Proprioception in aging:

Effects of a healthy active lifestyle and Parkinson's disease

on ankle position sense

A DISSERTATION

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Dedication

This dissertation is dedicated to

Grammy and all people with Parkinson's disease.

Let this be a step towards making the disease a little less burdensome.

Abstract

Introduction: Proprioceptive afferents are processed at multiple levels of the central nervous system and give rise to the conscious perception of body and limb position (i.e. the proprioceptive sense) and unconscious regulation of muscle tone. Proprioceptive function declines in typical aging. This cumulative dissertation concerns the proprioceptive sense in two neurologically polar aging populations: healthy active adults (Project 1) and people with Parkinson's disease (PD, Project 2).

Project 1: Emerging evidence indicates that physical activity may spare older adults from age-related proprioceptive decline. However, the role of physical activity in preserving position sense at the ankle was unknown, in part because objective and precise measures of ankle proprioception have not been available. **Aim 1:** Determine the influence of a physically active lifestyle on ankle position sense acuity in healthy aging adults. **Methods:** This study applied sensory psychophysics to obtain a just-noticeable-difference (JND) threshold and Uncertainty Area (UA) as measures of ankle position sense acuity in young, middle-aged, and older adults. Participants were tested at two reference positions, 15° and 25°. **Results:** At the 15° reference, younger adults had smaller JND thresholds than both older groups ($\chi^2_{(2)} = 7.953$, $p = 0.019$, $\eta^2 = 0.048$). The effect size was small as 74% and 71% of middle-aged and older adults, respectively, had thresholds within the range of controls. No differences between groups were found for JND threshold at the 25° reference position nor for UA at either reference position. Only a subset of participants adhered to Weber's law (young adults: 81%, middle-aged: 67%, older adults: 52%), which is a principle in psychophysics stating that the JND threshold is proportional to the magnitude of the stimulus.

Project 2: Parkinson's disease alters the processing of proprioceptive information resulting in impaired limb proprioception and increased muscle rigidity. Research has not firmly established that ankle proprioception is

systematically impaired in people with PD, nor has the relationship been delineated between ankle proprioception and muscle rigidity. **Aim 2a:** Determine the extent to which ankle position sense is impaired in people with mild-to-moderate PD. **Aim 2b:** Examine the relationship between ankle position sense acuity and lower extremity rigidity in mild-to-moderate PD. **Methods:** Using the same methods established in Project 1, JND threshold and UA were obtained as measures of ankle position sense acuity in people with mild-to-moderate PD and age-matched controls. The MDS-UPDRS was used to obtain a clinical impression of rigidity. The more affected leg was assessed for both ankle position sense acuity and rigidity in people with PD. **Results:** Median ankle position sense JND threshold and UA were significantly larger in the Parkinsonian group than controls (JND threshold: $z = 66$, $p = 0.020$, $r = 0.413$; UA: $z = 68.5$, $p = 0.044$, $r = 0.366$). Yet, 62.5% and 80% of participants with PD had JND thresholds and UA values, respectively, within the range of the controls. JND threshold correlated with lower extremity rigidity ($\rho = 0.50$, $p = 0.047$). Disease duration was moderately correlated with JND threshold ($r = 0.52$, $p = 0.039$) and the clinical assessment of rigidity ($\rho = 0.57$, $p = 0.020$). JND threshold also correlated moderately with levodopa equivalent dosage ($r = 0.54$, $p = 0.03$).

Discussion and conclusion: This dissertation challenges prevailing assumptions about ankle proprioceptive decline in aging, demonstrating that a habitually active lifestyle can preserve ankle proprioceptive function. In contrast, people with PD showed evidence of impaired position sense. Importantly, proprioceptive decline was associated with Parkinsonian muscle rigidity, establishing for the first time, a link between abnormal proprioceptive perception and abnormal control of muscle tone.

Table of Contents

List of Tables

List of Figures

Chapter 1. Introduction

1.1 Background

Proprioceptive afferents derived from muscle spindles encode muscle length, position, and contractile velocity. Such signals are processed at multiple levels of the central nervous system, including the spinal cord, brainstem, cerebellum, basal ganglia, and somatosensory cortex. Intact processing of the sensory afferents at various nervous system levels is required for the control of muscle tone, postural reflexes (Allum & Honegger, 1998) and spatial (Gordon et al., 1995) and temporal aspects (Gentilucci et al., 1994) of voluntary movement.

The word proprioception was coined from the combination of the Latin word *proprius*, signifying “one’s own” and *perception*, denoting awareness through the senses (Sherrington, 1907). Within the framework of this dissertation, proprioception is defined as the *conscious* perception of body and limb position and movement, meaning that proprioceptive signals have been processed at the cerebral cortex and are consciously perceived. Multiple modalities of conscious proprioception exist including position sense, motion sense, and the sense of heaviness. This dissertation focuses on conscious position sense of the ankle joint. *Unconscious* proprioception will refer to the processing of proprioceptive afferents which are not perceived. Studies in this dissertation focus on the conscious proprioceptive sense and the unconscious processing of proprioceptive afferents specifically giving rise to muscle tone.

Empirical evidence indicates that ankle proprioception declines with age (Deshpande et al., 2003; Ko et al., 2015; Westlake & Culham, 2006) and continues to decline in very old adulthood (75 – 90 years, Yang et al., 2019). For example, when detecting passive ankle motion, adults over the age of 60 years exhibited thresholds that were 2.4 times higher than those of younger adults (Deshpande et al., 2003; Westlake & Culham, 2006). Older adults also showed larger errors in passively reproducing target ankle positions than younger counterparts (Westlake & Culham, 2006). This decline may be attributed to

structural and functional abnormalities of muscle spindles, the primary informant of joint position sense. Age-related decrements in muscle spindles include an increase in spindle capsular thickness (Liu et al., 2005; Swash & Fox, 1972), a decline in the total number of intrafusal bag and chain fibers within the spindle (Liu et al., 2005), and decreased discharge frequency during both static and dynamic movements (Miwa et al., 1995). Moreover, there are changes in the motor innervation of the muscle spindles (Swash & Fox, 1972), which may have downstream consequences on the sensitivity of the muscle spindle as gamma motor neuron innervation is required to keep the muscle spindle taut during muscle shortening.

Yet, proprioceptive function is malleable and is known to change with proprioceptive training or with neurological impairments. Ample evidence has documented that training focused on improving proprioceptive function can improve both proprioceptive and motor function (Aman et al., 2015; Winter et al., 2022). Additionally, there is emerging evidence to suggest that a physically active lifestyle may provide some protective effects against lower extremity proprioceptive decline in healthy aging populations (Yang et al., 2022). In contrast, neurological disease is associated with proprioceptive impairments. Parkinson's disease is a progressive neurodegenerative disease that affects brain stem nuclei and alters the processing of somatosensory and motor networks. As a result, people with PD exhibit a range of somatosensory and motor impairments, such as impaired limb proprioception (Konczak et al., 2009) and rigidity (i.e., increased muscle tone during passive movement, Goetz, 2011).

Proprioceptive function has been quantified using various methods. Clinicians measure position sense by displacing a digit, and then ask the person to actively reproduce the target angle. The clinician subjectively determines position sense ability from the binary scale of "unremarkable" or "impaired". Empirical assessments of proprioceptive function have higher resolution than clinical tests and therefore are more sensitive to the deficit.

Empirical assessments can utilize passive or active methods, such that the limb is passively rotated by the experimenter/device or actively controlled by the participant. During passive rotation of the limb, muscle spindles and mechanoreceptors in the joints respond to changes in muscle length and joint deformation, respectively, without the contribution of muscle activity. As such, these perceptual processes are not influenced by motor control processes (Elangovan et al., 2014). Conversely, voluntary active movements require the activation of cortical neural motor centers that have reciprocal connections to somatosensory cortex. In studies that directly compare passive to active tests, the perception of position sense using passive assessments resulted in higher acuity compared to utilizing active methods (Elangovan et al., 2014). Passive methods isolate proprioceptive function whereas active methods measure proprioceptive-motor function, which may be elevating perceptual acuity thresholds as found in Elangovan and colleagues (2014). *In order to measure proprioceptive function in the purest form, muscle activity must not be involved in the assessment.*

Previous research attempting to understand proprioceptive function in the lower extremities of active aging adults and people with PD have only utilized active assessments (Ribeiro Artigas et al., 2016; Ribeiro & Oliveira, 2010; Teasdale et al., 2017; Yang et al., 2022). Therefore, it remains unclear the extent of the proprioceptive deficit, without motor convolution, in active aging adults and people with Parkinson's disease. As the motor system is intact in healthy aging individuals, proprioceptive-motor function may be similar to the pure proprioceptive function. Yet, to understand the normal thresholds of proprioception, we must also quantify the pure proprioceptive sense in healthy aging individuals. Parkinson's disease is compromised motorically and necessitates isolating the proprioceptive sense from motor control to truly understand the proprioceptive deficit.

This dissertation utilized an unweighted, passive method employing a two-alternative forced choice sensory psychophysics paradigm to measure sagittal

plane ankle position sense acuity (**Figure 1-1**). Sensory psychophysics is widely used in perception research. In general, sensory psychophysics describes the relationship between the physical stimulus and the resulting perceptual experience. A psi-marginal Bayesian adaptive method was utilized to estimate bias (i.e., systematic error) and precision (i.e., random error) psychometric parameters (Prins, 2013). The bias specifies the minimum intensity at which the stimulus is reliably perceived whereas the precision reflects the width of the transitional range of just detectable to undetectable (Kontsevich & Tyler, 1999). The present research investigated the ability to discriminate between two ankle positions and yielded a *just-noticeable-difference (JND) threshold* as a measure of bias and *Uncertainty Area (UA)* as a measure of precision (**Figure 1-1C**). The JND threshold was the degree difference from the physical position of the foot that the individual could correctly perceive their ankle position with 75% accuracy. Smaller JND thresholds indicate high position sense acuity. The UA was calculated as the range of degrees of physical foot position that could be perceived with 60% and 90% accuracy. A smaller UA indicates more certainty when discriminating between two stimuli.

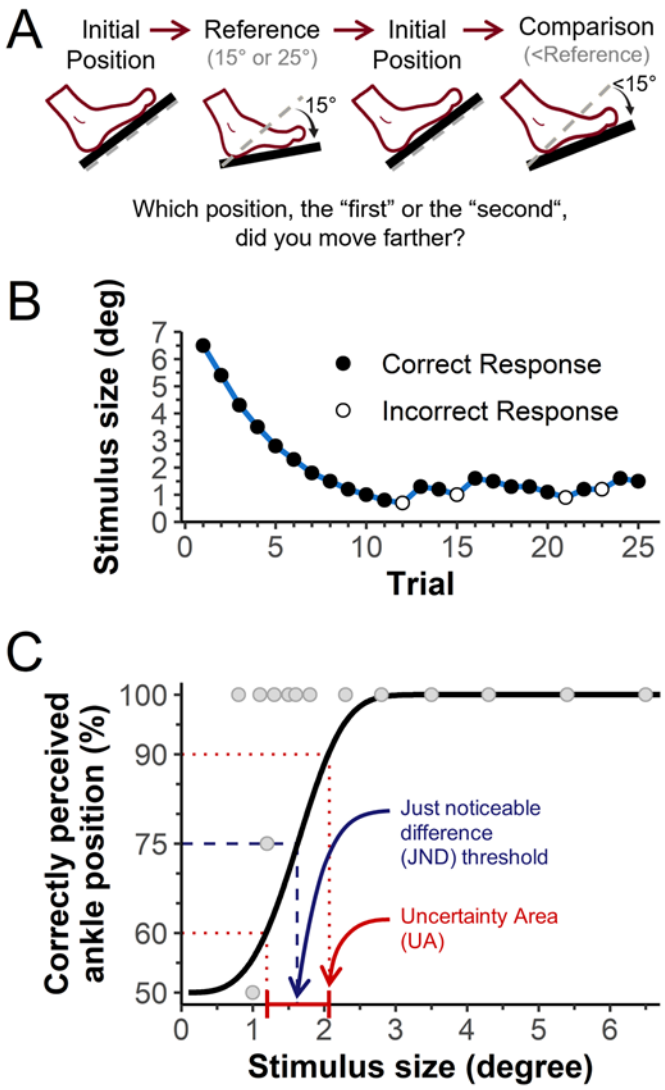

Figure 1-1. Sensory psychophysics methods employed in the dissertation studies. (A) Schematic of a single trial of ankle position sense testing. The foot is initially in the neutral position with the shank at 90° from the longitudinal axis of the foot. Next, the examiner passively rotates the foot to the reference position, 15° of plantarflexion from the initial position, and then back to the initial position. Finally, the examiner rotates the foot to the comparison position, which is always smaller than the reference position, and then back to the initial position. The participant then responds with which position they perceived their foot to have been moved farther. **(B)** Participant responses at each stimulus size. Stimulus size is the difference between the *reference* position, which is always fixed at either 15° or 25°, and the *comparison* position, which is given by an adaptive psi-marginal algorithm which takes the participant's previous (in)correct response and the stimulus size to determine the next stimulus size. **(C)** Dots are the stimulus sizes from (B) at their correct response rate. The JND threshold is the stimulus size that the participant can correctly perceive their ankle position with 75% accuracy. JND threshold is represented by the dashed blue line. The Uncertainty Area (UA, the range between dotted lines) is the random error and calculated by subtracting the stimulus sizes at 60% and 90% correct perception of position.

1.2 Rationale

There are gaps in the literature regarding ankle position sense in active aging adults and people with PD. This cumulative dissertation sought to close these knowledge gaps. The knowledge gained will provide a more comprehensive understanding of proprioceptive function in healthy aging and diseased aging. Gaps in the literature supporting the need to conduct this research include:

1. It is well established that proprioceptive function declines with aging. Emerging evidence indicates that physical activity may spare older adults from such age-related proprioceptive-motor decline. However, the role of physical activity in preserving position sense at the ankle had not previously been delineated.
2. Lower extremity proprioception is critical for the control of balance and gait. Yet, there is little empirical information on ankle proprioceptive function in people with Parkinson's disease. Previous reports have measured ankle proprioceptive-motor function while in the medicated state. Proprioceptive-motor function does not provide an accurate evaluation of proprioceptive function, as the motor system confounds the sensory measure. Moreover, the effect of anti-parkinsonian medication on proprioceptive function is unclear. To understand the proprioceptive deficit as a function of the disease, proprioception must be isolated from the motor system and must be measured in the withdrawn state. At present, there are no systematic data on the deficit of ankle position sense as a function of the disease, without transient dopaminergic intervention.
3. Signals from proprioceptive mechanoreceptors form the basis of the conscious perception of limb and body movement (proprioception) and are essential for the unconscious regulation of posture and muscle tone. Processing of such proprioceptive afferents at supraspinal levels is impaired in Parkinson's disease. As a result, people with PD exhibit impaired limb proprioception and abnormally elevated muscle tone during

passive movement. There are presently no data that associate the degree of proprioceptive dysfunction with the extent of abnormal muscle tone.

1.3 Specific Aims and Hypotheses

To address the current gaps in the literature, the purpose of this cumulative dissertation is twofold: **First**, to understand the development of ankle proprioception in healthy aging adults who have a physically active lifestyle. **Second**, to determine the deficit, if any, of ankle proprioception in people with Parkinson's disease. As an auxiliary aim, this study sought to identify the relationship between ankle proprioception and muscle rigidity in people with PD. The following specific aims and hypotheses are proposed to answer these research questions.

Aim 1. Determine the influence of a physically active lifestyle on ankle position sense acuity in healthy aging adults.

Hypothesis. Ankle position sense acuity will not systematically change from young adulthood to middle-aged and older adulthood. No significant differences between groups in either outcome measure would verify this aim.

Aim 2a. Determine the extent to which ankle position sense is impaired in people with mild-to-moderate PD.

Hypothesis. People with PD will have significantly lower ankle position sense acuity relative to controls. A significantly larger JND threshold or UA in the PD group relative to the control group would verify this aim.

Aim 2b. Examine the relationship between ankle position sense acuity and lower extremity rigidity in mild-to-moderate PD.

Hypothesis. Ankle position sense outcome measures will scale with muscle rigidity. A significant correlation of rigidity to either ankle position sense outcome measure will verify this aim.

Chapter 2. Literature Review

2.1 The Origin and Central Processing of Proprioception

Proprioceptive mechanoreceptors give rise to the proprioceptive sense

Proprioceptive signals arise from mechanoreceptors in the muscles, tendons, and joints and sense physical deformations which provide information about muscle length and tension, contractile velocity, and joint position (MacKinnon, 2018). There are three primary mechanoreceptor groups which inform the proprioceptive sense: muscle spindles, Golgi tendon organs, and joint receptors (**Table 2-1**). Muscle spindles are located within the muscle belly and primarily function to encode changes in muscle length and contractile velocity. Golgi tendon organs are located at the junction of muscle and tendon and provide afferent signals about the tensile load applied to the tendon. Receptors lining the synovial joint capsules encode joint deformation.

Muscle spindles, which signal muscle length and contractile velocity, are used for the conscious and unconscious control of motor behavior. Muscle spindles are composed of intrafusal muscle fibers, afferent sensory axons, and motor efferents. Intrafusal muscle fibers include dynamic nuclear bag1, static nuclear bag2, and nuclear chain fibers (**Figure 2-1**). Primary sensory endings, which innervate dynamic nuclear bag1, static nuclear bag2 and nuclear chain fibers, encode both changes in muscle stretch (i.e. contractile velocity) and length (i.e. position) (Santuz & Akay, 2023). Secondary endings innervate only static nuclear bag2 and nuclear chain fibers and encode changes in muscle length. Such primary and secondary endings wind around and innervate the central regions of the intrafusal fibers. Stretching of the extrafusal muscle causes stretching of the central region of the muscle spindle, which provides a deforming stimulus that depolarizes the sensory endings. The central region of the intrafusal muscle fibers are non-contractile.

The sensitivity of the muscle spindle is modulated by gamma motor neurons. Gamma motor neurons (i.e., the fusimotor system) innervate the end regions of

the intrafusal muscle fibers and keep them sensitive to changes in muscle length during muscle contraction. There are two types of gamma motor neurons: dynamic and static fusimotor efferents. Dynamic fusimotor efferents innervate dynamic nuclear bag1 fibers to maintain sensitivity to changes in muscle length. Static fusimotor efferents function to keep static nuclear bag2 and nuclear chain fibers sensitive to changes in muscle length.

Table 2-1. Mechanoreceptor type in proprioceptive sensation. Adapted from Tables 22-1, 22-2, and 35-1 from *Principles of Neural Science, edition 5.*

	Fiber type	Fiber group	Modality	Resulting Perception
Muscle spindle (primary)	Ia	Large diameter, myelinated	Muscle length and speed	Joint position and velocity of movement
Muscle spindle (secondary)	II	Medium diameter, myelinated	Muscle stretch	Joint position
Golgi tendon organ	Ib	Large diameter, myelinated	Muscle contraction	Heaviness or force
Joint capsule receptor	II	Medium diameter, myelinated	Joint angle	Extreme joint position
Free nerve endings	III	Small diameter, myelinated	Excess stretch or force	Pain, chemical stimuli, and temperature

Alpha motor neurons innervate extrafusal muscle fibers. Alpha motor neuron stimulation causes extrafusal muscle fibers contract and thus shorten. If the intrafusal muscle fibers were not co-contracted with the extrafusal muscle fibers, then the muscle spindle would remain elongated and slacked during muscle contractions. The mechanism which keeps intrafusal fibers taut during muscle shortening is alpha-gamma co-contraction, in which the gamma motor neurons stimulate the polar regions of the intrafusal fibers to contract with the contracting extrafusal fibers. Alpha-gamma co-contraction allows the muscle spindle to

remain under tension during muscle contraction, thus keeping the muscle spindle sensitive to changes in muscle length (MacKinnon, 2018). Beta motor neurons are another form of motor neuron and innervates both extrafusal and intrafusal muscle fibers, providing the equivalent of alpha-gamma co-contraction.

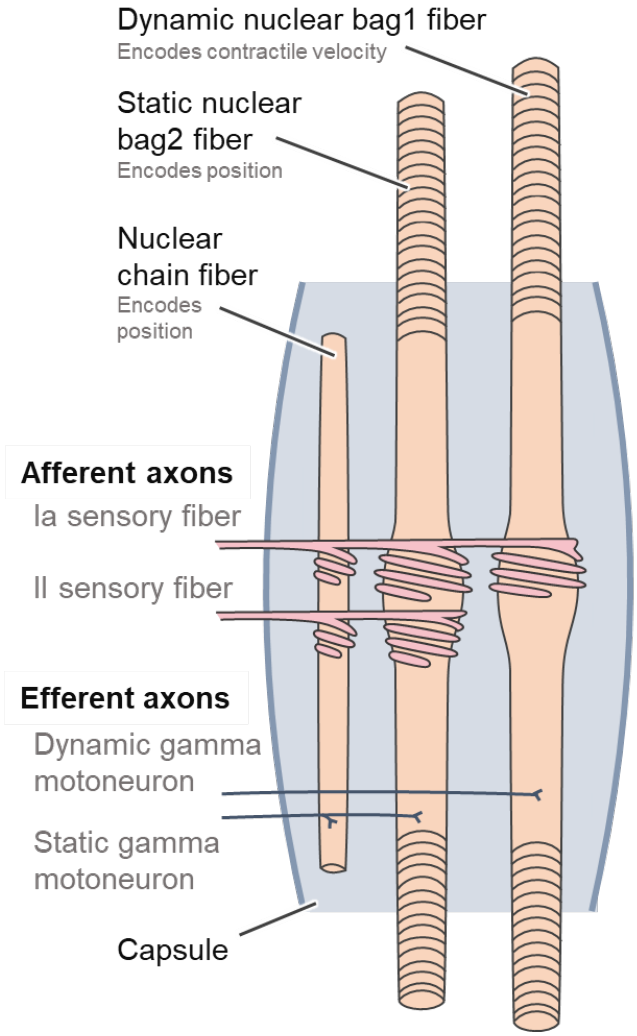

Figure 2-1. Muscle spindle structure and innervation. The muscle spindle is composed of intrafusal fibers and is surrounded by a capsule. The three types of intrafusal fibers include dynamic nuclear bag1 fibers, static nuclear bag2 fibers, and nuclear chain fibers. Dynamic nuclear bag1 fibers sense changes in muscle length and thus encode contractile velocity of the muscle. Static nuclear bag2 fibers and nuclear chain fibers sense changes in muscle length and thus encode changes in joint position. Afferent sensory axons wind around the central regions of the intrafusal fibers and are stimulated with mechanical deformation of the intrafusal fibers. Gamma motor neurons innervate the polar regions of intrafusal muscle fibers and contract the intrafusal fiber. Original image by Jacquelyn Sertic.

Transmission of proprioceptive signals to the central nervous system

There are two major ascending sensory tracts with clinical importance for transmitting proprioceptive information from the body to supraspinal processing centers (**Figure 2-2**). First, the *dorsal column-medial lemniscal pathway* transmits proprioceptive and tactile information to the primary somatosensory cortex. Afferents from proprioceptive mechanoreceptors travel through Ia and II fibers and dorsal root ganglion neurons. From there, axons from dorsal root ganglion neurons are sent via primary sensory axons through either the dorsal or lateral funiculus. For proprioceptive afferents traveling through the dorsal funiculus, primary sensory axons travel through the dorsal columns where they synapse onto the gracile (for lower extremity) or cuneate (for upper extremity) nucleus of the caudal medulla. Axons encoding truncal proprioceptive information travel through both the gracile and cuneate funiculus and synapse on both nuclei. The axons of these relay neurons then cross the midline at the sensory decussation and ascend to the ventral posterior lateral nucleus of the thalamus as the medial lemniscus. Tertiary axons from the thalamus ascend to the appropriate region of the primary somatosensory cortex (**Figure 2-2**). Such proprioceptive afferents arriving at the cortex can be consciously perceived.

Second, proprioceptive afferents also travel through axons in the *spinocerebellar tract* synapses on the ipsilateral vermis of the cerebellum. Proprioceptive information at the cerebellum is not consciously perceived. Rather, proprioceptive afferents in the cerebellum are utilized for online adjustments of movement. Somatosensation from the face is transmitted via the trigeminal nerve through the mid-pons before decussating in the brainstem and synapsing on the ventral posterior medial nucleus of the thalamus (Huff et al., 2023). The third order neurons in the thalamus send facial somatosensation to the primary somatosensory cortex.

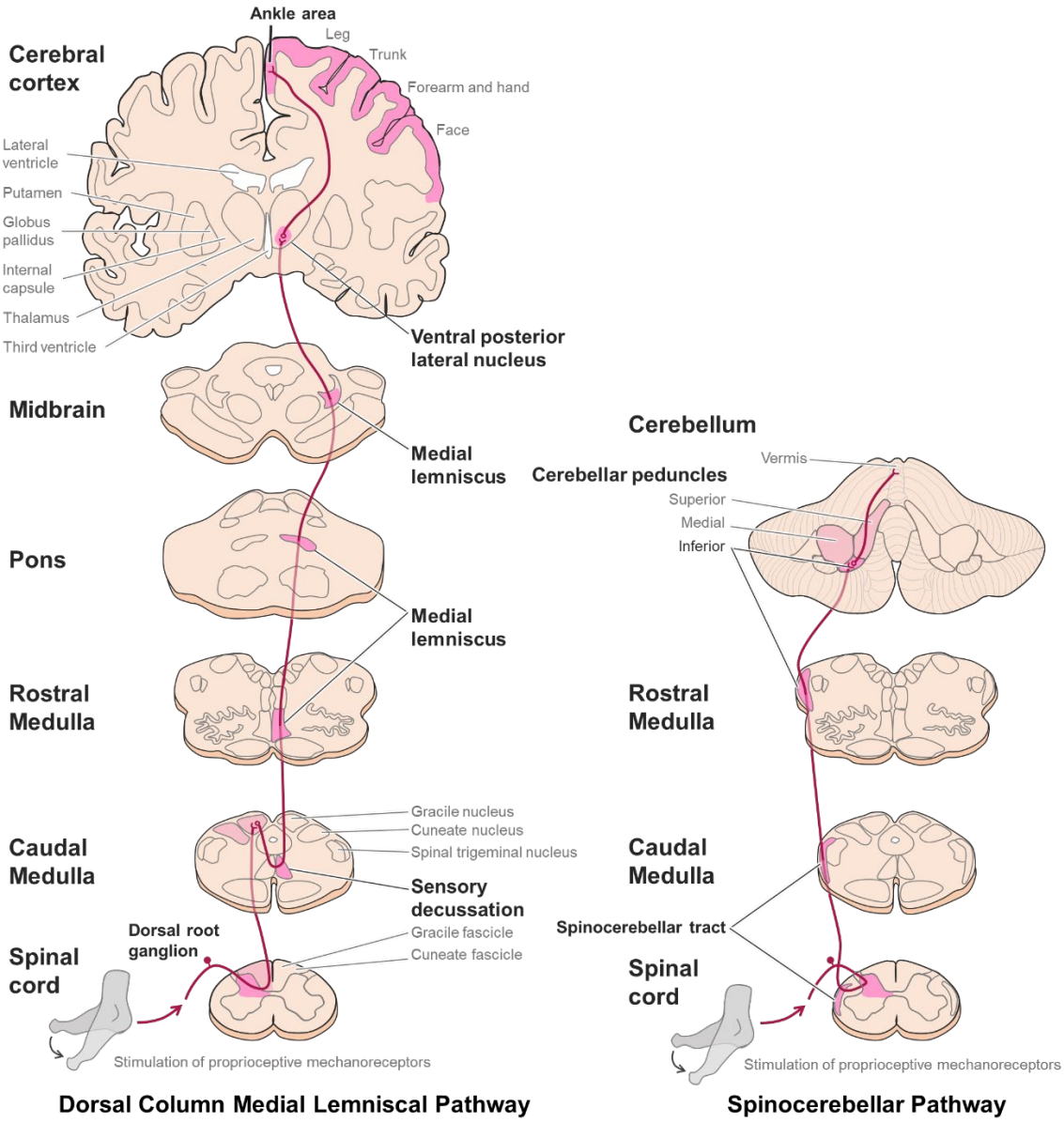

Figure 2-2. Ascending pathways transmitting proprioceptive information from the body to supraspinal levels. Dorsal column medial lemniscal pathway (left) and spinocerebellar tract (right) transmit proprioceptive afferents from the periphery to supraspinal levels. Dorsal column medial lemniscal pathway adapted from *Principles of Neural Science, edition 5.*

Somatosensation, like vision and audition, is topographically represented in the central nervous system. Somatotopic representation is found in the spinal cord, brainstem, thalamus, basal ganglia, cerebellum, and primary somatosensory cortex. In the spinal cord, axons in the gracile fascicle contain proprioceptive

information from the lower extremity whereas upper extremity proprioceptive afferents travel through the cuneate fascicle. Axons of dorsal root ganglion neurons align medially to laterally, such that the proprioceptive afferents from the toes and ankles are represented most medially in the gracile fasciculus whereas axons containing finger afferents would be more laterally in the cuneate fasciculus. In the cerebrum, the body is represented caudally to rostrally along the medial to lateral primary somatosensory cortex.

Cortical regions involved in processing of proprioceptive information have been elucidated from studies assessing behavioral proprioceptive deficits of people with a history of stroke. There is strong evidence that lesions to the somatosensory cortex and posterior parietal cortex affect proprioceptive function (Kenzie et al., 2014). Emerging evidence also implicates the temporoparietal regions (i.e. supramarginal gyrus, superior temporal gyrus, and Hershl's gyrus), the arcuate fasciculus, and insular regions for processing of proprioceptive afferents (Chilvers et al., 2021; Findlater et al., 2018).

2.2 The Role of Proprioceptive Afferents in Motor Control

To appreciate the role of proprioception in motor control, it is important to understand the variety of motor control processes. First, at the level of the spinal cord are spinal reflexes. Spinal reflexes are involuntary, automatic, stereotyped but flexible motor responses that occur when mechanoreceptors are stimulated. In normal behavior, spinal reflexes are directly modulated from supraspinal centers to accomplish desired behaviors such as modulating the amount of muscle activity required to complete a task. Voluntary motor behaviors are those that are under conscious control by the brain and is controlled through feedforward and feedback mechanisms.

Processing of proprioceptive afferents for involuntary motor control

Spinal reflexes can have polysynaptic or monosynaptic pathways. Reflexes involving polysynaptic pathways produce contractions in both the ipsilateral and

contralateral limb. Muscle groups that are activated and inhibited are opposite between the limbs. For example, in the crossed extensor reflex, if a stimulus were to excite the motor neurons that innervate ipsilateral flexors, then the contralateral extensors would also be excited (Kandel et al., 2014, p. 793). Monosynaptic pathways mediates the stretch reflex. Muscle spindle Ia sensory afferents synapse on two targets: the homonymous alpha motor neurons and inhibitory interneurons which synapse with antagonist muscles (Kandel et al., 2014, p. 794). The stretch reflex involves a stretch of the muscle spindle, transmission of that stretch through the Ia sensory afferent axon, and synapses on both the alpha motor neuron of the agonist muscle, which contracts the agonist muscle, and the inhibitory neuron which relaxes the antagonist muscle. Such excitation of one group of muscles with simultaneous inhibition of their antagonists is *reciprocal inhibition*. This inhibition prevents muscle contractions that would otherwise impede agonist movements produced by the stretch reflex. Renshaw cells are another class of inhibitory interneurons. Renshaw cells are excited by collateral alpha motor neurons and make inhibitory synaptic connections with the alpha motor neurons that excite them and the Ia inhibitory interneurons (Kandel et al., 2014, p. 797).

Reflexes can be modulated by descending cortical projections at the alpha motor neuron, interneurons in polysynaptic reflex circuits, and presynaptic terminals of afferent fibers (Kandel et al., 2014, p. 801). In response to a sudden stretch, the monosynaptic stretch reflex (M1) will evoke a motor response of around 40ms. One will also see a long-latency response (M2-3) of around 70-90ms. The long-latency response involves supraspinal centers (**Figure 2-3,** Kandel et al., 2014, p. 805) and modulates motor output based on the task (Lee & Tatton, 1975; Tatton & Lee, 1975). This modulation is shown by differences in the M1 and M2-3 responses based on an active resistance to a perturbation or no resistance to a perturbation. In normally functioning neurological systems, M1, M2, and M3 responses will be increased for the active task compared to the passive task (see bottom of **Figure 2-3**).

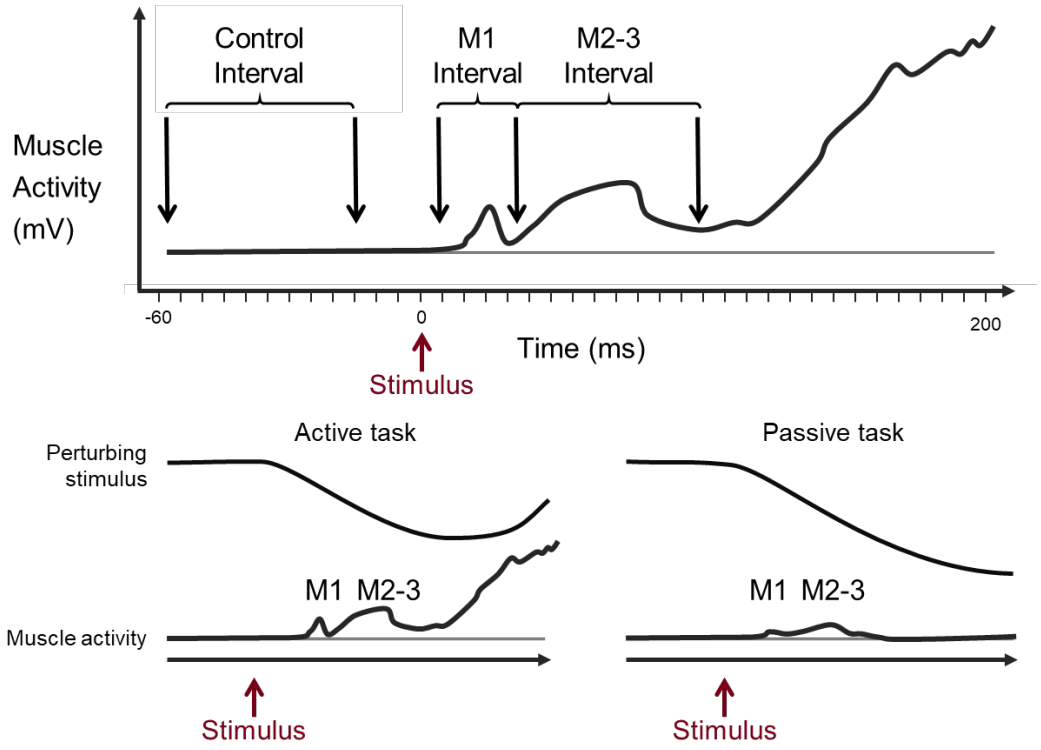

Figure 2-3. Illustration of the M1 and M2-3 motor responses to perturbation. Stimulus is the perturbation of a joint. The M1 response (i.e., spinal reflex) will elicit a motor response around 40ms. The afferent sensory signal takes approximately 70-90ms to travel to supraspinal levels and elicit the M2-3 motor response. The bottom section of the figure demonstrates how the task goal elicits modulatory responses to the motor output of the reflexes. An active resistance to the perturbation will elicit larger motor responses than no resistance to the perturbation. This figure is adapted from Tatton and Lee (1975).

At the spinal level, sustained activation of the stretch reflex modulates muscle tone. Primary sensory afferents make monosynaptic connections to the spinal cord and synapse with excitatory alpha motoneurons of homonymous muscles and 1a inhibitory interneurons of antagonist muscle groups. This monosynaptic connection forms the basis of the short-latency stretch reflex. During sustained muscle stretch, nuclear chain fibers and the secondary sensory endings send afferent signals to the spinal cord. Efferent signals projected through alpha motoneurons cause the extrafusal fibers to asynchronously contract, yielding sustained mild contraction of the fibers (Ganguly et al., 2021). Spinal interneurons are an important component of the stretch reflex arc and are

modulated by descending fiber tracts. Supraspinal control via the dorsal and medial reticulospinal descending pathways modulate spinal and interneurons in the control of muscle tone (Takakusaki et al., 2016).

Processing of proprioceptive afferents for voluntary motor control

The brain makes predictive computations using state sensory information and past experiences to achieve desired movement goals. Internal models of biological motor control are used to represent such computations and demonstrate how the central nervous system contains an internal representation of the kinematic and kinetic properties of the body and how that the body uses this knowledge to perform computations to complete desired movements.

Proprioceptive afferents are a vital piece for updating these internal models for the coordinated control of movement both in feedforward and feedback pathways. Feedforward motor commands are generated by the motor cortex and without regard for sensory consequences. In contrast, feedback control uses sensory signals to correct movements and is processed in the cerebellum. There are three major computational models of motor control which are described below: inverse dynamics, forward dynamics, and forward kinematics models (**Figure 2-4**).

The *forward kinematics model* uses end effector state information and transforms the desired trajectory of the end effector into proximal joint trajectory kinematics required to achieve such end effector trajectory. That is, this model adjusts joint kinematics to achieve the desired end effector trajectory (Kandel et al., 2014, p. 754). Accurate estimates of anthropometric properties i.e., segment length and girth, the degrees of freedom, and the segment lengths of the controlled system are required for accurate computations. The output of the forward kinematic model, the joint kinematics, are used as the input for inverse dynamics model. The *inverse dynamics model* transforms limb kinematics required to achieve the trajectory of the end effector to estimate joint torques and forces required to achieve such trajectory (Wolpert & Kawato, 1998). The model requires estimates

of anthropometric properties including mass of the segments and environmental forces exerted on the system. That is, joint and muscle position, velocity, and acceleration of the current state are transformed into stiffness i.e., elastic forces proportional to displacement, viscosity i.e., the resistive forces proportional to velocity, and inertia, i.e., the mass resisting acceleration that are produced by muscles and tendons to oppose movement and gravity, respectively.

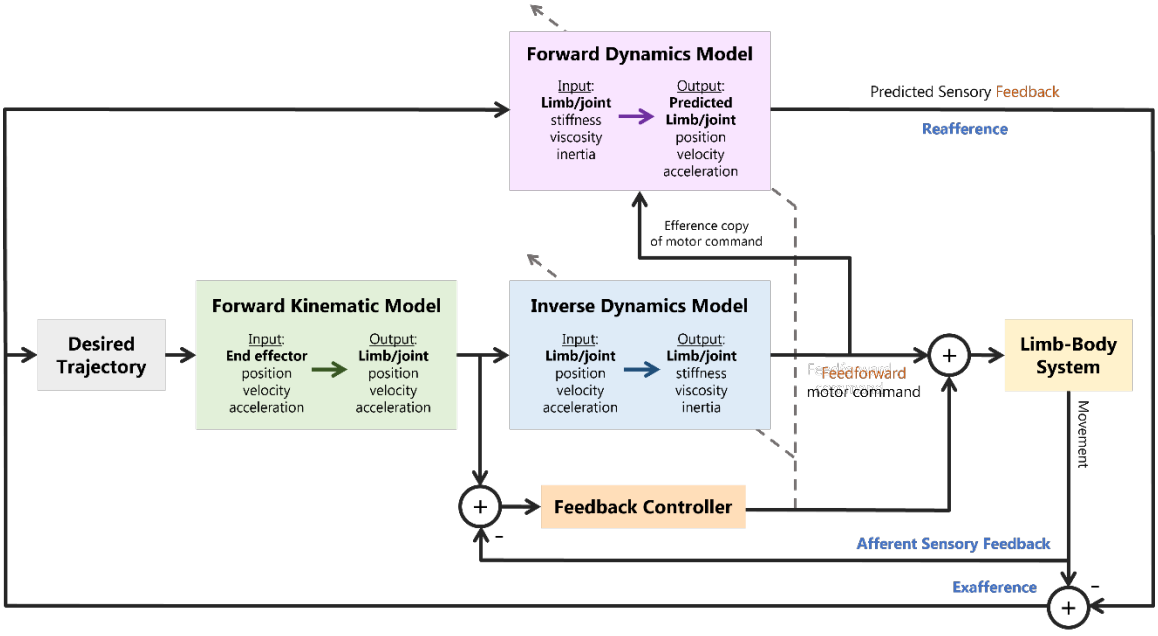

Figure 2-4. A computational model of voluntary sensorimotor control. Parallel feedback and feedforward mechanisms from internal models shape voluntary motor commands. A feedforward dynamics model generates predicted sensory feedback based on the specified motor commands. Predicted and afferent sensory feedback are compared (reafference vs. afference) resulting in an exafferent signal. With respect to one's own movement, this signal indicates how well the movement was executed in relation to the plan. If movement is executed as expected, reafference and afferent feedback cancel each other and exafference is zero. Adapted from Konczak & Abbruzzese (2013).

Inverse dynamics models operate under feedforward control, in which the model generates the motor command to achieve a desired movement trajectory (Miall & Wolpert, 1996). Feedforward control is an open-loop system, in that movement is planned without regard for sensory consequences (Wolpert & Kawato, 1998). Feedforward control is useful during ballistic movements, as the movement is

completed faster than it would take to be updated by peripheral sensory feedback (Kandel et al., 2014, p. 754). Planned state information can be compared to the state information to produce an error signal. This error signal can be used to update the desired trajectory of the end effector (which feeds into the forward kinematic model) and train the inverse dynamics model (Wolpert et al., 1998). Shadmehr and colleagues (1994) used a novel force field to demonstrate that the inverse dynamic model is updated upon repeated exposure to an external novel force field.

The motor command generated by the inverse dynamic model is also used as an efference copy for the forward dynamic model. The *forward dynamic model* transforms estimated joint forces and torques (stiffness, viscosity, inertia) required of the proximal segments to achieve of the desired end effector trajectory into the predicted kinematic state (position, velocity, acceleration) of the controlled limb (Bhushan & Shadmehr, 1999; Wolpert et al., 1998). Forward dynamics models are part of feedback control, in which sensory consequences are used to update the desired trajectory (Miall & Wolpert, 1996). The difference between the predicted sensory feedback from the forward dynamics model i.e., reafference copy, and the state sensory information i.e., afferent proprioceptive sensory feedback, produce the error of the desired trajectory i.e., exafference. The resulting movement errors, the exafference, are used to update future motor commands. This prediction of the sensory feedback is important because of time delays of the real-time feedback (Johansson & Westling, 1984), as sensory information from the periphery is both noisy and slow. Extrinsic (external to the body, i.e., visual and auditory feedback) and intrinsic (within the body, i.e., proprioceptive feedback) sensory feedback are delayed due to mechanical transmission of neural signals from the periphery to the central nervous system, central processing of these efferent signals, and the motor responses of the muscles to this sensory feedback. Delay of proprioceptive feedback from the current state will result in unstable movements. Predictions of the current state stabilizes the movement by compensating for feedback delays in the state of the

motor system. Despite the powerful ability of predicting sensory experiences, sensory feedback is still necessary for online updating of the motor commands.

Unconscious supraspinal processing of proprioceptive afferents occurs in the cerebellum

The cerebellum is the brain structure which integrates the efferent copy, state sensory feedback, and the predicted sensory consequences of the movement. Such processing occurs in the Purkinje cells of the cerebellar cortex (Popa et al., 2017). Purkinje cell bodies reside in the Purkinje layer, their dendrites are located within the molecular layer of the cerebellar cortex and the axons are located within the granule cell layer (**Figure 2-5**). The shape resembles a fan that is perpendicular to the direction of the cerebellar folia. Purkinje cells are the only output of the cerebellar cortex. Information arrives to the cerebellar cortex through two main inputs: *climbing fibers* and *mossy fibers*. Climbing fibers originate from the inferior olivary nucleus of the medulla, travel through the inferior cerebellar peduncle, and wrap around Purkinje cell dendrites in the molecular layer of the cerebellum. Each Purkinje cell synapses with a single climbing fiber. Mossy fibers originate in the pontine nuclei, travel through the middle cerebellar peduncle, and synapse on granule cells in the granule layer of the cerebellum. Granule cells send axons to the molecular layer where they split and run parallel to the cerebellar folia. As such, they are termed “parallel fibers” when in the cerebellar cortex. Such parallel and perpendicular anatomy of the respective parallel fibers and Purkinje dendrites allow a single parallel fiber to synapse on many Purkinje cells. Purkinje axons synapse on the deep cerebellar nuclei, which outputs through the superior cerebellar peduncle and onto the red nucleus or ventrolateral thalamus. There are also excitatory glutamatergic (granule and unipolar brush cells) and inhibitory GABAergic (Golgi, stellate, and basket cells) interneurons which populate the cerebellar cortex and function to facilitate sensorimotor information processing (Brown et al., 2019; Consalez & Hawkes, 2013).

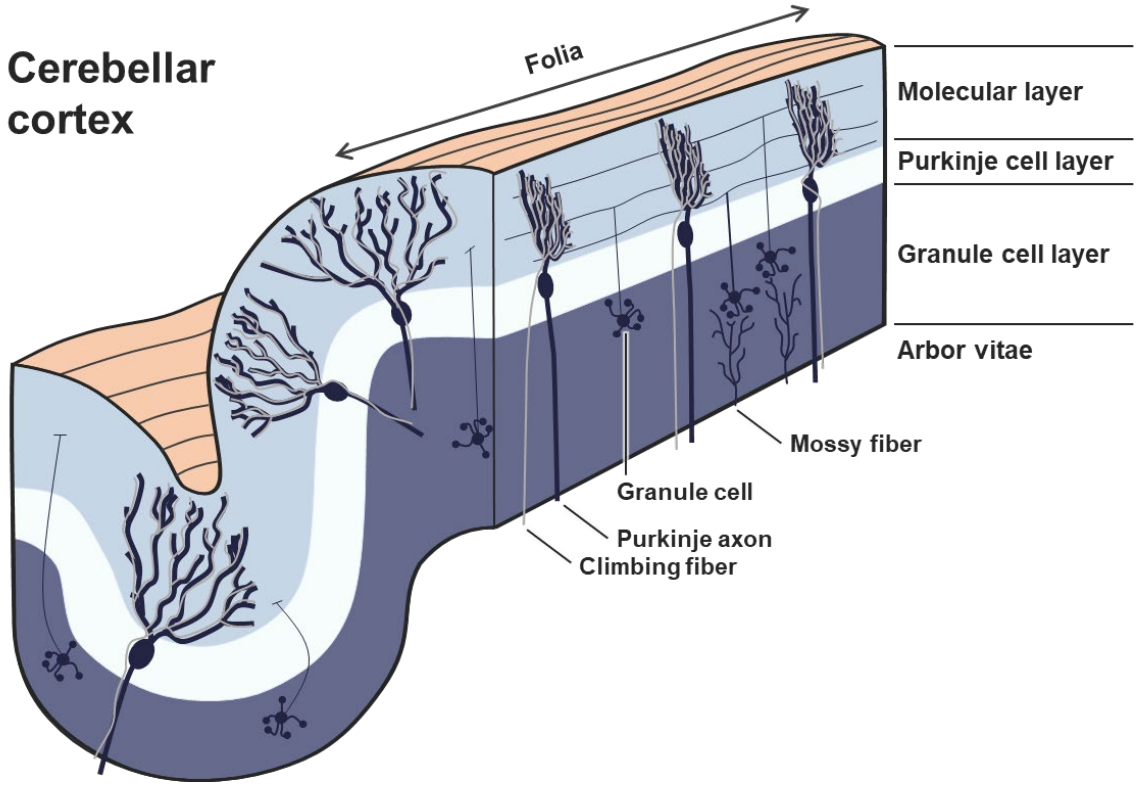

Figure 2-5. Schematic of cerebellar cortex anatomy. The Purkinje cell layer hosts the cell bodies of Purkinje cells, with their dendrites extending into the molecular layer. Axons of Purkinje cells traverse through the granule cell layer, projecting through the arbor vitae and synapsing on deep cerebellar nuclei (not shown). Input to the cerebellar cortex arrives via climbing fibers from the inferior olivary nucleus and mossy fibers from the pontine nuclei. Climbing fibers wrap around Purkinje dendrites, while mossy fibers synapse on granule cells in the granule layer. Parallel fibers, originating from granule cells, run parallel to the cerebellar folia within the molecular layer, facilitating synapses with multiple Purkinje cells. The cortex also harbors various interneurons, which are not shown. Original image by Jacquelyn Sertic.

Sensory afferent feedback is thought to be processed in the molecular layer of the cerebellum. Parallel fiber activation of the Purkinje cell produces high frequency simple spike discharge. Climbing fibers strongly activate the entire dendritic tree of a Purkinje cell, generating low frequency complex spikes. Complex spike discharges have been shown to encode non-error information about motor behavior, represent state changes (Streng et al., 2022), and modulate simple spike firing, causing changes in the kinematic and position error in the simple spike (Streng et al., 2017). Simple spike discharges encode predictive and current kinematic and error signals (Popa et al., 2012, 2017). That

is, simple spike discharge has been shown to predict both position and velocity up to 2000ms before the movement, representing the *feedforward* motor command, and provide position and velocity feedback up to 2000ms after movement, representing the *actual sensory feedback* (Popa et al., 2017). Predictions of future kinematics and actual sensory feedback are used to update future motor commands. This prediction of the sensory feedback is also important because of the time delays of the real-time feedback. Delay of the current state reaching the cerebellum will result in unstable movements and predictions of the current state stabilizes the movement.

Spinocerebellar regions, which are composed of the vermis and intermediate hemispheres, process afferent sensory feedback. Proprioceptive afferents travel to the spinocerebellum via the spinocerebellar tract (described in ***Section 2.1***). Processed sensory information from Purkinje cells are projected to the interposed nuclei and then the red nucleus. The red nucleus subsequently projects to the spinal cord and cranial nerve nuclei through the rubrospinal tract. Such proprioceptive information is used for postural control and to coordinate movements. Cerebrocerebellar regions are composed of the lateral hemispheres of the cerebellum. Input to the cerebrocerebellum originates from the cerebral cortex via the pontine nuclei. The pontine nuclei send axons to the contralateral side of the cerebellum via the middle cerebellar peduncle. Purkinje cells in the cerebrocerebellum output to the dentate nucleus, which then projects to the ventrolateral nucleus of the thalamus. The thalamus then projects to the cerebral cortex. Such processed information is involved in coordinating movement planning and learned movements.

2.3 Methods to Assess Proprioceptive Function

Proprioceptive function can be quantified by applying various methods; clinicians and researchers operate under different methods to test the proprioceptive sense. Clinicians typically measure position sense by displacing a digit, and then asking the person to actively reproduce the target angle. The clinician

subjectively determines position sense ability from the binary scale of “unremarkable” or “impaired”. Consequently, position sense deficits are often missed when assessed clinically.

Empirical assessments of proprioceptive function have a higher resolution and are more sensitive to the deficit. Researchers have developed both low- and high-technology methods for measuring position sense and can subsequently employ designs that target different modalities of proprioceptive function. These are discussed below:

First, assessments can utilize passive or active movements, meaning that the limb is passively rotated by the experimenter or device or the limb is actively controlled by the participant. During passive rotation of the limb, muscle spindles and mechanoreceptors in the joints respond to changes in muscle length and joint deformation, respectively, without the contribution of muscle activity. As such, these perceptual processes are not influenced by motor control processes (Elangovan et al., 2014). Conversely, voluntary active movements require the activation of cortical neural motor centers that have reciprocal connections to somatosensory cortex. Elangovan and colleagues (2014) assessed judgements of position sense using a passive-passive and passive-active paradigm with the purpose of determining whether motor involvement influences proprioceptive outcomes. Participants were tested three times for their position sense acuity by applying psychophysical threshold hunting, contralateral matching, and ipsilateral matching methods. The participants’ arm was passively moved twice during psychophysical threshold hunting. During the active contra- and ipsilateral matching tasks, the arm was first passively moved to the target position and then the participant actively reproduced the target position. Elangovan and colleagues (2014) demonstrated that the perception of position sense using passive assessments resulted in higher acuity compared to utilizing both passive-active methods. As such, active assessments may be useful for understanding the integrity of the proprioceptive-motor network.

Second, during proprioceptive assessments, the ipsilateral or contralateral limbs are used to match a target angle or movement velocity. Ipsilateral movements imply that the same limb is repositioned twice. This can involve either a passive-passive movement or a passive-active movement. Passive-passive movement involves the experimenter or device passively moving the limb to the target position, back to the neutral position, and then again moving the limb and requiring the participant to indicate when they perceive to have reached the target position. Passive-active movements are such that the experimenter passively moves the limb to the target position and the participant actively matches that position. Ipsilateral assessments are useful in that they test proprioceptive function of the same limb and mostly reflects activation of the contralateral brain hemisphere. However, this method is limited in that cognitive function and working memory are required to “hold” the first position in working memory to make a perceptual judgment (Oh et al., 2022). Contralateral testing is a bimanual task involving both limbs to reproduce the target angle. These assessments involve passively moving one limb to the target position and either actively or passively moving the other limb to mirror-match the target position. This type of assessment does not require the use of working memory. However, it does introduce interhemispheric activation and the exchange of proprioceptive information from the two limbs.

Third, to purely measure the proprioceptive sense of the isolated joint, other forms of sensory feedback used during voluntary movement must be occluded. Coordinated voluntary movement requires the integration of vision, vestibular information, and proprioceptive feedback. In quantifying proprioceptive function, vision can be occluded using vision-occluding goggles or by shutting the eyes. Vestibular information supplies critical information regarding head orientation and acceleration. Therefore, the head must be immobilized or unused during the task. Moreover, the joint must be measured in isolation in order to evaluate the proprioceptive function of the nearest neighboring muscles. If multiple joints were involved in the assessment, as during a standing task, then proprioceptive

afferents of multiple joints would confound the measure. Therefore, only the single joint to be tested should be moved during the assessment.

This dissertation utilized an ipsilateral passive-passive method employing a psychophysical paradigm to determine the bias and precision of the perception of ankle position. Here, *bias* refers to the systematic error between the perceived and true position of the limb, representing perceptual accuracy. *Precision* refers to the random error between independent repeated responses, representing the amount of uncertainty of responses (*International Organization for Standardization*, 1994). The ankle to be assessed was unloaded and the participant seated. Thus, the proprioceptive assessment isolated the proprioceptive sense at the ankle from other joints. Vision was occluded using blacked-out goggles and the vestibular system was uninvolved during testing as there was no head movement during the seated task.

2.4 Age-Related Development of Proprioception

Proprioceptive function develops across the lifespan. In the early years of life, there is an age-dependent change in proprioceptive precision until approximately 12 years when proprioceptive function matures to adult performance. Such age-related development of position sense precision has been shown at the forearm (Holst-Wolf et al., 2016), wrist (Marini et al., 2017) and the finger (Oh et al., 2022). However, there are conflicting results with regards to position sense bias. The studies by Holst-Wolf and colleagues (2016) and Oh and colleagues (2022) do not identify age-related changes in forearm nor finger position sense bias. In contrast, Marini and colleagues (2017) documented age-related improvements in wrist positioning accuracy up until the age of 12. Such perceptual changes in early aging are likely not attributable to changes in peripheral mechanoreceptors nor spinal cord circuitry. Muscle spindles reach morphological maturation around three years of age (Österlund et al., 2011) and threshold amplitudes for eliciting the stretch reflex reach adult levels by 6 years (O'Sullivan et al., 1991). The development of proprioceptive function may instead be influenced by the

development of subcortical and cortical networks involved in involved in modulating muscle spindle sensitivity and transmitting and processing proprioceptive afferents.

At the opposite end of the lifespan, evidence suggests that proprioceptive function declines with aging (Deshpande et al., 2003) and continues to decline into very old adulthood (75-90 years (Yang et al., 2019). Such declines may be attributed to age-related structural and functional abnormalities in proprioceptive mechanoreceptors (Liu et al., 2005; Swash & Fox, 1972). Specifically, muscle spindles increase capsular thickness with aging (Miwa et al., 1995; Swash & Fox, 1972), which can impair the muscle spindle's ability to deform and thus decrease the sensitivity to stretch (Mynark & Koceja, 2001). Conduction velocity of sensory afferents slows by 21% with aging (Boxer et al., 1988). Such degradation may be attributed to age-related demyelination of sensory axons (Ludatscher et al., 1985). Central processing of proprioceptive afferents may also be affected with aging due to a progressive decrease of basal dendrites of pyramidal cells in layer V of the motor cortex (Nakamura et al., 1985) and alterations in the expression of neurotransmitters (Wenk et al., 1989).

2.5 The Proprioceptive Sense is Trainable

Proprioception is a dynamic sense in that it can be impaired, such as with neurological disease, or improved with proprioceptive training. Proprioceptive training yields improvements in motor control and proprioceptive function and affects neural processing in both the somatosensory and motor cortical areas (Ostry et al., 2010). The ability for the proprioceptive sense to improve is imperative for those with degraded somatosensory function.

In the first study of my doctoral training, I was a major contributor on a systematic review (Winter et al., 2022) which documented that training focusing on improving proprioceptive function improved both proprioceptive and motor outcome measures. We conducted this review as a follow up to the study by Aman and colleagues (2015) to review empirical interventions published between

2013-2020 to gain an understanding of which outcome measures are most sensitive to proprioceptive training, which populations may benefit most, and the effects on proprioceptive and motor systems. After searching four major databases, we identified 3,297 articles and narrowed the studies to 70 which fit our inclusion criteria. The main findings were: (1) Proprioceptive training led to comparable gains in both proprioceptive (+46%) and motor performance (+45%); (2) Most studies (50/70) applied active movement interventions, yet interventions isolating the proprioceptive system yielded the largest proprioceptive benefits; and (3) Joint position sense error was the most commonly used proprioceptive measure. Many neurological, orthopedic, and healthy populations were studied, none of which was distinguished with the different proprioceptive malleability than others.

Interestingly, proprioceptive training elicits benefits to the untrained joints and limbs. Recently, it was demonstrated that proprioceptive training at one joint (i.e. wrist) transfers such proprioceptive benefit to other joints (i.e. ipsilateral elbow , Zhu et al., 2023). In the same study, proprioceptive training of the wrist was also shown to improve movement accuracy at the trained wrist and untrained ipsilateral elbow. Moreover, proprioceptive training may improve movement accuracy in motor tasks that were not trained (Elangovan et al., 2017).

2.6 A Brief Overview of Parkinson's Disease

Parkinson's disease (PD) affects well over one million individuals in North America. Its prevalence is predicted to increase markedly with the aging population (Marras et al., 2018). Incidence (Hirsch et al., 2016) and prevalence rates (Pringsheim et al., 2014) of PD increase nearly exponentially with age, rising rapidly after the age of 60 in both men (Driver et al., 2009) and women (Mayeux et al., 1995). The disease produces annual economic burdens amounting to $23 billion (Huse et al., 2005) in the form of inpatient care, outpatient services, drug prescriptions, emergency room visits, and early retirement (Keränen et al., 2003). Not only are health care systems taxed, people

living with PD experience reduced quality of life with disease progression (Keränen et al., 2003).

PD is a progressive neurodegenerative disease that affects brainstem nuclei and alters the processing of somatosensory and motor networks. As a result, people with PD exhibit a range of somatosensory and motor problems, such as impaired limb proprioception (Konczak et al., 2009), tremor, increased rigidity, abnormal slowness and balance problems (Goetz, 2011). Diagnosis of PD is contingent on the person exhibiting bradykinesia and at least one other cardinal motor symptom (i.e., rigidity, postural instability, or tremor). These symptoms become more severe with disease severity. Such motor symptoms manifest when approximately 70% of the dopamine producing cells in the basal ganglia degenerate.

The basal ganglia's main function, with respect to movement, is to influence the motor cortex to optimize movement. The basal ganglia are a series of interconnected subcortical nuclei distributed throughout the telencephalon, diencephalon, and mesencephalon (**Figure 2-6**). Forebrain structures include the striatum and globus pallidus. The striatum is composed of the caudate nucleus, putamen, and nucleus accumbens. The caudate nucleus and putamen are separated by the internal capsule and are connected rostrally and ventrally by the nucleus accumbens. The globus pallidus is comprised of the external (GPe) and internal (GPi) segments. The subthalamic nucleus is located in the diencephalon and is located just below the thalamus. The substantia nigra is composed of the pars compacta (SNc) and pars reticulata (SNr). The substantia nigra is located between the red nucleus and the cerebellar peduncle of the ventral midbrain.

PD results from a loss of dopaminergic neurons in the substantia nigra pars compacta. Degeneration of the SNc reduces dopamine concentration in the striatum which have downstream consequences leading to bradykinesia and akinetic movements (Groenewegen, 2003).

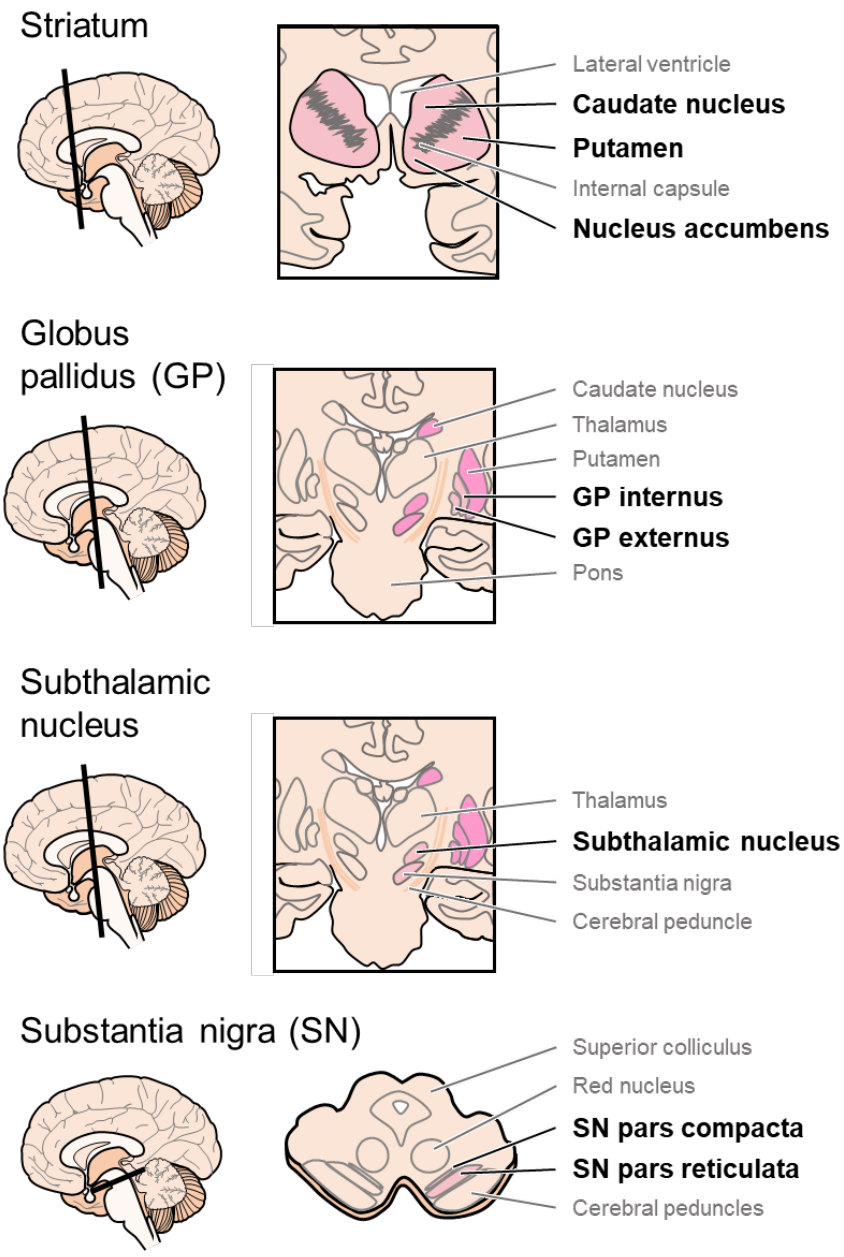

Figure 2-6. Anatomy of basal ganglia structures. Coronal sections in top three diagrams show the basal ganglia anatomical location. Transverse section in the bottom diagram show the midbrain and substantia nigra anatomy. Original image by Jacquelyn Sertic.

2.7 Proprioception in Parkinson's Disease

Conscious perception is impaired in PD

Parkinson's disease (PD) is a complex neurological disorder and has been associated with somatosensory deficits that adversely affect motor behavior (Elangovan et al., 2019; Konczak et al., 2009). As early as 1987, researchers have identified proprioceptive deficits in PD. Schneider and colleagues (1987) first showed that during passive movements, people with PD made significantly more errors in determining the direction of displacement (or if movement had even occurred) of the finger, wrist, and shoulder joints. Later, Klockgether and colleagues (1995) provided more evidence that passive proprioception is impaired in PD. Participants were shown a target position and, with vision occluded, had their hands passively moved towards the target position. Hypometria was consistently shown in the people with PD, as evidenced by undershooting the target position by 3 to 5 cm whereas controls undershot by only approximately 1 to 2 cm. At the turn of the century research groups started to test the impairment of position sense more systematically and specifically.

In a series of experiments, Zia and colleagues (2000) demonstrated that joint position sense is impaired in PD. Two paradigms were utilized: contralateral joint matching and psychophysics. During the contralateral joint matching experiment, one of the subject's elbows was moved from 90° of flexion to the target position (60° of flexion). The other limb (the test elbow) was passively moved to the matched target (between 51° to 69° with equal step distances) and the participant responded with which elbow was the more flexed limb. For all of the test angles combined, people with PD responded with 17% fewer correct responses than the healthy controls. In the psychophysical task, participants' reference arm was flexed from 90° to a position of 60° flexion and the comparison arm was flexed to a reference position of 54°, 57°, 60°, 63°, or 66°. This was a two-alternative forced-choice design, such that participants responded to which of the two limbs was more flexed. People with PD

demonstrated 80% and 50% larger Weber's ratios for the more and less affected arms, respectively, than the control counterparts. That is, people with PD had higher discrimination thresholds compared to controls.

More recently, research groups have employed psychophysical methods to demonstrate that all modalities of the conscious perception of proprioception – position sense, motion sense, and the sense of heaviness – are impaired in PD. Position sense acuity can be quantified through detection or discrimination thresholds. Detection thresholds, as measured by the magnitude of displacement before detection of movement of the limb, was two times larger in the parkinsonian group than in controls (Maschke et al., 2003). That is, controls could perceive that their elbow had been moved after 1° whereas people with PD required 2° of displacement. Further, relative to controls, people with PD demonstrated impairments in the detection of finger displacements at 0.2° and 0.4° movement and in knowing the direction of the movement (Putzki et al., 2006). At present, the literature lacks empirical evidence identifying the extent to which position sense discrimination thresholds are impaired in PD. Evidence for motion sense impairment was shown using a passive motion apparatus which passively moved the elbow until participants indicated perception of limb movement (Konczak et al., 2007). Angular velocity of movements were randomized between 0.15 – 1.65 deg/s, with increasing steps of 0.15 deg/s. People with PD required 92-166% more time to detect the displacement than controls. Haptic function has also been reported to be impaired, as people with PD demonstrated 103% elevated haptic thresholds relative to older adult controls (Konczak et al., 2012).

Upper extremity function is important for activities of daily living such as reaching for and grasping items. Perhaps this is the reason that most previous studies focused on upper limb function. Lower extremity proprioception is critical for the control of balance and gait. Yet, there is little empirical information about the role of lower extremity proprioception in people with PD (Khudados et al., 1999; Ribeiro Artigas et al., 2016; Teasdale et al., 2017). The experiments indicate a

proprioceptive-motor deficit at the knee (Ribeiro Artigas et al., 2016) and ankle (Teasdale et al., 2017) and Khudados and colleagues (1999) describe proprioceptive processing deficits using a target reproduction task at the ankle. All three studies conduct their assessments while participants with PD are in the medicated state. At present, it is unclear the effect of anti-parkinsonian medication on position sense (see ***section Dopaminergic medication on the proprioceptive sense in PD*** for a more detailed discussion). Moreover, it remains unclear the extent of the deficit of pure ankle position sense function in Parkinson's disease.

The proprioceptive sense is trainable in Parkinson's disease

Indeed, both people with Parkinson's disease and healthy older adults have demonstrated an ability to enhance their proprioceptive function (Elangovan et al., 2018). Using a wrist-robotic device, people with PD and age-matched controls rotated the device in such a way that would move a virtual ball into a virtual hole on a screen. Successful trials resulted in more difficult game parameters, which required participants to have finer proprioceptive acuity to successfully move the ball to the hole. In less than one hour of training, people with PD improved their wrist joint proprioceptive acuity by 28%. Notably, all participants with PD in this study demonstrated proprioceptive improvements. Control participants (mean age: 67 +/- 6.5 years) also showed improvements at the group level. As such, proprioceptive interventions specifically targeting joints can quickly improve proprioceptive acuity in both people with PD and aging adults.

Notably, there is an absence of evidence that whole-body movement interventions improve the pure proprioceptive sense. In contrast, whole-body interventions have been shown to improve proprioceptive-motor function. People with PD have demonstrated improvements in active repositioning of the wrist and knee joints after participating in the Lee Silvermann Voice Treatment-BIG (LSVT-BIG) therapy (Peterka et al., 2020) and a trampoline rebound therapy

(Daneshvar et al., 2019), respectively. In both studies, the proprioceptive outcome measures that demonstrated improvements involved the motor system. Importantly, passive wrist joint repositioning error did not improve as a function of the LSVT-BIG therapy. Still, these studies show that proprioceptive-motor performance can be trained through multi-week whole-body interventions, which does clinically benefit the individual. It is important to note that whole-body movement interventions require much greater dosage than joint specific training to elicit proprioceptive improvements (Winter et al., 2022). The LSVT-BIG therapy was conducted over four weeks and the trampoline study for eight weeks. Perhaps whole-body exercise should be reframed as a lifestyle choice which can improve proprioceptive-motor function and joint specific interventions should be performed to target joint-specific somatosensory impairments.

Neurophysiological evidence for impaired processing of proprioceptive afferents in Parkinson's disease

Behavioral proprioceptive assessments show abnormalities in the perception of body and limb position in PD. Evidence does not suggest that such proprioceptive abnormalities are attributed to peripheral dysfunction. Some evidence suggests PD-related muscle spindle abnormalities (e.g., enlargements in the diffuse endings, Saito et al., 1978) that are unrelated to the normal aging process. However, muscle spindle afferents to the primary somatosensory cortex (Seiss et al., 2003) and the monosynaptic stretch reflex have normal latencies (Lee & Tatton, 1975; Tatton & Lee, 1975), which is consistent with normal mechanoreceptor and afferent sensory pathway function.

Proprioceptive deficits in PD are thought to be attributed to impairment in central processing of proprioceptive information (Khudados et al., 1999; Rickards & Cody, 1997; Seiss et al., 2003). Vibrating the muscles is an experimental method of misinforming the central nervous system of the actual kinematics of movement and can be used to demonstrate central integrity of proprioceptive feedback in PD. In studies employing this method, participants move a joint to a target angle

without visual feedback. Vibratory stimulation of healthy controls elicits large undershooting of target angles, whereas people with PD exhibit only minor undershooting of the target (Khudados et al., 1999; Rickards & Cody, 1997), indicating impaired processing of proprioceptive afferents in PD. Seiss and colleagues (2002) attempted to temporally located the processing deficits. They measured the latencies of muscle spindle afferents at the onset of flexion and extension movements of the finger joint and found normal latencies in early cortical processing (N90) yet abnormalities in the longer latency processing of proprioceptive afferents from finger movement. Collectively, these studies suggest that in PD, peripheral function is intact whereas proprioceptive dysfunction arises from abnormalities in central processing.

Dopaminergic medication on the proprioceptive sense in PD

Dopaminergic medications are prescribed to treat the motor symptoms of PD. They are extremely effective at reducing rigidity and bradykinesia but less effective at treating tremor or postural instability in some people with PD. Dopaminergic medication takes approximately 30-60 minutes after ingestion to become active and, at least in early disease state, the effects last upwards of 4 to 5 hours.

The effect of anti-parkinsonian medication on somatosensation is not fully understood. There is some evidence that dopaminergic medication diminishes somatosensory function (O'Suilleabhain, 2001; Wright et al., 2010; Mongeon et al., 2009). For example, people with PD in the on-state were found to exhibit an average of 31% more errors in discriminating the more flexed elbow from the less flexed elbow and 26% lower score in passively matching the angle of both elbows (O'Suilleabhain, 2001). A study employing a psychophysical paradigm reported contrasting evidence, showing that dopaminergic medication improved haptic sensitivity (Li et al., 2010). There is no evidence that the dosage of medication is related to proprioceptive function (Maschke et al., 2003) or heaviness perception (Maschke et al., 2006).

Deep brain stimulation (DBS) may offer promising results for somatosensory improvements. Yet, there is only one study to report on this effect warranting further evidence. In the study by Aman and colleagues (2014), controls and people with PD were assessed for their ability to perceive differences in the haptic stimuli. Participants tactically probed two blocks and indicated the block that was perceived to be taller. The discrimination threshold at which the block heights were correctly perceived with 75% accuracy was the outcome measure. People with PD were in the off state of anti-parkinsonian medication and were assessed both off and on state of DBS. The researchers found a scaling effect of the DBS, with controls having the highest haptic sensitivity, followed by DBS-ON and finally DBS-OFF in the more affected arm (Aman et al., 2014). Haptic assessments in the off-state DBS were performed with a minimum of 20 minutes between state changes. However, the washout of beneficial effects from DBS is highly variable, with some people requiring upwards of one hour to lose the benefit for bradykinesia (Cooper et al., 2013). Further studies should elucidate the washout effects of somatosensory gain from DBS and replicate the study by Aman and colleagues.

2.8 Rigidity in Parkinson's Disease

Rigidity is form of hypertonia, or upregulated muscle tone, and is a cardinal motor symptom of Parkinson's disease. Parkinsonian rigidity is classically defined as the uniform, velocity-independent resistance to passive motion imposed on a muscle (Fung et al., 2000). Emerging evidence implicates a role of velocity in the magnitude of muscle activity after passive stretch (Asci et al., 2023). Muscle activity in response to passive stretching suggests that proprioceptive feedback from the stretched muscles plays a role in increasing muscle activity to oppose the stretch (Linn-Evans et al., 2020). Muscle spindles normally oppose muscle stretch through activation of the agonist muscle group via the monosynaptic pathway and reciprocally inhibiting the antagonist muscles through 1a inhibitory interneurons. However, in Parkinsonian rigidity, presynaptic inhibition of the 1a

inhibitory interneurons causes the antagonist muscles to contract. This co-contraction of both the agonist and antagonist muscles during muscle stretch may lead to the clinical manifestation of parkinsonian rigidity. Increased sensitivity of the fusimotor system may also lead to the increases in stiffness.

The severity of rigidity is strongly correlated with disease severity and thus rigidity plays a crucial role in diagnosis and treatment regimens. Rigidity contributes to a decreased range of motion (Cano-de-la-Cuerda et al., 2020), slowed movement (Kwon et al., 2014) and postural instability (Bartolić et al., 2005). Elevated levels of neck and trunk tone have been associated with elevated Timed Up and Go and Get Up and Go times, respectively (Cano-de-la-Cuerda et al., 2017; Franzén et al., 2009). The Timed Up and Go test is an updated version of the Get Up and Go test and is an accurate predictor of falls in people with PD (Nocera et al., 2013). Furthermore, neck muscle tone was also associated with other measures of functional mobility. In the study by Franzén and colleagues (2009), axial muscle tone was measured by fixating the head, trunk, and hips to an earth-fixed frame and the lower body segments were rotated by a platform. Neck tone accounted for a large variability in performance of the Figure of Eight test, in which participants walked in a figure eight as fast as possible. Performance in the functional reach test and Berg Balance Scale were influenced by the neck and trunk tone in participants with PD on medication. MDS-UPDRS section III lower extremity rigidity subscores have also been associated fall history in people with PD, such people who were fallers had significantly greater lower extremity rigidity than those who were not fallers (McKay et al., 2019). Together these studies indicate that rigidity is associated with postural instability. If the processing of proprioceptive afferents are involved in parkinsonian rigidity, one may theorize that the relationship of rigidity to postural instability is driven by proprioceptive dysfunction.

Pathophysiological mechanisms of rigidity

The pathophysiological mechanism underlying parkinsonian rigidity is presently unclear. The primary hypothesis implicates a role of the exaggerated long-latency stretch reflex in the phenomenon of rigidity. The long-latency reflex response is a measurement of the magnitude and duration of muscle activity responding to a mechanical perturbation. That is, stretching the muscle will cause the muscle spindles to send afferent signals through the dorsal column medial lemniscus pathway to the somatosensory cortex. These proprioceptive afferents are processed and shared with the motor cortex. The motor cortex sends an efferent volley to the agonist muscle to contract. The magnitude of the contraction scales with the task goal (*as shown in Section 2.2*). That is, without opposition to the mechanical perturbation, the long-latency stretch reflex response should be small. In contrast, active resistance to the mechanical perturbation would lead to larger amplitude long-latency stretch reflexes. When this experiment is performed in PD, the long-latency reflex is exaggerated in amplitude and duration and does not scale with the task (Lee & Tatton, 1975). These abnormalities have been correlated with the clinical impression of rigidity (Berardelli et al., 1983; Rothwell et al., 1983; Tatton & Lee, 1975). It has been suggested that this transcortical reflex may contribute to enhanced fusimotor drive, which increases muscle spindle responsiveness and resistance during passive movements (Bologna & Paparella, 2020).

Degeneration of brainstem nuclei which function to modulate muscle tone may play a role in the pathophysiology of rigidity (Boeve et al., 2007). The pedunculopontine nucleus (PPN) reticular formation, locus coeruleus and raphe nucleus all play a role in modulating muscle tone and have been shown to contain alpha synucleopathies in people with PD (Braak et al., 2006). However, there is no direct empirical evidence linking brainstem degeneration with rigidity.

Clinically quantifying parkinsonian rigidity

Parkinsonian rigidity is clinically tested by passively moving the limbs through the full range of motion while the person is relaxed. Stiffness is objectively rated on a scale of 0 to 4, based on the section 3.3 of the Movement Disorders Society – Unified Parkinson's Disease Rating Scale part III (MDS-UPDRS-III, Goetz et al., 2008). A score of 0 (normal) indicates no rigidity; 1 (slight) indicates that rigidity was only detected with an activation maneuver; 2 (mild) indicates rigidity was detected without the activation maneuver, but the full range of motion is easily achieved; 3 (moderate) indicates that rigidity was detected without the activation maneuver, but the full range of motion is achieved with effort; and 4 (severe) indicates that rigidity was detected without the activation maneuver and the full range of motion was not achieved (*see **Appendix B** for the MDS-UPDRS section 3.3 instructions*).

Stiffness is enhanced with an activation maneuver, which is voluntary movement in a contralateral limb. Clinicians use this technique to detect rigidity in people with early-stage PD. Activation maneuvers are typically rhythmic movements such as finger tapping. For example, when testing rigidity in right forearm, voluntary tapping of the left hand can increase right forearm stiffness. The Froment maneuver is an older example of an activation maneuver in which person "swings the arm around like a windmill" (Broussolle et al., 2007). The MDS-UPDRS clinical rating scale encourages using finger tapping or fist opening and closing as the activation maneuver. Activation maneuvers can also take the form of isometric voluntary muscle contractions such as fist clenching or the Jendrassik Maneuver. Indeed, neurologically healthy individuals of all ages can exhibit stiffness when employing an activation maneuvers (Camarda et al., 2021). Clinical assessments of rigidity are quick and inexpensive. A limitation is that the score of rigidity is ordinal, binning the severity into only five categories.

Chapter 3. Study 1: A Physically Active Lifestyle Can Protect Against Age-Related Decline in Ankle Proprioception

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3.1 Introduction

Empirical evidence indicates that ankle proprioception declines with age (Deshpande et al., 2003; Ko et al., 2015; Westlake & Culham, 2006) and continues to decline in very old adulthood (75 – 90 years, Yang et al., 2019). For example, when detecting passive ankle motion, adults over the age of 60 years exhibited thresholds that were 2.4 times higher than those of younger adults (Deshpande et al., 2003; Westlake & Culham, 2006). Older adults also showed larger errors in passively reproducing target ankle positions than younger counterparts (Westlake & Culham, 2006). Moreover, very old adults (aged 75 – 90 years) were significantly impaired in their ability to correctly identify ankle inversion positions relative to younger groups (Yang et al., 2019). There is comprehensive clinical and scientific evidence that lower extremity proprioceptive dysfunction is associated with poorer standing balance and gait (Kars et al., 2009; Nardone et al., 2014) and a higher risk of falling in older adulthood (Lord et al., 1991, 1999). At present, there is inconclusive evidence that physical activity positively influences ankle proprioceptive function in aging.

A recent study reported a difference in ankle proprioception scores between inactive, moderately active, and highly active older women (Yang et al., 2022).

That is, the more active the women, the better their ability to perceive active ankle inversion position relative to the less active groups. The proprioceptive task utilized a standing, active movement task in which the participant actively inverted their ankle to one of four target locations (10°, 12°, 14°, 16°) and then indicated which of the four targets the ankle was displaced. Similar findings implicating a beneficial effect of physical activity in aging have been shown at the hip (Pickard et al., 2003) and knee (Ribeiro & Oliveira, 2010; Tsang & Hui-Chan, 2003). These findings align with research showing that practice can improve proprioceptive and associated motor function in older adults (Chittrakul et al., 2020; Winter et al., 2022).

The present study seeks to substantiate current initial evidence that physical activity can slow age-related proprioceptive decline. This study employed a sensory psychophysics paradigm to investigate ankle position sense acuity. When perceiving a difference between two stimuli, perceptual bias increases with stimulus intensity – a relationship known as Weber's law (Bullough et al., 2023). To understand how conscious ankle proprioception scales with the magnitude of the ankle displacement, this study examined ankle position sense acuity at two different standards of 15° or 25° plantarflexion from the neutral foot position.

Assuming that physical activity has a beneficial effect on proprioception, we hypothesized that there will be no differences in ankle position sense bias and precision between young adults and physically active middle-aged and older adults. Based on our previous work, it was expected that JND threshold will range between 1.2° – 3.6° in the young adults (Mahnan et al., 2020). We further hypothesized that all groups will adhere to Weber's law, which means that JND thresholds at the 15° reference will be smaller than at the 25° reference position. Thus, would be expect that Weber's law is also valid for the ankle proprioception of aging populations.

3.2 Methods

Participants

Fourteen younger adults (age range 19 – 29 years, mean: 22.6 ± 2.8 years, F: 9), 28 middle-aged adults (age range: 50 – 64 years, mean: 58.4 ± 4.22 years, F: 14), and 29 older adults (age range: 65 – 80 years, mean: 71.1 ± 4.17 years, F: 19) volunteered for this study. Recruited participants did not meet any of the following exclusion criteria: (1) clinical diagnosis with a central or peripheral neurological pathology, (2) exposure to chemotherapy, (3) lower extremity fracture or luxation within the last six months, (4) lower limb amputation, knee replacement, or pathology leading to pain, or (5) were physically inactive as assessed through a modified LASA Physical Activity Questionnaire, which has been shown to be valid and reliable (Stel et al., 2004). All participants were physically active by walking, running, doing yoga, or playing one or more sports. We attempted to control for the effect of damaged bone, tendon, and ligament by setting the exclusion timeline for injuries at 6 months, as that is greater than the average time to heal fractures, tendon tears, and ligament injuries (Frank et al., 1983; Hope & Saxby, 2007; Karladani et al., 2001). Prior to testing, all participants provided information on prior lower limb injury. Broken bones, tendon, or ligament injuries to the shank, ankle, or foot were identified and separated into three groups based on the time since the injury: (1) *no reported* injury, (2) *no recent*: injuries that occurred longer than 2 years prior, and (3) *recent*: injuries that occurred within the last two years. In total, 52 participants reported *no* injuries, 11 had *no recent* injuries, and 5 presented with *recent* injuries. Written informed consent was obtained prior to participation in the study. The experimental protocol was approved by the University of Minnesota Institutional Review Board (STUDY00013044).

Testing Apparatus

We use the Ankle Proprioceptive Acuity System (APAS) to measure ankle position sense acuity (**Figure 3-1**). The APAS is a one degree-of-freedom

passive motion apparatus that rotates the ankle about the medio-lateral axis (dorsiflexion-plantarflexion). Participants placed their foot on the platform, with the lateral malleolus of the tibia aligned with the center of rotation of the platform. A Velcro strap secured the foot to the platform during testing. Using a handle, the experimenter rotated the foot from a start to a desired target position. To assure precise repeated displacement, metal pins were inserted into a pegboard representing the start and target positions. The pegboard has holes spaced 0.1° apart, meaning that displacements have a resolution of 0.1 degrees.

Figure 3-1. Ankle proprioceptive acuity system (APAS). (Top) Experimental set up. The examiner adjusts the leg rest and footrest to align the ankle with the system center of rotation before starting the testing procedure. **(Bottom)** A subset of holes in the pegboard. Each hole in the vertical direction indicates as 0.1-degree difference in angle and in horizontal direction illustrates a 1-degree difference. Stoppers are inserted to a specific hole to identify the initial and target locations of ankle position.

Procedure

The feasibility of measuring ankle position sense acuity using this system has been established (Mahnan et al., 2020) and yielded data within the range of the studies by Westlake and Culham (2006) and Deshpande (2003). During ankle position sense acuity testing, participants sat in an upright position with their foot resting on the APAS platform **(Figure 3-1)**. The shank was supported by a leg rest. Thus, testing occurred in an unweighted testing position which isolated the sensory experience from motor function. Participants' vision was occluded during testing. The experimenter used the system handle to manually rotate the foot platform in dorsiflexion and plantarflexion directions at approximately 6°/s.

One trial consisted of plantarflexing the ankle to two target positions **(Figure 1-1A)**. First, the experimenter moved the ankle from the initial neutral position (90°) to one of two reference positions (15° or 25° of plantarflexion) and held this position for two seconds. The foot was then moved back to the neutral position. Second, the ankle was plantarflexed from the neutral position to the comparison position, held for two seconds and then returned to neutral. We applied a forced-choice psychophysical paradigm requiring participants to verbally indicated which position, the first or the second, was further from the neutral position. If the participant lost focus during the testing, the trial was repeated. Knowledge of results was not provided to the participant which implies that learning could not occur.

After each trial, the comparison position for the next trial was determined using the Bayesian inference-based adaptive psi-marginal algorithm (Prins, 2013) based on the prior the angular difference between the reference and comparison position and the correctness of the participant's verbal response (for an exemplar response sequence, see **Figure 1-1B)**. Both ankles were tested at each reference position. Each test was composed of 25 trials. The order of presenting reference and comparison positions were randomized during testing. Similarly, the order of reference position and foot tested were randomized across all

participants. Breaks were offered to participants twice during and between tests to mitigate fatigue. Participants could take additional breaks upon request. During testing, participants did not have their shoes on but could choose to wear socks.

Measurements

Ankle position sense acuity outcome measures were the JND threshold and Uncertainty Area (**Figure 1-1C**). According to Weber's law, the just-noticeable-difference between two stimuli is not an absolute value, but rather a relative difference that is proportional to the magnitude of the original stimulus. That is, the larger the initial stimulus, the larger the change required to perceive a difference. The Weber fraction is the ratio of the JND threshold to the intensity stimuli. Weber's fraction (k) was calculated as the ratio of the JND threshold and the corresponding reference position,

$$k = \frac{JND\ threshold}{reference\ position} \quad (1)$$

Data Analysis

All variables were tested for normality using the Shapiro-Wilk's test of normality. JND thresholds were normally distributed and UA values were not normally distributed. For consistency, non-parametric Kruskal Wallis H-tests were performed for both outcome measures to determine group differences. Pairwise comparisons were performed as necessary using Dunn's (1964) procedure with Bonferroni correction for multiple comparisons. To investigate differences between reference positions Wilcoxon signed-ranked tests were performed on the JND threshold for all groups. A chi-square test of homogeneity was performed on the proportion of participants who adhered to Weber's law. Effect size was computed using eta squared computations for the Kruskal Wallis H-test and using rank-biserial correlation coefficient for the Wilcoxon signed-rank tests. Outliers in each dataset were identified as below the 5th percentile or larger than the 95th percentile and were subsequently removed from further analysis. All

statistical analyses were conducted using R software version 4.2.2 (R Core Team, 2022).

3.3 Results

In a first analysis, we investigated if the acuity outcome measures yielded differences between the left and right ankle. Ankle position sense acuity between left and right foot were not statistically significantly different at either the 15° or 25° reference position for JND threshold ($t_{(55)}$ = 0.90, p = 0.37 and $t_{(56)}$ = 1.25, p = 0.22, respectively) nor Uncertainty Area ($t_{(56)}$ = 1.45, p = 0.15 and $t_{(56)}$ = 1.12, p = 0.27, respectively). Subsequently, the data were collapsed and results are reported for the combined left and right ankles. In addition, there were no sex differences in any of the two position sense acuity measures at the 15° reference position nor the 25° reference position for JND threshold ($t_{(98)}$ = 0.26, p = 0.80 and $t_{(113)}$ = 0.51, p = 0.61, respectively) nor Uncertainty area ($t_{(101)}$ = 0.11, p = 0.91 and $t_{(118)}$ = 0.43, p = 0.67, respectively).

Aim 1: Age-related differences in JND threshold

Figure 3-2 illustrates the distribution of the JND thresholds for each group at both reference positions. The majority of JND threshold values of middle-aged and older adults were within the range of the young adult cohort. At the 15° reference, the JND thresholds of 74% of the middle-aged and 71% of the older adults were within the range of the young adult group. Similarly at the 25° reference, the JND thresholds of all the middle-aged and older adults were within or below the range of the young adult group.

At the 15° reference, median JND thresholds were 1.3°, 1.7°, and 1.6° for the young, middle-aged and older adults, which yielded statistically significant differences ($\chi^2_{(2)}$ = 7.953, p = 0.019), but with a small effect size (η^2 = 0.048). Subsequent post-hoc analyses revealed that median JND thresholds for the young adults were lower when compared to both the middle-aged (z = 2.53, p = 0.034) and older adult (z = 2.63, p = 0.025) groups (**Figure 3-2A, Table 3-1**).

There were no group differences between middle-aged and older adults (z = 0.11, p = 0.91). At the 25° reference, there were no statistical differences of JND threshold between age groups ($\chi^2_{(2)}$ = 2.434, p = 0.23, η^2 = 0.004; **Figure 3-2B, Table 3-1**). To appreciate these data, consider that the range of JND threshold for the young adults was 0.7° to 2.0°. That is, the smallest difference from 15° that could be perceived with 75% accuracy was 14.3° and the largest was 13°.

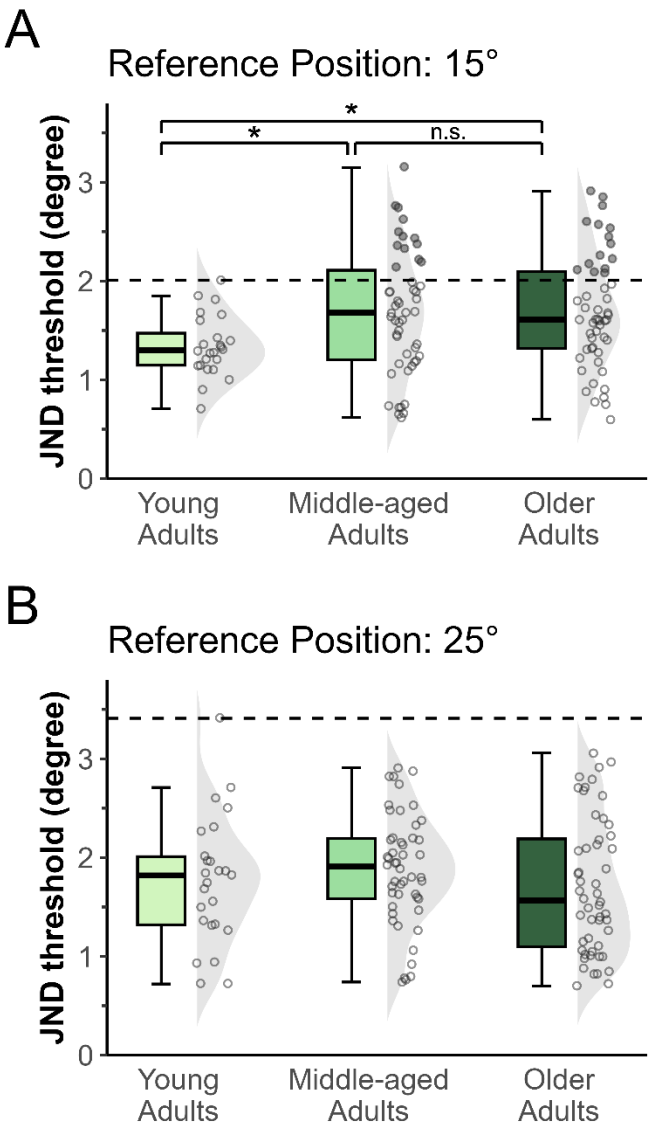

Figure 3-2. JND ankle position sense threshold across age groups. (A) JND threshold data for the 15° reference position. **(B)** JND threshold data for the 25° reference position. The lower end of the box represents the 25th percentile, the line within the box represents the median, and the top of the box represents the 75th percentile. The whiskers indicate 1.5 times the interquartile

range of the respective distribution. Each data point within the half-violin plot represents an individual threshold value of the left and right foot of each participant. Closed circles represent middle-aged and older individuals above range of the young adults. At the 15° reference, the young adult group was significantly smaller than both middle-aged and older adult groups (*p < 0.05). However, this effect is small (η^2 = 0.048) and 74% of middle-aged and 71% of older adults were within the range of the young adult JND threshold. At the 25° reference, all of participants for both middle-aged and older adults were within the range of the young adult JND threshold.

Aim 1: Age-related differences in Uncertainty Area

Figure 3-3 illustrates the distribution of the Uncertainty Area values for each age group. Most middle-aged and older adults demonstrated Uncertainty Area values within or below the range of the young adults. Specifically, 78% of middle-aged and 85% of older adults were within or below the range of the young-adult group at the 15° reference and 88% of middle-aged and 92% of older adults within or below the range at the 25° reference. Median UA for the young adults was 1.1° at the 15° reference meaning that the random error of responses was within 1.1° about the respective JND threshold. That is, for a JND threshold of 1.3°, one could correctly perceive their ankle position 60% of the time at 0.8° and 90% of the time at 1.9°. Middle-aged and older adult UA was 1.4° and 1.1°, respectively, at the 15° reference (see **Figure 3-3A** and **B** for data distributions). Median UA values at the 25° reference were 1.6°, 1.3°, and 1.1° for the young, middle-aged, and older adults, respectively (see **Table 3-1**). There were no statistically significant group differences in UA at either reference position (15° reference: $\chi^2_{(2)}$ = 2.858, p = 0.240, η^2 = 0.007; 25° reference: $\chi^2_{(2)}$ = 2.868, p = 0.248, η^2 = 0.007, **Figure 3-3**).

Influence of lower limb injury on JND threshold

We performed an ancillary analysis to determine whether a history of lower extremity injury influenced the magnitude of the observed JND thresholds. Distributions of JND thresholds were largely overlapping between no reported injury, no recent injury, and recent injuries. That is, neither recent nor older lower limb injuries could explain the group differences between young adults and the middle and older adult groups.

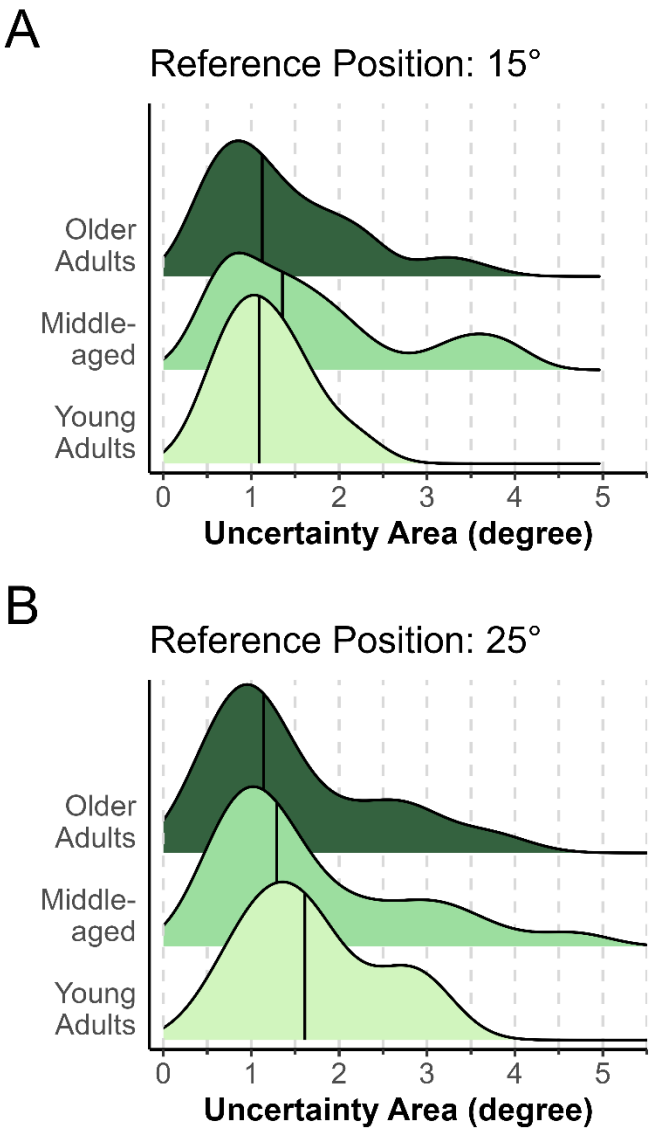

Figure 3-3. Uncertainty area of ankle position sense across age groups. (A) Density plots of UA at reference position 15°. **(B)** Density plots of UA at reference position 25°. The vertical black line in each density plot represents the group median. Medians between groups were not statistically different.

Age-related changes in adherence to Weber's Law

Young and middle-aged groups showed a median increase in JND threshold from the 15° reference to the 25° reference (**Table 3-1**). Specifically, median JND threshold showed a statistically significant increase from 1.3° to 1.8° for young adults (z = 193, p = 0.003, r = 0.59), and from 1.7° to 1.9° for middle-aged adults

(z = 707.5, p = 0.016, r = 0.32). In contrast, older adults demonstrate the same median JND threshold between the two reference positions (1.6°, z = 518.5, p = 0.591). After removing outlier values, some participant pairs were not complete resulting in 21/28 young adult pairs, 45/56 middle-aged pairs, and 46/58 older adult pairs. Based on these data, 81% of young adults, 67% of middle-aged, and 52% of older adults demonstrated an increase in JND threshold consistent with Weber's law (**Figure 3-4A**). The proportion of participants who adhered to Weber's law was not statistically significantly different between groups ($\chi^2_{(2)}$ = 5.49, p = 0.064). For participants who adhered to Weber's law, median JND threshold increased from the 15° to the 25° reference by 1.3° to 1.9° (+0.6°) for young adults, 1.3° to 2° (+0.7°) for middle-aged adults, and from 1.6° to 2.1° (+0.5°) for older adults (see left panel in **Figure 3-4B**). In contrast, those participants who did not adhere to Weber's law demonstrated a decrease in the median JND threshold from the 15° to the 25° reference of 1.5° to 1.1° (-0.4°) for young adults, 2.2° to 1.6° (-0.6°) for middle-aged adults, and from 1.9° to 1.4° (-0.5°) for the older adults (see right panel in **Figure 3-4B**).

Table 3-1. Descriptive statistics of JND threshold and UA for each age group.

	Reference Position	**JND threshold** median (range)	**Uncertainty Area** median (range)
Young Adults	15°	1.3° (0.7 – 2.0°)	1.1° (0.5 – 2.2°)
	25°	1.8° (0.7 – 3.4°)	1.6° (0.6 – 3.1°)
Middle-aged Adults	15°	1.7° (0.6 – 3.1°)	1.4° (0.4 – 4.0°)
	25°	1.9° (0.7 – 2.9°)	1.3° (0.5 – 4.7°)
Older Adults	15°	1.6° (0.6 – 2.9°)	1.1° (0.4 – 3.6°)
	25°	1.6° (0.7 – 3.1°)	1.1° (0.4 – 4.0°)

We subsequently calculated the Weber fraction, k, for age groups at both reference positions. Of the participants adhering to Weber's law, the median Weber fraction was between 0.8 – 0.11 at the 15° reference and between 0.7 – 0.8 at the 25° reference. Participants who violated Weber's law showed median

Weber fractions of 0.10 – 0.15 at the 15° reference and between 0.4 – 0.7 for the 25° reference.

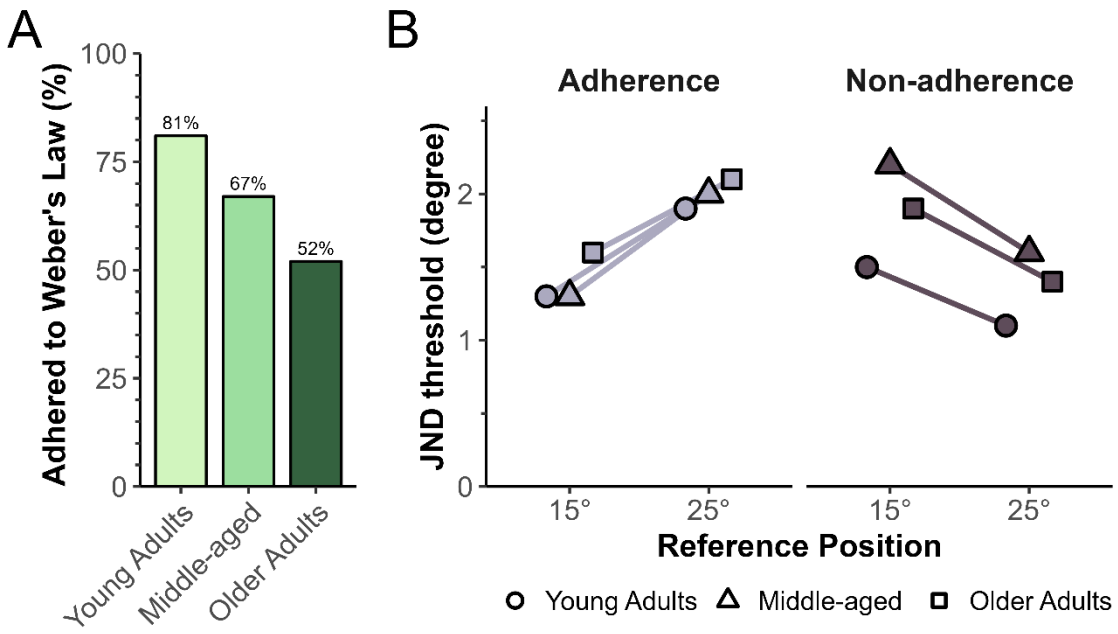

Figure 3-4. Adherence to Weber's Law. (A) Percentage of each group that adhered to Weber's law. That is, the percentage of each group that demonstrated an increase in JND threshold from the 15° to the 25° reference. **(B)** Median JND threshold for age groups across reference positions and separated based on adherence (left) and non-adherence (right) to Weber's law.

3.4 Discussion

This study examined the influence of physical activity and aging on proprioceptive function. This is the first study to report systematic data on ankle position sense acuity in physically active adults relative to younger counterparts. This study applied a psychophysical paradigm that yielded objective measures of ankle position sense bias and precision in young, middle-aged, and older adults. The main findings of the study are: First, ankle position sense acuity in healthy active aging is not characterized by a systematic decrease for most aging adults. Second, there was a decline in the percentage of participants whose perceptual

responses of ankle position adhered to Weber's law, as evidenced by an increase in JND threshold with increasing intensity in movement size.

Aging associated changes in proprioception

The normal aging process is associated with structural and functional abnormalities of mechanoreceptors. Age-related decrements in muscle spindles include an increase in spindle capsular thickness (Liu et al., 2005; Swash & Fox, 1972), a decline in the total number of intrafusal bag and chain fibers within the spindle (Liu et al., 2005), and decreased discharge frequency during both static and dynamic movements (Miwa et al., 1995). Moreover, there are changes in the motor innervation of the muscle spindles (Swash & Fox, 1972), which may have downstream consequences on the sensitivity of the muscle spindle as gamma motor neuron innervation is required to keep the muscle spindle taut during muscle shortening. Notably, the age-related decline in mechanoreceptor density has also been reported for Meissner's corpuscles, Merkel's cells (García-Piqueras et al., 2019), Ruffini endings, Pacini receptors, and Golgi tendon organ receptors (Aydoğ et al., 2006).

However, there is some evidence to suggest that these morphological changes may be muscle specific. Kararizou and colleagues (2005) found an age-related decline in the muscle spindle diameter and the total number of intrafusal fibers for the deltoid but did not observe such decline in the biceps brachii or quadriceps femoris muscles. Moreover, Boyd-Clark and colleagues (2002) did not observe any change in muscle spindle density of the longus colli or multifidus muscles with aging.

A physically active lifestyle can protect against age-related decline in ankle proprioception

There is solid empirical evidence showing that a multitude of interventions, including limb-specific training or whole-body activities, improve both somatosensory and motor function (Winter et al., 2022). Recently, a randomized controlled trial demonstrated that older adults (65 years or older) improved both

knee joint proprioceptive function and balance after 12 weeks of whole-body strength, reaction time, and balance training (Chittrakul et al., 2020). Participants exercised three days per week and for 60 minutes each session. Older adults in the intervention group significantly reduced their active knee joint position matching errors and sway paths after the 12 weeks and retained these benefits at the 24-week follow up. In addition, at those time points, the intervention group had significantly better proprioception and balance than the control group. These findings indicate that three days per week of 60-minute whole-body exercise is sufficient to improve both somatosensory and motor function.

Previous research reported an age-related decline in joint proprioception (Deshpande et al., 2003; Ko et al., 2015; Verschueren et al., 2002; Westlake & Culham, 2006; Yang et al., 2019). However, other research demonstrated that a physically active lifestyle can protect against proprioceptive decline at the hip, knee, and ankle joint (Petrella et al., 1997; Pickard et al., 2003; Ribeiro & Oliveira, 2010; Tsang & Hui-Chan, 2003; Yang et al., 2022). Older sedentary adults exhibited poorer joint perception relative to active older adults (Petrella et al., 1997; Ribeiro & Oliveira, 2010; Yang et al., 2022). Yet, active older adults had similar hip joint repositioning errors as young adults (Pickard et al., 2003).

The present study showed that ankle position sense does not systematically change from young to older adulthood when adults are physically active in their later parts of life. The variability in the middle-aged and older adult groups is not explained by lower extremity injury history. The middle-aged and older adult groups in the present study were active for an average of 8.7 hours per week and participated in outside walking, running, biking, yoga or playing at least one sport recreationally.

Adherence to Weber's law declines with aging

Weber (1834) formulated a psychophysical law stating that the minimum perceivable difference between two stimuli is proportional to the magnitude of the reference stimulus. For the present study, Weber's law implies that JND

thresholds at the smaller reference (15°) should be smaller than thresholds at the larger reference (25°). This study found that the percentage of participants whose perception followed this law declined from young to middle-aged to older adulthood (see **Figure 3-4A**). Participants with adherence to Weber's law demonstrated Weber fractions similar to those previously reported at the ankle (Huang et al., 2023).

There was a subset of participants in each group who violated Weber's law by demonstrating larger JND thresholds at the smaller displacement relative to the larger amplitude displacement. Violations of Weber's law has also been reported in other sensory modalities (Carriot et al., 2021). A plausible explanation for the present findings may reside in ankle joint range of motion. Perhaps those who violated the law have smaller ankle range of plantarflexion motion than those who adhered to the law. Muscle spindles are the primary source of proprioceptive information within the intermediate range of motion and Ruffini endings are stimulated when the joint is deformed (Grigg & Hoffman, 1982). Moving the ankle closer to the end range of motion would provide a larger population of proprioceptive mechanoreceptors to be activated and subsequently provide a stronger signal. This is supported by a study assessing shoulder proprioceptive acuity, in which position sense acuity was higher when the shoulder was at the near-end range of motion relative to the mid-range of motion (Janwantanakul et al., 2001). In the present study, the 25° movement is closer to the end range of motion, particularly if the range of motion is relatively smaller, and the additional somatosensory inputs may contribute to the lower perceptual bias. There is evidence for an age-related decline of ankle joint range of motion (Soucie et al., 2011) which may explain the increasing proportion of participants in the middle-aged and older adult groups who violated the law. However, this is merely speculative as ankle joint range of motion was not measured in the present study.

Limitations

A limitation of this study concerns the lack of a sedentary older adult group. However, based on a recent finding showing that active older women have higher ankle inversion acuity relative to sedentary older women (Yang et al., 2022), it seems plausible that one would have delineated differences based on physical activity level in this study as well.

Chapter 4. Study Two: Ankle Proprioception in Parkinson's disease

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4.1 Introduction

Parkinson's disease (PD) is a progressive neurodegenerative disease that affects brainstem nuclei and alters processing within somatosensory and motor networks. As a result, people with PD exhibit a range of somatosensory and motor symptoms, such as impaired limb proprioception (Konczak et al., 2009) and increased muscle rigidity (Goetz, 2011). Lower extremity proprioception is critical for the control of balance and gait. Yet, there is little empirical information quantifying the deficit in PD. Previous reports have employed active movement proprioceptive assessments and have described proprioceptive-motor deficits at the knee (Ribeiro Artigas et al., 2016) and ankle (Teasdale et al., 2017). Proprioceptive assessments which require muscle activation do not purely measure proprioception as proprioceptive function cannot be disentangled from motor function (Elangovan et al., 2014).

Increased muscle rigidity is a hallmark symptom of PD and is described as the resistance to passive motion. Abnormal muscle rigidity leads to smaller range of joint motion and has been associated with falls (McKay et al., 2019). Muscle activity in response to passive stretching suggests that proprioceptive feedback from the stretched muscles plays a role in increasing muscle activity to oppose the stretch (Linn-Evans et al., 2020). However, up to date we lack data that associate the degree of proprioceptive dysfunction with the extent of abnormal muscle tone.

Thus, the present study sought to close these knowledge gaps by (1) quantifying the deficit, if any, of ankle proprioceptive function using a passive motion

apparatus and (2) relating measures of proprioceptive function in people with PD with clinical measures of muscle rigidity. Sensory psychophysics was used to measure ankle position sense acuity in the more affected leg. A clinical assessment of rigidity was obtained by utilizing the Movement Disorders Society-Unified Parkinsonian Disease Rating Scale (MDS-UPDRS) subitem 3.3 to evaluate the level of rigidity in the more affected leg.

We hypothesized that median JND threshold and UA values would be larger in the people with PD than in controls. A power analysis was performed using G*Power (Faul et al., 2007) and assumed the same effect size as in Maschke and colleagues (2003, Cohen's d = -0.9438). With an $\alpha = 0.05$ and $\beta = 0.80$, a sample size of N = 30 participants would detect a significant difference between two independent groups. Based on the previous work by Maschke and colleagues (2003) it was expected that average JND thresholds and UA will be two times larger in the people with PD than in controls. Based on our previous work (Sertic et al., 2023), we expected that controls will have an average JND threshold of 1.6° and UA of 1.1°. Therefore, in the Parkinsonian group, mean JND threshold was expected to be 3.2° and UA to be 2.2°. We also hypothesize that at least one of the ankle position sense outcome measures will scale with rigidity such that larger values of JND threshold or UA will be correlated with larger rigidity scores. If such a relationship exists, this would indicate that abnormal processing of proprioceptive afferents is involved in parkinsonian rigidity. If no relationship is found, then abnormal processing of proprioceptive afferents may not be involved in parkinsonian rigidity.

4.2 Methods

Participants

Sixteen participants with idiopathic Parkinson's Disease (PD) and sixteen age-matched controls volunteered for this study. Demographic summary of study participants can be found in **Table 4-1**.

Table 4-1. Demographics of study participants.

	Healthy controls (n = 16) mean ± SD (range)	**Parkinson's disease (n = 16) mean ± SD (range)**
Female / Male	7 / 9	10 / 6
Age (years)	66.7 ± 6.4 (52.4 – 75.6)	66.9 ± 6.3 (55.1 – 75.3)
Disease Duration (years)	*NA*	6.6 ± 3.0 (0.5 – 11.7)
MDS-UPDRS III Total Score *OFF medication*	3 ± 1 (0 – 4)	31 ± 12 (15 – 52)
MDS-UPDRS III Section 3.3 Rigidity Subscore	0 ± 1 (0 – 2)	7 ± 4 (1 – 14)
MDS-UPDRS III Section 3.3 Rigidity Subscore of more affected limb	0 ± 0.3 (0 – 1)	1 ± 1 (0 – 3)
MOCA Score	28 ± 2 (25 – 30)	27 ± 2 (23 – 30)
PA Score	47 ± 22 (9 – 83)	61 ± 44 (25 – 185)

MDS-UPDRS-III = Movement Disorders Society – Unified Parkinson's Disease Rating Scale; MOCA Score = Montreal Cognitive Assessment; PA score = Godin Shephard Activity Scores < 14 are Insufficiently Active, 15-23 are Moderately Active, and >24 are Active.

Healthy controls were age-matched within 3 years of a volunteer with PD. Enrolled participants did not meet any of the following criteria: (1) Inability to consent as assessed by the UCSD Brief Assessment of Capacity to Consent score <14, (2) clinical diagnosis of peripheral neurologic pathology, (2) deep brain stimulation or other neurosurgery, (3) tremor larger than 1 cm in the OFF-medication state for participants with PD, (4) inability to achieve at least 24° of ankle range of motion, (5) exposure to chemotherapy, (6) previous or current use of benzodiazepine, (7) lower extremity orthopedic or musculoskeletal injury within the last six months, and (8) lower limb amputation, knee replacement, or pathology leading to pain. Participants with PD were excluded if they had any neurological disorder other than idiopathic PD. Healthy controls did not have any

diagnosis of neurological conditions. To determine eligibility prior to participating, all participants provided a verbal medical history using REDCap electronic data capture tools hosted at the University of Minnesota (Harris et al., 2009, 2019; Lawrence et al., 2020).

Participants with PD were recruited from the movement disorders outpatient clinic at the University of Minnesota, from an IRB-approved registry of former participants, and by word of mouth. All were diagnosed as having idiopathic PD. According to their Hoehn and Yahr classification, participants with PD were at a mild or moderate stage (Hoehn & Yahr range 1-3). Disease severity was determined using the MDS-UPDRS part III. Cognitive function was assessed using the Montreal Cognitive Assessment (MOCA, Nasreddine et al., 2005). Physical activity levels of participants were taken using the Godin-Shephard Leisure-Time Physical Activity Questionnaire (Godin & Shephard, 1985). Based on self-reported physical activity, participants were classified as *Insufficiently Active*, *Moderately Active*, or *Active*. Clinical characteristics of participants with PD are summarized in **Table 4-2**.

Again, we attempted to control for the influence of lower extremity injuries on ankle proprioceptive function by setting the exclusion timeline for injuries at six months, as six months is greater than the average time to heal fractures, tendon tears, and ligament injuries (Frank et al., 1983; Hope & Saxby, 2007; Karladani et al., 2001). All participants provided written informed consent prior to participation in the study. The experimental protocol was approved by the University of Minnesota Institutional Review Board (STUDY00018992).

Procedure

Participants with PD were in the clinically defined OFF medication state during all study procedures. Prior to data collection, participants abstained from taking their medication for 12 hours for immediate-release and extended-release medications that are taken more than one time per day. Extended-release medications taken only once per day were withdrawn for 24 hours prior to the data collection.

Table 4-2. Clinical characteristics of participants with Parkinson's disease

ID	Age (years)	More affected side	Disease duration (years)	H&Y	MDS-UPDRS-III OFF state	MOCA	LED (mg/ diem)	Medication
1	75.1	R	9.8	2	24	26	900	L IR
2	71.5	L	11.7	3	39	28	750	L IR & ER
3	58	R	8	2	29	30	450	L IR
4	64.9	R	5.6	2	16	27	900	L IR
5	67.3	R	6.9	2	39	26	600	L IR, THP
6	65.2	L	4.8	2	34	26	600	L IR
7	74.5	L	6	2	16	30	1100	L IR, PH
8	75.3	L	4.2	2	48	29	750	L IR
9	55.1	R	6.9	2	19	30	600	L IR
10	68	R	11.7	2	31	29	1050	L IR, AH, PH
11	63.5	R	3.4	1	25	23	600	L IR
12	72.7	L	7.4	3	52	28	1131	Rytary
13	58.1	L	0.5	2	24	29	650	L IR
14	66.6	R	5.1	2	15	27	300	Selegiline, oral
15	63.3	R	5	2	42	23	700	L IR
16	71.4	R	8.4	2	38	26	750	L IR & ER

MDS-UPDRS-III = Movement Disorders Society – Unified Parkinson's Disease Rating Scale; Medication: L IR = Carbidipa/Levodopa Immediate Release, L ER = Carbidipa/Levodopa Extended Release, THP = Trihexyphenidyl, PH = pramipexole; Levodopa equivalent dose (LED) = 100 mg standard levodopa equals 75 mg extended release levodopa, 100 mg pramipexole, 60 mg rytary, 10 mg oral selegiline (Tomlinson et al., 2010)

Motor severity was evaluated using the MDS-UPDRS section III rating scale. This assessment was conducted prior to the proprioceptive assessment. JS assessed all participants for their motor severity. The clinical impression of rigidity was obtained using the MDS-UPDRS section 3.3, in which the hip, knee, and ankle were moved through the range of motion and evaluated for the resistance required to move the limb.

Ankle range of motion in the sagittal plane was assessed both passively and actively using a one degree-of-freedom electrogoniometer (Twin axis goniometer SG150/B, Biometrics Ltd, Newport, UK). The electrogoniometer was aligned to

the longitudinal axis of the shank and ankle and crossed the lateral malleolus of the tibia. To measure passive range of ankle motion, the experimenter dorsiflexed and plantarflexed the participant's ankle to the maximum structural range. Active range of ankle motion was obtained by asking the participant to actively dorsiflex and plantarflex to their maximum range. Each assessment was performed three times. Range of ankle motion was calculated adding the maximum value of dorsiflexion to the maximum value of plantarflexion. Electrogoniometer data were saved to a file and analyzed off-line using R.

Ankle position sense acuity was measured using the Ankle Proprioceptive Acuity System (APAS, **Figure 3-1**) and with the same approach as described in **Chapter 3**. Based on the limitations and lessons learned from Study 1, some minor adjustments were made to this protocol and are described. During testing, participants sat in an upright position with their foot resting on the foot platform. The chair participants sat in was raised with bed raisers such that their upper leg was fully supported. Thus, testing occurred in an unweighted position with the participant elevated above the device. One trial consisted of passively rotating the ankle to two target positions (**Figure 1-1A**). Participants were instructed to fully relax during the movements and electromyographic recordings of the tibialis anterior and medial and lateral heads of the gastrocnemius were taken during each trial to ensure that the movement was passive (Trigno Research+ System, Delsys, Natick, MA, USA). Trials were repeated if participants activated the muscles for longer than 250 ms above their resting muscle activity during the displacement. Some people with PD exhibited rigidity during testing. That is, muscle activity increased upon passive displacement. For those participants, muscle activity during displacement was used as the baseline reference. Any muscle activity above that activity induced by the rigidity was noted as a voluntary activation and the trial was repeated. Angular displacement of the platform by the experimenter was recorded with an optical encoder at a frequency of 42.6 Hz and analyzed offline to determine movement velocity. On average, angular velocity of the plantarflexed movement was 6.2 ± 1.04 deg/s.

As the Parkinsonian sample was expected to have elevated and more variable thresholds than controls, each test was composed of 35 trials in order to ensure that enough trials were performed to converge on the threshold. Breaks were taken every seven trials to mitigate fatigue.

Outcome measures

Ankle position sense testing yielded two primary outcome measures, the JND threshold and an Uncertainty Area, which are described in **Chapter 1**. Rigidity was assessed on a scale of 0 to 4, with 0 indicating no rigidity, 1 representing rigidity only detected with an activation maneuver, 2 representing rigidity detected without an activation maneuver and the full range of motion is achieved, 3 indicating that rigidity was detected without an activation maneuver and the full range of motion was achieved with effort, and 4 indicates that rigidity was detected without an activation maneuver and the full range of motion was not achieved (**Appendix B**). Rigidity scores of the more affected limb are reported and related to proprioceptive outcome measures, which were also obtained for the more affected, or yoked, limb.

Data Analysis

The distribution of all variables were tested for normality using Shapiro-Wilk's test of normality. Demographic features were compared between groups using independent samples t-test for Age and Mann-Whitney U tests for MOCA scores and physical activity levels. Ankle range of motion was normally distributed and compared using independent samples t-tests. Position sense JND threshold was normally distributed for both groups and Uncertainty area was not normally distributed for the parkinsonian group. For consistency, non-parametric Mann-Whitney U tests were performed for both outcome measures to determine group differences. Spearman's rank-order correlations were used to determine the relationships between lower extremity rigidity and other continuous outcome measures such as position sense acuity and disease duration. Pearson product-moment correlations were performed to determine relationships between position

sense acuity and physical activity level, motor severity, duration of disease, dosage of medication, and cognitive function. Effect size was computed using rank-biserial correlation coefficient for the Mann-Whitney U tests. Outliers were identified as greater than 3 times the interquartile range. One outlier was detected and removed from analysis in the PD group for UA. The significance level for all tests was set to $\alpha = 0.05$. All statistical analyses were conducted using R software version 4.3.1 (R Core Team, 2023).

4.3 Results

Age, MOCA scores, and physical activity levels were comparable between groups ($p > 0.05$). All participants with PD were sufficiently physically active, as indicated by Godin-Shephard scores greater than 24. Controls were insufficiently active (n = 1), moderately active (n = 3) and active (n = 12). Neither position sense acuity measure significantly correlated to physical activity levels ($p > 0.05$). Ankle range of motion was comparable between groups for both passive ($t = 0.28$, $p = 0.79$) and active ($t = 0.02$, $p = 0.98$) movements. As expected, people with PD had significantly larger MDS-UPDRS part III motor scores than people without PD ($p < 0.001$).

Aim 2a: Ankle position sense acuity between groups

Figure 4-1A illustrates the distribution of JND threshold for each group. Six of the 16 participants with PD (37.5%) had JND threshold values larger than the maximum of the healthy controls. That is, while many of the people with PD demonstrated impairments in ankle position sense bias, 10 of 16 participants exhibited normal thresholds. We explore whether people with elevated thresholds also present with higher rigidity in Aim 2b. Median JND thresholds were 1.5° (range: 1.0° to 2.7°) for controls and 2.1° (range: 1.2° to 4.4°) for the Parkinsonian group, which yielded statistically significant differences ($z = 66$, $p = 0.020$) with a moderate effect ($r = 0.413$). To appreciate these data, consider that the range of JND threshold for the Parkinsonian group was 1.2° to 4.4°, meaning that the smallest difference from 15° that could be perceived with 75% accuracy

was 13.8° and the largest was 10.6°.

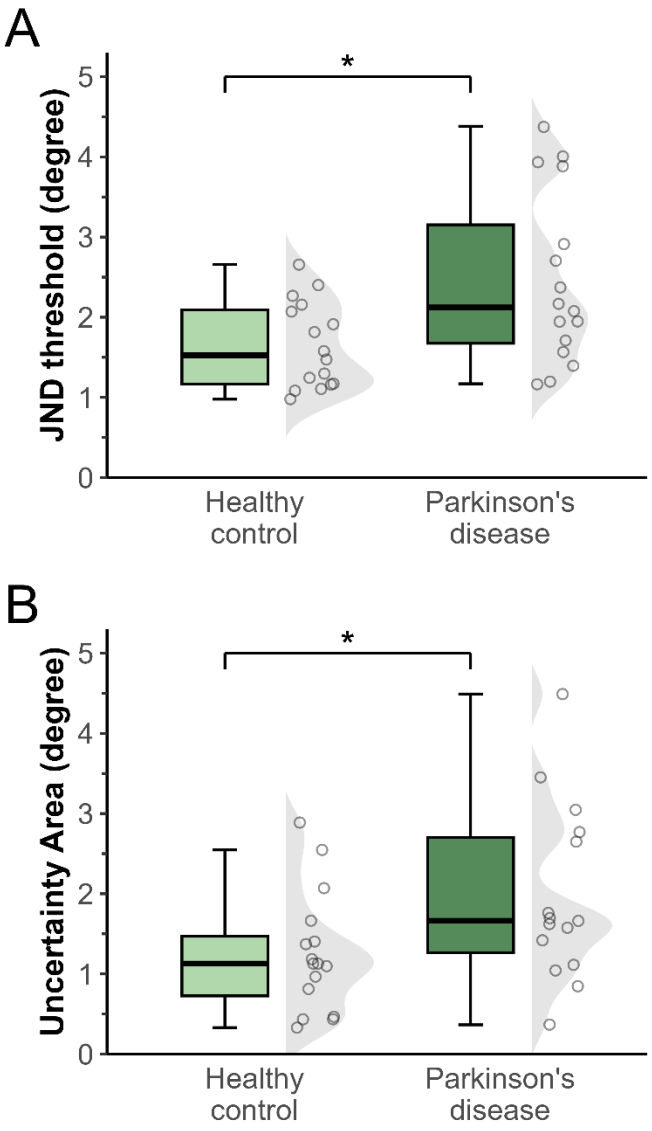

Figure 4-1. Ankle position sense acuity between people with Parkinson's disease (PD) and healthy controls. (A) JND position sense threshold and **(B)** UA position sense values. The lower end of the box represents the 25th percentile and the upper end of the box indicates the 75th percentile. The line within the box is the median. The whiskers indicate 1.5 times the interquartile range of the respective distribution. Each datapoint within the half violin represent an individual threshold. Both position sense acuity outcome measures were larger in the parkinsonian group than the control group (*$p < 0.05$).

Figure 4-1B illustrates the distribution of Uncertainty Area values for controls and people with PD. One outlier was identified and removed from the Parkinsonian group. Three of the 15 (20%) participants with PD had UA values outside the range of controls. Median UA was 1.1° (range: 0.3° to 2.9°) for controls and 1.7° (range: 0.4° to 4.5°) for the parkinsonian group after removing one outlier, which yielded statistically significant differences (z = 68.5, p = 0.044) with a moderate effect (r = 0.366). Median UA for the Parkinsonian group was 1.7° meaning that the random error of responses was within 1.7° about the respective JND threshold. That is, for a JND threshold of 2.1°, participants could correctly perceive their ankle position 60% of the time at 1.3° and 90% of the time at 3°. Overall, 44% of individuals with PD exhibited impairments in either JND threshold, UA, or both. These findings confirm the hypothesis that ankle position sense acuity is impaired in the Parkinsonian group relative to controls.

Lower extremity rigidity between groups

Figure 4-2 illustrates the distribution of the rigidity score of the MDS-UPDRS section 3.3. Fifteen controls demonstrated rigidity scores of 0, indicating no stiffness felt during passive movement. Rigidity was felt with the use of an activation maneuver in one control. The Parkinsonian group had 5 participants with no rigidity (score: 0), 4 participants with rigidity detected only with an activation maneuver (score: 1), 5 participants with a score of 2, and 2 participants with a score of 3. This sample did not contain anyone with a score of 4, representing the highest degree of rigidity. People with PD had significantly larger clinical rigidity scores than controls (z = 37, p = 0.001).

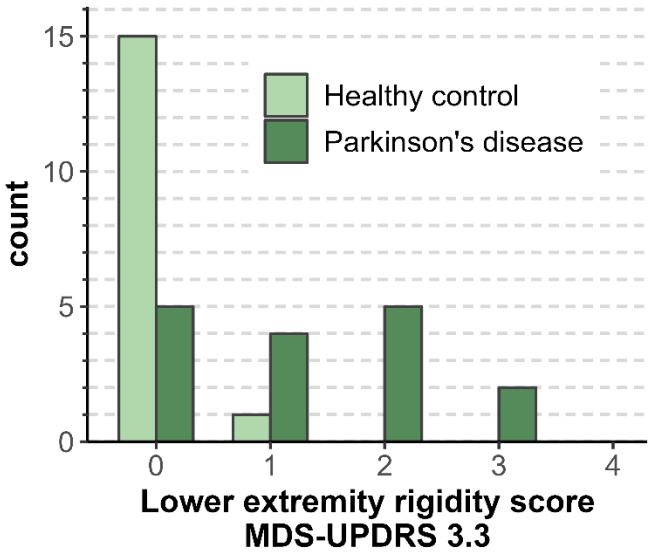

Figure 4-2. Clinical assessment of muscle rigidity in PD and controls. The histogram illustrates the distribution MDS-UPDRS 3.3 sub score of the more affected leg between people with Parkinson's disease (PD, red) and healthy controls (grey). Each bar represents a range of rigidity scores with the height of the bar corresponding to the number of participants falling within that score. Rigidity scores represent the amount of rigidity felt: 0 indicates no rigidity; 1 is scored when rigidity was only detected with activation maneuver; 2 represents that rigidity is detected without the activation maneuver, but full range of motion is easily achieved; 3 indicates that rigidity detected without an activation maneuver; full range of motion is achieved with effort; and 4 is scored when rigidity is detected without the activation maneuver and full range of motion not achieved. Clinical assessment of rigidity is significantly higher in the PD group relative to controls (p = 0.001).

Aim 2b: Relationship between ankle proprioception and rigidity

Figure 4-3 illustrates the relationship between position sense acuity outcome measures and the clinical assessment of lower extremity rigidity, assessed using section 3.3 of the MDS-UPDRS part III. Lower extremity rigidity of the more affected leg, as assessed through clinical examination, was statistically significantly correlated with JND threshold (ρ = 0.50, p = 0.047). JND threshold tended to be larger in participants with a score of 2 and 3, which is scored as rigidity detected without an activation maneuver and range of motion can be achieved without or with effort, respectively. This finding confirms the tertiary hypothesis of this dissertation that at least one measure of position sense will scale with rigidity. Uncertainty area did not correlate with the clinical assessment

of lower extremity rigidity ($p > 0.05$). In addition, there was no association between MDS-UPDRS section 3 tremor, bradykinesia, nor postural instability subscores and either position sense outcome measure ($p > 0.05$).

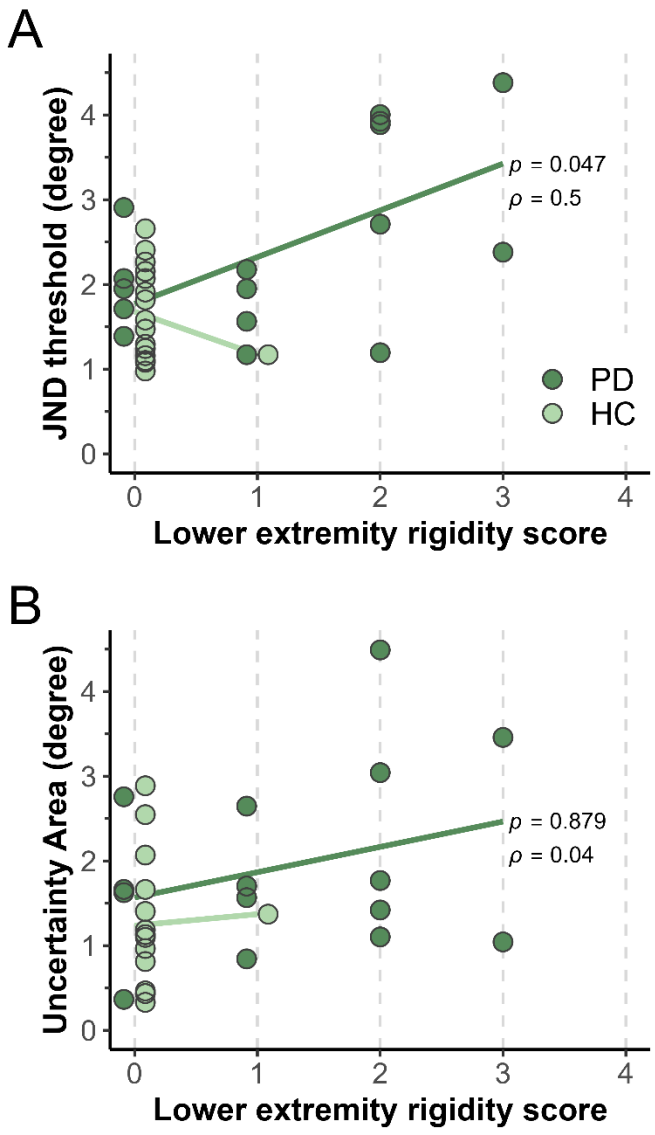

Figure 4-3. Correlation of muscle rigidity to ankle position sense. Spearman correlation of the MDS-UPDRS part III section 3.3 score of the more affected leg against position sense acuity **(A)** JND position sense threshold and **(B)** UA position sense values in controls (HC, light green) and people with Parkinson's disease (PD, dark green). JND position sense threshold significantly increased with increasing rigidity scores, meaning that as proprioceptive bias declines rigidity severity also worsens.

Effects of Disease Duration, Disease Severity and Medication on Conscious and Unconscious Proprioceptive Outcome Measures

Disease duration was moderately correlated with JND threshold (r = 0.52, p = 0.039) and the clinical assessment of rigidity (ρ = 0.57, p = 0.020). These data indicate that JND threshold and rigidity explain 27% and 33% of the variance in disease duration, respectively, indicating that disease duration is associated with impairments in both the conscious and unconscious processing of proprioceptive afferents. JND threshold also correlated moderately with levodopa equivalent dosage (r = 0.54, p = 0.03), meaning that levodopa equivalent dosage explains 29% of the variance in JND threshold. There were no other significant correlations. UPDRS motor score did not yield significant correlations with any outcome measure.

4.4 Discussion

This study examined ankle position sense acuity in Parkinson's disease and the relationship to Parkinsonian rigidity. This study applied a psychophysical paradigm that yielded objective and precise measures of ankle position sense bias and precision in people with Parkinson's disease relative to healthy age-matched controls. Rigidity was assessed using the MDS-UPDRS section 3.3. The main findings of the project are: First, ankle position sense acuity is impaired in people with PD. That is, group median just-noticeable-difference (JND) thresholds and uncertainty area (UA) values were larger in PD than controls. Second, the clinical assessment of rigidity scaled with position sense JND threshold, suggesting that proprioception declines with increases in rigidity. Third, both JND threshold and the clinical impression of rigidity increased with increasing disease duration. People with PD also show larger L-dopa dosages with larger JND thresholds.

Parkinson's disease associated changes in proprioception

There is solid empirical evidence showing that all modalities of conscious proprioceptive function – the sense of heaviness, motion and position – are impaired in the upper extremities in Parkinson's disease (Konczak et al., 2009). At present, there are little empirical data on lower extremity proprioceptive function, despite its critical role in balance and gait control. Two studies have aimed to systematically map the proprioceptive-motor deficit at the at the knee (Ribeiro Artigas et al., 2016) and ankle (Teasdale et al., 2017) and have both shown deficits in the Parkinsonian group relative to controls. The study by Riberio Artigas and colleagues (2016) found active knee repositioning errors ~2 times larger in people with PD than controls, which is similar to the magnitude of the deficit seen at the forearm in PD (Maschke et al., 2003).

The present study assessed the proprioceptive sense isolated from the motor system and show deficits in both ankle position sense bias and precision in PD relative to age-matched controls. The proprioceptive outcomes in the control cohort are comparable to that found in Project 1 (Sertic et al., 2023), meaning that position sense values in this age-matched group is a representative sample. At the group level, people with Parkinson's disease have elevated thresholds of proprioceptive perception. It has been previously reported that at the individual level, 27 – 66% percentage of people with PD demonstrate perception outside of the control range (Konczak et al., 2008; Maschke et al., 2003). Here, 37.5% of people with PD showcased elevated JND thresholds and 20% had elevated UA values above the control range, resulting in a total of 7/16 participants with a deficit in at least one of the position sense outcomes. Collectively, these data indicate that more than half of people with PD have normal position sense, but that as a group, thresholds are primarily on the higher end of normal rather than elevated above the controls.

Relationship between proprioception and rigidity in Parkinson's disease

Evidence does not suggest that proprioceptive abnormalities are attributed to peripheral dysfunction. Some histological research shows PD-related muscle spindle abnormalities (e.g., enlargements in the diffuse endings, Saito et al., 1978) that are unrelated to normal aging. However, muscle spindle afferents to the primary somatosensory cortex (Seiss et al., 2003) and the monosynaptic stretch reflex have normal latencies (Asci et al., 2023; Lee & Tatton, 1975; Tatton & Lee, 1975), which is consistent with normal mechanoreceptor and afferent sensory pathway function. Proprioceptive deficits in PD are thought to be attributed to impairment in supraspinal central processing of proprioceptive information (Khudados et al., 1999; Rickards & Cody, 1997; Seiss et al., 2003).

Parkinsonian rigidity is the velocity-dependent (Asci et al., 2023) upregulation of muscle tone during passive stretch. While the pathomechanism of rigidity is still unclear, an exaggerated long-latency stretch reflex response from the stretched muscle has been correlated to the clinical impression of rigidity (Berardelli et al., 1983; Rothwell et al., 1983; Tatton & Lee, 1975). A stretch response from the stretched muscle implies that proprioceptive afferents play a role in the generation of rigidity. Evidence to support this is shown by the relief in rigidity with a local anesthetic block to afferent nerve fibers while sparing alpha motor neuron function (Pollock & Davis, 1930; Rushworth, 1960). We report that the impairment of proprioceptive function is related to the clinical impression of rigidity, suggesting that proprioceptive processing deficits are related to both proprioceptive perception and rigidity. This hints at the possibility that abnormal proprioceptive processing may be the generator of the abnormal long-latency stretch reflex.

Contrary to our findings, Ribeiro Artigas and colleagues (2016) show that people with tremor dominant subtype had greater proprioceptive deficits than people with akinetic rigid subtype. Here, there were no differences in position sense bias nor precision between tremor dominant and akinetic rigid subtypes. Subtypes

were classified based on recent guidelines for using the MDS-UPDRS (Adams et al., 2023). Differences in the methods may explain the differential findings, as the study by Ribeiro Artigas and colleagues (2016) employed an active repositioning task which measured proprioceptive-motor function whereas the current study isolated proprioceptive sensory processing.

Disease duration and anti-parkinsonian medication as it relates to sensory function

Expectedly, rigidity increased with disease duration. It was also found that position sense thresholds increased with the length of disease, corroborating earlier findings (Elangovan et al., 2018; Maschke et al., 2003). In our sample, people with shorter duration of the disease had JND thresholds comparable to controls whereas people with disease durations longer than 5 ½ years tended to have elevated thresholds. Braak's stage 3 is considered the point in disease progression when the pathology appears in the midbrain but the cortex is still mostly uninvolved (Braak et al., 2006). Upon entering stage 4, enough neurons of the substantia nigra pars compacta have degenerated to give rise to the clinically recognizable motor phase of the disease. The basal ganglia has proprioceptive receptive fields (Rodriguez-Oroz et al., 2001), but somatosensation may be preserved until Lewy bodies and α-synucleophathies affect cortical regions in disease stages 5 and 6. However, this is only speculative as we do not have data on lesion locations in our participant sample.

The relationship of measures of somatosensory function and the total MDS-UPDRS III motor score is unclear. Some studies utilizing psychometric measures showed that proprioceptive acuity decreased with increased disease severity (Konczak et al., 2007; Maschke et al., 2003, 2006), whereas others show no relationship (Elangovan et al., 2018; Konczak et al., 2008). The present study found that neither position sense acuity measure correlated with the total MDS-UPDRS III motor score. These conflicting findings may be due to the different resolution of the measures, as the low-resolution clinical measure may miss

subtle changes which are captured in the high-resolution objective psychometric measures. Moreover, Parkinson's disease progresses differently for each person, resulting in a highly variable population regarding individual sensory and motor deficits. This may explain why some studies yield results showing a relationship while others do not.

It is important to note that our sample consisted of mild-to-moderate PD with the most severe participant scoring 52 on the MDS-UPDRS III (maximum score 132). Motor severity of our sample is comparable to most other literature. Based on the findings from our study and others, there is clear evidence that somatosensory dysfunction is a feature of early-to-mid stage PD. As most studies recruit and test people with only mild-to-moderate PD, is unclear how proprioceptive function may progress in later stages of PD.

Our study sheds light on the nuanced relationship between anti-parkinsonian medication dosage and proprioceptive function. Contrary to most prior reports predominantly conducted in the ON medication state, which largely found no significant relationship between L-dopa dosage and somatosensory function (Elangovan et al., 2018; Konczak et al., 2007, 2012; Maschke et al., 2003, 2006), our data indicate a decline in proprioceptive abilities with increasing medication dosage. This disparity suggests that previous studies may have overlooked the potential confounding effects of somatosensory function on medication. While there is conflicting evidence on whether L-dopa has an influence on the proprioceptive sense (Li et al., 2010; O'Suilleabhain, 2001; Wright et al., 2010), the one study with a similar study design as employed by this dissertation found that anti-parkinsonian medication restored proprioceptive outcomes by ~15% (Li et al., 2010). Our results, derived from participants washed out of medication, unveil the true disease state of proprioceptive function and hint at the possibility of a therapeutic role for medication in managing proprioceptive deficits in Parkinson's disease.

Limitations

The findings of this study should be interpreted within the context of the following limitations. The sample population consisted of individuals with Parkinson's disease who were highly active and predominately exhibited mild disease severity. Consequently, the generalizability of our results to individuals with more advanced stages of the disease may be limited. Additionally, it is important to note that the sample consisted solely of individuals who were willing to temporarily withdraw from their anti-parkinsonian medication. Multiple participants withdrew from the study due to intolerance being off medication. Lastly, motor severity was assessed by a single unblinded experimenter which could potentially introduce bias to the results of the study. To mitigate such bias, the MDS-UPDRS was conducted prior to proprioceptive testing and the analysis relating clinical rigidity to position sense outcome measures was not performed until data collection was completed by all people with Parkinson's disease.

Chapter 5. Conclusion

This cumulative dissertation examined proprioceptive function at the ankle in neurologically polar aging populations: active adults and people with Parkinson's disease (PD). In contrast to previous work measuring proprioceptive-motor function, the studies in this dissertation investigated proprioceptive acuity under a passive movement condition. Passively rotating the ankle isolated the sensory processing, thus truly reflecting the perception of ankle position. The results of Project 1 challenged the prevailing assumptions about ankle proprioceptive decline in aging, demonstrating that a habitually active lifestyle can preserve ankle proprioceptive function. Over two-thirds of participants demonstrated position sense acuity within the range of the young adults, indicating that habitual physical activity protects most adults against age-related ankle proprioceptive decline. The findings underscore the importance of remaining active during aging. The findings also necessitate probing participants' physical activity to account for potential confounders of proprioceptive performance. Future studies should explore the extent to which cardiovascular health supports the proprioceptive system as a means of elucidating the mechanism of proprioceptive preservation with exercise.

The results of Project 2 add to the empirical evidence documenting that somatosensory function becomes compromised in PD, here showing that PD is associated with impaired ankle position sense. There were 44% of participants with PD with abnormalities in either JND threshold or UA, or both. These findings complement previous research identifying upper extremity proprioceptive deficit and provides evidence that the impairment also generalizes the lower extremities. Given that ankle proprioceptive deficits impair balance and gait and that proprioception can be trained in Parkinson's disease, future research may explore an ankle proprioceptive training task to improve associated motor outcomes. Additional findings show that proprioceptive decline was associated with Parkinsonian muscle rigidity, which establishes, for the first time, that impairments in proprioceptive processing contribute to both proprioceptive

perceptual dysfunction and elevated muscle tone in PD. This opens an avenue for further research to explore the functional role of proprioceptive processing in rigidity.

The findings from this dissertation underscore the complexity and emphasize the malleability of proprioceptive function based on lifestyle and neurologic condition. Proprioceptive function should be monitored annually in the outpatient clinic. The sensory psychophysical position sense assessment takes approximately ten minutes to perform and outcomes can be used to identify changes over time. Based on the long-term trends, clinicians may identify deficits and prescribe proprioceptive interventions to potentially reduce or prevent falls.

Chapter 6. References

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Chapter 7. Appendices

Appendix A. Measurement scales used to assess physical activity levels.

Modified LASA Physical Activity Questionnaire (LAPAQ) (Stel et al., 2004)

1. Do you walk outside?
    a. No (go to question 5)
    b. Yes
2. Did you walk during the past two weeks?
    a. No (go to question 5)
    b. Yes
3. How many times did you walk during the past two weeks?
4. How long did you usually walk each time?
5. Do you do sports? Explanation: with sports we mean the activities on the list (see question 6).
    a. No (go to question 13)
    b. Yes
6. Which sport did you do most time during the past two weeks?
    a. Distance walking
    b. Distance cycling
    c. Gymnastics
    d. Cycling on hometrainer
    e. Swimming
    f. Dancing
    g. Bowling
    h. Tennis, badminton
    i. Running, fast walking
    j. Rowing
    k. Sailing
    l. Playing billiards
    m. Fishing
    n. Playing soccer/basketball/hockey
    o. Playing volleyball/baseball
    p. Skiing
    q. Else _____
7. How many times did you do this sport during the past two weeks?
8. How long did you usually do this sport each time?
9. Do you do another sport?
    a. no (go to question 13)
    b. yes

10. Which other sport did you do during the past two weeks?
    a. Distance walking
    b. Distance cycling
    c. Gymnastics
    d. Cycling on hometrainer
    e. Swimming
    f. Dancing
    g. Bowling
    h. Tennis, badminton
    i. Running, fast walking
    j. Rowing
    k. Sailing
    l. Playing billiards
    m. Fishing
    n. Playing soccer/basketball/hockey
    o. Playing volleyball/baseball
    p. Skiing
    q. Else _____
11. How many times did you do this sport during the past two weeks?
12. How long did you usually do this sport each time?
13. You just told me about your usual activities of the past two weeks. Were the past two weeks normal as compared to the rest of the past year?
    a. No
    b. Yes (end of questionnaire)
14. Why were the past two weeks not normal?
    a. Disease
    b. Depression
    c. Bad weather
    d. Family occasion
    e. Holiday
    f. Else _____

Godin-Shephard Leisure-Time Exercise Questionnaire (Godin & Shephard, 1985)

During a typical 7-day period (a week), how many times on the average do you do the following kinds of exercise for more than 15 minutes during your free time?

a) Strenuous exercise (heart beats rapidly)
   (e.g., running, jogging, hockey, football, soccer, squash…)
b) Moderate exercise (not exhausting)
   (e.g., fast walking, baseball, tennis, easy bicycling, volleyball…)
c) Mild exercise (minimal effort)
   (e.g., yoga, archery, fishing from a river bank, bowling…)

Appendix B. Assessment of Parkinson's Disease rigidity severity.

Movement Disorders Society – Unified Parkinson's Disease Rating Scale Section III 3.3 RIGIDITY (Goetz et al., 2008)

Instructions to examiner: Rigidity is judged on slow passive movements of major joints with the patient in a relaxed position and the examiner manipulating the limbs and neck. First, test without an activation maneuver. Test and rate neck and each limb separately. For arms, test the wrist and elbow joints simultaneously. For legs, test the hip and knee joints simultaneously. If no rigidity is detected, use an activation maneuver such as tapping fingers, fist opening/closing, or heel tapping in a limb not being tested. Explain to the patient to go as limp as possible as you test for rigidity.

0: Normal: No rigidity.

1: Slight: Rigidity only detected with activation maneuver.

2. Mild: Rigidity detected without the activation maneuver, but full range of motion is easily achieved.

3: Moderate: Rigidity detected without an activation maneuver; full range of motion is achieved with effort.

4: Severe: Rigidity detected without the activation maneuver and full range of motion not achieved.