* If in any case you are really indifferent, *put a check in both columns.*

Some of the activities listed below require the use of both hands. In these cases, the part of the task, or object, for which hand preference is wanted is indicated in parentheses.

Please try and answer all of the questions, and only leave a blank if you have no experience at all with the object or task.

	Left	Right
1. Writing	<input type="checkbox"/> <input type="checkbox"/>	<input type="checkbox"/> <input type="checkbox"/>
2. Drawing	<input type="checkbox"/> <input type="checkbox"/>	<input type="checkbox"/> <input type="checkbox"/>
3. Throwing	<input type="checkbox"/> <input type="checkbox"/>	<input type="checkbox"/> <input type="checkbox"/>
4. Scissors	<input type="checkbox"/> <input type="checkbox"/>	<input type="checkbox"/> <input type="checkbox"/>
5. Toothbrush	<input type="checkbox"/> <input type="checkbox"/>	<input type="checkbox"/> <input type="checkbox"/>
6. Knife (without fork)	<input type="checkbox"/> <input type="checkbox"/>	<input type="checkbox"/> <input type="checkbox"/>
7. Spoon	<input type="checkbox"/> <input type="checkbox"/>	<input type="checkbox"/> <input type="checkbox"/>
8. Broom (upper hand)	<input type="checkbox"/> <input type="checkbox"/>	<input type="checkbox"/> <input type="checkbox"/>
9. Striking Match (match)	<input type="checkbox"/> <input type="checkbox"/>	<input type="checkbox"/> <input type="checkbox"/>
10. Opening box (lid)	<input type="checkbox"/> <input type="checkbox"/>	<input type="checkbox"/> <input type="checkbox"/>
TOTAL(count checks in both columns)	<input type="text"/>	<input type="text"/>

Difference	Cumulative TOTAL	Result
<input type="text"/>	<input type="text"/>	<input type="text"/>

Scoring:

Add up the number of checks in the “Left” and “Right” columns and enter in the “TOTAL” row for each column. Add the left total and the right total and enter in the “Cumulative TOTAL” cell. Subtract the left total from the right total and enter in the “Difference” cell. Divide the “Difference” cell by the “Cumulative

TOTAL" cell (round to 2 digits if necessary) and multiply by 100; enter the result in the "Result" cell.

Interpretation (based on Result):

below -40 = left-handed

between -40 and +40 = ambidextrous

above +40 = right-handed

|

Appendix D – Electroencephalography Safety Checklist

Safety checklist:

The following questions are to ensure it is safe for you to complete this study. If you answer yes to any of the questions below, we may need to exclude you from participating.

QUESTION	ANSWER	
1. Do you suffer from epilepsy, or have you ever had an epileptic seizure?	Yes	No
2. Does anyone in your family suffer from epilepsy?	Yes	No
3. Do you have any metal implant(s) in any part of your body or head? (Excluding tooth fillings)	Yes	No
4. Do you have an implanted medication pump?	Yes	No
5. Do you wear a pacemaker?	Yes	No
6. Do you suffer any form of heart disease?	Yes	No
7. Do you suffer from reoccurring headaches**?	Yes	No
8. Have you ever had a skull fracture or serious head injury?	Yes	No
9. Have you ever had any head surgery?	Yes	No
10. Are you pregnant?	Yes	No
11. Do you take any medication or use recreational drugs (including marijuana)*?	Yes	No
12. Do you suffer from any known neurological or medical conditions?	Yes	No

Comments _____

Name _____

Signature _____

Date _____

*Note if taking medication or using recreational drugs please read through the medication list on the next page to see if you use contraindicated drugs or medications. You do not need to tell the researcher which medications or drugs you use, unless you wish to. However, all researchers have signed confidentiality agreements and this information will not be recorded in writing, if you do wish to discuss this issue.

**Dr. Murphy will meet with participants who answer yes to this question to seek further information.

Medications contraindicated with magnetic stimulation:

1) Tricyclic antidepressants

Name	Brand
amitriptyline (& butriptyline)	Elavil, Endep, Tryptanol, Trepiline
desipramine	Norpramin, Pertofrane
dothiepin hydrochloride	Prothiaden, Thaden
imipramine (& dibenzepin)	Tofranil
iprindole	-
nortriptyline	Pamelor
opipramol	Opipramol-neuraxpharm, Insidon
protriptyline	Vivactil
trimipramine	Surmontil
amoxapine	Asendin, Asendis, Defanyl, Demolox, Moxadil
doxepin	Adapin, Sinequan
clomipramine	Anafranil

2) Neuroleptic or Antipsychotic drugs

A) Typical antipsychotics

Phenothiazines:	Thioxanthenes:
o Chlorpromazine (Thorazine)	o Chlorprothixene
o Fluphenazine (Prolixin)	o Flupenthixol (Depixol and Fluanxol)
o Perphenazine (Trilafon)	o Thiothixene (Navane)
o Prochlorperazine (Compazine)	o Zuclopenthixol (Clopixol and Acuphase)
o Thioridazine (Mellaril)	• Butyrophenones:
o Trifluoperazine (Stelazine)	o Haloperidol (Haldol)
o Mesoridazine	o Droperidol
o Promazine	o Pimozide (Orap)
o Triflupromazine (Vesprin)	o Melperone
Levomepromazine (Nozinan)	

B) Atypical antipsychotics

Clozapine (Clozaril)	Quetiapine (Seroquel)
• Olanzapine (Zyprexa)	• Ziprasidone (Geodon)
Paliperidone (Invega)	• Amisulpride (Solian)
• Risperidone (Risperdal)	

C) Dopamine partial agonists: Aripiprazole (Abilify)

D) Others

Symbyax - A combination of olanzapine and fluoxetine used in the treatment of bipolar depression.

Tetrabenazine (Nitoman in Canada and Xenazine in New Zealand and some parts of Europe)

Cannabidiol One of the main psychoactive components of cannabis.

Regular Cannabis use more often than once per week and/or cannabis use in the past 4 days.

Regular use of other recreational drugs, or single episode within the past three weeks.

Appendix E – Chiropractic Adjustment Safety Checklist (CASC)

Chiropractic Adjustment Safety Checklist

The following questions are to ensure it is safe for you to have a chiropractic adjustment. If you answer yes to any of the questions below, we will ask you more questions to see whether it is safe for you to receive chiropractic adjustments. We will do our best to provide an alternate study for you to take part in if unable to take part in the chiropractic component.

QUESTION	ANSWER	
1. Do you have rheumatoid arthritis or other inflammatory conditions?	Yes	No
2. Do you have a history of spine trauma or injury from the last three months, or trauma with persistent symptoms beyond three months?	Yes	No
3. Have you had cervical spine surgery?	Yes	No
4. Have you had any infection or systemic disease related to your neck pain in the past twelve months?	Yes	No
4. Have you had a known fracture or dislocation to the shoulder or spine?	Yes	No
5. Do you experience pain that spreads along your arm from your spine (radicular arm pain)?	Yes	No
6. Do you have any known bleeding disorders?	Yes	No
7. Are you on anticoagulant medications?	Yes	No
8. Do you have a history of stroke or transient ischemic attacks?	Yes	No
9. Do you have a history of cancer, or have you had a tumor, in the past five years?	Yes	No
10. Do you experience vertigo or dizziness?	Yes	No
11. Do you suffer from any other known neurological or medical conditions that might keep you from having chiropractic care?*	Yes	No

Comments _____

Name _____

Signature _____

Date _____

*Dr. Murphy will meet with participants who answer yes to this question.

Appendix F – Borg 10-point Rating of Perceived Exertion Scale

Rating	Descriptor
0	Rest
1	Very, Very Easy
2	Easy
3	Moderate
4	Somewhat Hard
5	Hard
6	.
7	Very Hard
8	.
9	.
10	Maximal

(Maupin et al., 2019)

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