Clinical and Laboratory based Proprioceptive Assessments in Older Adults and People with Multiple Sclerosis

by

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Statement of Contributors

I hereby declare that I am the sole author of this Master of Science thesis. My contributions include: A review of literature in the area of interest, participant recruitment, participant testing, data collection, data compilation, statistical analyses, and the write-up of this thesis manuscript. All of these duties were performed under the guidance and mentorship of my research supervisor, Dr. Erin K. Cressman.

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List of Abbreviations

Abbreviation	Explanation
ADL	Activities of Daily Living
AEX	Absolute Error in the X direction
AEY	Absolute Error in the Y direction
CNS	Central Nervous System
DCML	Dorsal Column-Medial Leminscus
EDSS	Expanded Disability Status Scale
|EPAE|	Absolute Endpoint Angular Error
FM	Fugl-Meyer Assessment
GTOs	Golgi Tendon Organs
MS	Multiple Sclerosis
MT	Movement Time
9HPT	Nine Hole Peg Test
OA	Older Adults
PMS	Progressive Multiple Sclerosis
PNS	Peripheral Nervous System
PTAPV	Proportional Time after Peak Velocity
PTTPV	Proportional Time to Peak Velocity
PV	Peak Velocity
|PVAE|	Absolute Peak Velocity Angular Error
PwMS	People with Multiple Sclerosis
RA	Rapidly Adapting
R-Error	Resultant Error
RRMS	Relapsing-Remitting Multiple Sclerosis
RT	Reaction Time
SA	Slowly Adapting
SD	Standard Deviation
SDMT	Symbol-Digit Modalities Test
S1	Primary Somatosensory Cortex
TAPV	Time after Peak Velocity
TTPV	Time to Peak velocity
UL	Upper Limb

Abstract

Proprioception is the sense of body position in space (Gilman, 2002; Goble, Coxon, et al., 2012), and can be evaluated using both clinical assessments and laboratory based tasks. To date, normal aging has been shown to lead to a decline in proprioceptive acuity as assessed via laboratory based proprioceptive matching tasks, while proprioceptive deficits have been assumed to be present in people with multiple sclerosis (PwMS) based on performance on clinical assessments. The objective of the current study was to determine if performance on clinical assessments and laboratory based proprioceptive matching tasks is similar across older adults (OA) and PwMS (Adamo et al., 2007; Goble, 2010; Herter et al., 2014; Jamali et al., 2017; Khan et al., 2018; Scherder et al., 2018). Twenty-four OA participants (70+ years old) and twenty PwMS from the Ottawa community were recruited to take part in this study. Proprioceptive sense was assessed using clinical assessments (i.e., superficial sensation, vibration sense and joint position sense) and laboratory based proprioceptive matching tasks. Analysis revealed that while OA performed better on the clinical assessments, PwMS were more accurate in the laboratory matching tasks. Furthermore, analysis of goal directed movements in the matching tasks, revealed that PwMS spent more time in the initial, planning stage of the movement compared to OA, who spent more time executing their movements. These results indicate that OA and PwMS do not demonstrate similar deficits across clinical assessments and laboratory based proprioceptive tasks, and in fact plan and execute their movements differently. Moreover, results also call into question the relationship between clinical and laboratory based assessments of proprioception.

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Chapter 1 Introduction

1.1 Introduction

Proprioception is the sense of body movement and position of the body in space (Gilman, 2002; Goble, Coxon, et al., 2012). Proprioception can be assessed using both clinical assessments and laboratory based proprioceptive matching tasks. Clinical assessments examining proprioception evaluate nervous system function at the peripheral and central level by assessing the sensitivity of mechanoreceptors and detection of joint movement. Clinically, the 9-hole peg test (9HPT; Kellor et al., 1971) is typically performed in conjunction with other clinical assessments to assess upper limb (UL) function (Feys et al., 2017; Yozbatıran et al., 2006), specifically providing insight into manual dexterity (i.e., the ability to make coordinated movements; Makofske, 2011). In laboratory settings, proprioception is typically assessed through proprioceptive matching tasks, in which limb position sense is assessed in the same (ipsilateral matching task) or opposite limb (contralateral matching task). Proprioceptive deficits in these laboratory based proprioceptive matching tasks are detected through analyzing endpoint errors (Goble, 2010). In addition to providing insight into proprioceptive acuity, the proprioceptive matching tasks can also be used to gain insight into planning and execution processes underlying goal directed movements.

To date, proprioception in older adults (OA) has typically been assessed via laboratory based matching tasks, whereas clinical assessments are used to assess proprioception in people with multiple sclerosis (PwMS; Adamo et al., 2007; Goble, 2010; Herter et al., 2014; Jamali et al., 2017; Khan et al., 2018; Scherder et al., 2018). Results indicate that OA and PwMS demonstrate deficits in proprioception compared to younger participants (Adamo et al., 2007; Goble, 2010; Herter et al., 2014; Jamali et al., 2017). Given that multiple sclerosis (MS) has been

suggested to lead to brain aging, resulting in similar structural changes as seen in OA (Cole et al., 2019; Høgestøl et al., 2019), this thesis aims to determine if performance on clinical assessments and laboratory based proprioceptive matching tasks is similar across OA and PwMS.

This thesis is organized into 4 chapters. Following this introduction, Chapter 2 provides an in-depth literature review, outlining the importance of proprioception to motor control and then focussing on an overview of proprioception and how it is typically assessed in both clinical and laboratory settings. Proprioceptive acuity in OA and PwMS is also discussed, as well as the control of proprioceptively guided movements. Following the literature review, Chapter 3 discusses our experiment conducted to address our research objectives. The implications of our findings are further described in a general discussion (Chapter 4), along with our conclusion that OA and PwMS do not have similar proprioceptive deficits.

Chapter 2 Literature Review

2.1 Importance of Proprioception

Humans make goal directed reaching movements every day, whether to grasp a coffee mug, tap a key on their keyboard, or reach for a book. These movements require the central nervous system (CNS) to know where the limbs are in space. Sensory information related to limb position is provided through two main senses, vision (i.e., viewed position of the limb) and proprioception (Sarlegna & Sainburg, 2009), where proprioception is defined as the perception of body movement and position of the body in space (Sherrington, 1906). The significant role of proprioception in the accurate guidance of upper limb (UL) movements is well documented. Specifically, experiments done on surgically deafferented monkeys (Bossom, 1974; Gauthier & Mussa Ivaldi, 1988; Gilman et al., 1976) demonstrate impaired reaching accuracy and coordination following surgery. In humans, motor deficits including abnormal reaching trajectories, increased limb drift and reduced reaching accuracy are prevalent in patients with large-fiber sensory neuropathy, a condition in which large diameter sensory neurons that carry proprioceptive information are damaged (Ghez et al., 1995; Sanes et al., 1985). These results clearly demonstrate the significance of proprioception for accurate and controlled UL movements.

2.1 The Physiology of Proprioception

The term proprioception was first introduced by Sherrington in 1906 and was defined as the perception of body movement and position of the body in space. It is now known that this sense of body movement and position is derived from sensory input detected by specialized sensory receptors, called mechanoreceptors, in the absence of vision (Gilman, 2002; Goble, Coxon, et al., 2012). Physical changes in mechanoreceptors, located in the joints (Ferrell et al.,

1987), muscles and/or tendons (Goodman, 2015), and glabrous and/or hairy skin (Delhaye et al., 2018; Edin, 2001) lead to activation of afferent neurons, which relay information to the spinal cord and brainstem. This information is then transmitted to the brain (i.e., the primary somatosensory cortex (S1)), and the cerebellum (Delhaye et al., 2018; Gilman, 2002)

Mechanoreceptors located in the joints respond to tensile strain within the joint. However, because these receptors are only activated under extreme conditions, they are presumed to have a minimal role in position sense (Gilman, 2002; Macefield, 2009). On the other hand, mechanoreceptors located in the muscle and/or tendons (muscle spindles and Golgi tendon organs (i.e., GTOs)) and glabrous and/or hairy skin (skin mechanoreceptors) have been proposed to be essential for deriving position sense in the absence of vision (Delhaye et al., 2018; Goble, Coxon, et al., 2012; Proske & Gandevia, 2012). Specifically, input from muscle spindles provide the primary source of information for proprioceptive sense (Goble, Coxon, et al., 2012; Proske & Gandevia, 2012). Muscle spindles consist of intrafusal muscle fibers (nuclear bag and nuclear chain fibers) and are located within the belly of skeletal muscles. The nuclear bag and nuclear chain fibers convey afferent information through primary (Type Ia) and secondary (Type II fibers) afferent neurons. Type Ia fibers relay information regarding dynamic changes in muscle length and the rate of change in muscle length (i.e., dynamic changes) to the CNS. Type II fibers convey information regarding the length (i.e., static and dynamic position) of a muscle (Delhaye et al., 2018; Goodman, 2015). GTOs are found in the muscle tendon at the muscle-tendon junction. GTOs provide information related to the tension and vibration on the tendon and muscular stretch (Delhaye et al., 2018; Proske & Gandevia, 2012). GTOs convey afferent information through Type Ib fibers to the CNS.

While the muscle spindles and GTOs are found in the muscles and tendons, the skin mechanoreceptors are found in glabrous and hairy skin (Gilman, 2002). There are five types of skin mechanoreceptors including Merkel discs, Ruffini endings, Meissner corpuscles, Pacinian corpuscles and hair follicles. Firstly, Merkel disc respond to sustained indentation, such as light touch, and convey afferent information to the CNS through slowly adapting (SA) Type I afferent neurons (Gilman, 2002; Johnson, 2001). Ruffini endings sense skin stretch and transmit afferent information through SA Type II neurons to the CNS (Gilman, 2002; Johnson, 2001). On the other hand, Meissner corpuscles respond to low-frequency vibrations and dynamic skin deformations and convey afferent information to the CNS through rapidly adapting (RA) Type 1 afferent neurons (Gilman, 2002; Johnson, 2001). Pacinian corpuscles also respond to vibrations but are activated at higher frequencies than Meissner corpuscles. In addition, Pacinian corpuscles respond to deep pressure and transmit afferent information through RA Type II afferent neurons to the CNS (Johnson, 2001; Roudaut et al., 2012). In general, SA afferent neurons carry information regarding ongoing stimulation (i.e., static indentation of the skin), whereas RA afferent neurons carry information related to changes in the stimuli (i.e., onset and offset of skin indentation). Lastly, hair follicles respond to light touch and hair motion and convey information to the CNS through C-tactile afferent neurons (Jönsson et al., 2017; Morrison, 2012). Combined, input from these mechanoreceptors (i.e., muscle spindles, GTOs and skin receptors) provide the CNS with continuous information regarding body movement and position of the body in space, with contributions varying across receptors.

2.2 Physiological Changes in Proprioception with Aging

Normal aging is typically associated with proprioceptive decline due to changes in both the peripheral nervous system (PNS) and CNS (Goble et al., 2009; Lee et al., 2013). In the PNS,

aging has been shown to lead to changes in the integrity of muscle spindles, including decreased spindle diameter (Kararizou et al., 2005), increased capsular thickness (Swash & Fox, 1972), reduced sensitivity (Geertsen et al., 2017; Liu et al., 2005), as well as an overall decrease in number of muscle spindles (Liu et al., 2005; Swash & Fox, 1972). In addition, the number and mean density of cutaneous mechanoreceptors per unit of skin area have been shown to decline with age (Aydoğ et al., 2006; Bolton et al., 1966; Iwasaki et al., 2003). Similarly, aging is associated with a fewer number of GTO type receptors (Morisawa, 1998). These peripheral changes could compromise accurate proprioceptive information coding in the elderly.

In conjunction with alterations in the PNS, changes occur in the CNS that can impact proprioceptive processing. The dorsal column-medial leminscus (DCML) pathway transmits sensory information from the mechanoreceptors (e.g., muscle spindles, GTOs and skin mechanoreceptors) to S1 (Al-Chalabi & Alsalman, 2019; Gilman, 2002). The sensory information enters the dorsal funiculus, which is comprised of the fasiculus gracilis and fasiculus cuneatus. The fasiculus gracilis contains afferent fibers that originate from the lower extremities. On the other hand, the fasiculus cuneatus is composed of afferent fibers from the upper extremities. The fibers are surrounded by a myelin sheath, which aids in transmission of information to S1 (Rumsey et al., 2013). A study by Xie and colleagues (2013), demonstrated age related reductions in proteins found within the myelin sheaths in the dorsal funiculus of rats. This age related compromise of the myelin sheath surrounding afferent fibers could compromise transmission of sensory information to S1, leading to sensory loss (Verdú et al., 2000). Aging has also been associated with decreased grey matter (i.e., nerve cell bodies and dendrites) in S1 (Good et al., 2001; Quiton et al., 2007). As S1 is responsible for receiving and processing sensory inputs from mechanoreceptors, decreased grey matter could lead to insufficient

processing of proprioceptive input (Yamada et al., 2016). Combined, these age-related changes in the PNS and the CNS result in less sensory input, problems with transmission and processing of proprioceptive input, which in turn could negatively affect one's overall sense of proprioception.

2.3 Physiological Changes in Proprioception in People with Multiple Sclerosis

Multiple sclerosis (MS) is an immune-mediated, progressive neurological disorder (Compston & Coles, 2008). There are four subtypes of MS which include relapsing-remitting MS (RRMS), secondary progressive MS, primary progressive MS (PMS) and progressive-relapsing MS. The majority of patients are diagnosed with relapsing-remitting MS between 20 and 40 years of age (Miehm et al., 2020; Wootla et al., 2012). In all subtypes of MS, the immune system causes inflammation, which leads to chronic demyelinating of the neurons in the CNS. Similar to OA, PwMS experience sensory impairments, including a decline of proprioceptive acuity in the UL (Jamali et al., 2017). However, impairments (i.e., muscle weakness) generally affect one side of the body more than the other (Lambert et al., 2001). Interestingly, differences in UL proprioception have been found between MS subtypes such that patients with PMS have greater proprioceptive deficits than RRMS (Miehm et al., 2020).

Similar to OA, one's sense of proprioception is thought to be impaired with MS due to dysfunction in the transmission and processing of sensory input (Cameron et al., 2008; Feys et al., 2006; Fling et al., 2014). Specifically, proprioceptive input can be delayed or inaccurate, which could drive declines in proprioceptive acuity (Cameron et al., 2008; Feys et al., 2006). Furthermore, grey matter atrophy in the post central gyrus (where S1 is located) has been found in PwMS, which could lead to inadequate processing of proprioceptive input (Han et al., 2017). In contrast to OA, impairments in mechanoreceptors (i.e., muscle spindles) have not been studied

directly with PwMS. Instead, studies have suggested that impaired transmission of sensory input is the cause of proprioceptive decline (Feys et al., 2005; Feys et al., 2006; Fling et al., 2014).

2.4 Assessing Proprioception: Clinical assessments

Proprioception can be assessed in clinical and/or laboratory settings. Clinical assessments of proprioception include a superficial sensation task, vibration sense task and joint position sense task (at the finger or shoulder). In laboratory settings, proprioception is typically assessed through laboratory based proprioceptive matching tasks, in which the motion of the matching limb may be monitored (i.e., position data is recorded). Together, clinical assessments and laboratory based proprioceptive matching tasks evaluate the sensitivity of cutaneous receptors directly, and the integrity of muscle spindles and GTOs, as well as deficits in the transmission and higher-level processing of proprioceptive input indirectly.

The superficial sensation task, vibration sense task and joint position sense task are often used by clinicians to provide an overall index of sensory function (Kurtzke, 1983; Prosperini et al., 2010; Şen, 2018). For the purpose of this study we refer to these tasks as providing an index of proprioception. The superficial sensation task and vibration sense task evaluate sensitivity of cutaneous receptors. The superficial sensation task uses a neurological pin with a dull and sharp side, and participants report which side is pressed to their skin. This task assesses the sensitivity of Merkel discs, one of the cutaneous mechanoreceptors that respond to sustained indentation (specifically, light touch; Gilman, 2002). An inability to correctly identify which side of the pin is pressed to the participant's skin indicates loss of sensation (Kurtzke, 1983). In the vibration sense task, a tuning fork is placed on the participant's hand and they are to report when they detect vibration termination. This task assesses the integrity of the Pacinian corpuscles, a cutaneous mechanoreceptor responsible for detecting vibration (Gilman, 2002; Wu et al., 1999).

Thus, inability to detect accurate vibration termination could be due to atrophy and/or reduction in the number of Pacinian corpuscles (Gilman, 2002; Shaffer & Harrison, 2007; Wende et al., 2012). While these tasks look to establish the integrity of peripheral mechanoreceptors, it is important to keep in mind that deficits in identification or detection could also be due to damage in afferent neurons (i.e., transmission of information or processing of proprioceptive information within the CNS).

The next task described here assesses joint point position sense. In general, this 'matching' task establishes one's ability to correctly determine the position of their limb in space in the absence of vision (i.e., when their eyes are closed). In the joint position sense task, a participant's index finger or shoulder is passively moved either up or down by the experimenter, and the participant reports which direction the experimenter moved their finger or shoulder. Assessment at the finger provides insight into detection of fine movements, while assessment at the shoulder provides insight into proprioceptive acuity related to gross movements.

In typical clinical assessments, these tasks described so far are part of a larger assessment (e.g., Expanded Disability Status Scale (EDSS; Kurtzke, 1983) or Fugl-Meyer assessment (FM; Fugl-Meyer et al., 1975)), and individual scores on each task are often not reported. For example, it is more common for research with PwMS to report a composite score reflecting one's level of disability across seven functional systems, including visual, brainstem, pyramidal, cerebellar, sensory, bowel and bladder, cerebral and ambulatory ability, as opposed to scores related to a particular system, or task itself (Kurtzke, 1983; Prosperini et al., 2010; Şen, 2018) . If the sensory function system score is provided, it reflects participants' performance across all 3 tasks. The total sensory score is reported out of 6, with a higher score indicating a greater deficit (i.e., a score of 6 is given if participants are unable to complete all the tasks due to loss of sensation,

whereas a score of 0 reflects normal functioning of the sensory system). With respect to the FM assessment, the number of correct responses in the joint position sense task across 4 trials for each limb is recorded. The more incorrect responses, the lower the score (i.e., 0 if unable to correctly identify position in 75% of trials), indicating deficits in proprioceptive acuity. In the clinic, the 9-hole peg test (9HPT; Kellor et al., 1971) is often performed in conjunction with the tasks described above to assess UL function (Semenko et al., 2015), specifically with respect to manual dexterity (i.e., the ability to make coordinated movements; Makofske, 2011). Please refer to the methods (Chapter 3, Pg. 32), for more information regarding scoring of clinical assessments related to proprioception.

2.5 Assessing Proprioception using Proprioceptive Matching Tasks

Alternatively, position sense of a limb can be assessed in the laboratory by examining participant's ability to match the position of their limb in space (Paillard & Brouchon, 1968). The benefit of assessing proprioception in a laboratory setting is that limb motion can be controlled and movements monitored (Herter et al., 2014). In general, during the position matching tasks, a participant's limb is moved into a specific position, known as the reference position. This movement can be completed actively by the participant or passively, such that the experimenter/robotic device moves the participant's arm into position. After establishing the reference position, participants are to reproduce the position with their testing limb. The testing limb could be the same limb (i.e., ipsilateral matching task with the location of the reference position unavailable during movement of the testing limb), or opposite limb (i.e., contralateral matching task with the location of the reference position available during movement of the testing limb). Matching accuracy is measured by endpoint errors, defined as the difference

between the end position of the testing limb and the reference location (Goble, 2010; Li & Wu, 2014).

In general, participants are more accurate (i.e., have lower errors), when the reference limb is actively moved into position (Gandevia et al., 1992; Jones, 1972; Niespodziński et al., 2018; Paillard & Brouchon, 1968). That said, a limited number of studies have found no difference in accuracy regardless of how the reference position is established (Goble & Brown, 2007), or improved accuracy when the reference limb is passively moved into position (Gurari et al., 2018). The benefit for matching tasks when the limb is actively positioned seems to disappear in populations with unilateral motor impairments (Zia et al., 2002). For example, Zia et al. (2002) compared proprioceptive acuity in people with Parkinson's disease and control participants after participants' reference arms were actively or passively positioned. Although controls had greater errors in the passive condition compared to the active condition, there was no difference in people with Parkinson's disease.

Researchers have suggested that lower endpoint errors are typically observed when the reference position is actively attained by the participant versus passively positioned for them due to participants having access to additional information from the motor system. Following active movement, an efference copy is generated based on the motor command used to establish the reference position. The efference copy is thought to be an internal reproduction of the efference signal (movement producing signal; Niziolek, Nagarajan, & Houde, 2013), that may provide additional position related information that can be used when moving the testing limb (Goble & Brown, 2007; Gurari et al., 2018). Thus, in attempt to establish proprioceptive deficits, without interference from the motor system, most laboratory tasks passively move the reference limb to the reference position during the matching tasks (Goble, 2010). Using this protocol, ipsilateral

and contralateral matching tasks have been conducted looking at proprioceptive acuity in the upper (e.g., elbow; Elangovan, Herrmann, & Konczak, 2014) and lower extremities (e.g., knee; Kaplan, Nixon, Reitz, Rindfleish, & Tucker, 1985; Salgado, Ribeiro, & Oliveira, 2015).

Additional experimental design factors that have been shown to influence position errors in matching tasks include the choice of task (i.e., ipsilateral vs. contralateral), the limb being examined (i.e., upper vs. lower limb), and the relative position of the reference position from the body. Generally, in healthy populations positional angular errors for contralateral matching tasks are greater than for ipsilateral matching tasks (Adamo & Martin, 2009; Goble, 2010). One explanation is that using both limbs adds an additional cognitive factor that is not present during ipsilateral matching tasks. Specifically, the contralateral matching task requires interhemispheric communication, which is not required in the ipsilateral matching task (Goble, 2010). Together, both tasks are typically used to provide an overall assessment of proprioceptive acuity.

In general, UL matching errors tend to be smaller than lower limb matching errors across both ipsilateral and contralateral matching tasks (Elangovan et al., 2014; Kaplan et al., 1985; Salgado et al., 2015). For example, Elangovan and colleagues (2014) reported a mean absolute angular error of 1.5° when performing an ipsilateral matching task vs. 1.8° when performing a contralateral matching task after the elbow had been actively moved into position. In the lower limb, mean absolute angular errors of approximately 4° have been reported for both ipsilateral and contralateral matching tasks (Kaplan et al., 1985; Salgado et al., 2015).

Finally, the relative position of the reference position is an addition factor that could influence position errors. Adamo and colleagues (2007), reported absolute matching endpoint errors increased the further away the reference position was from the body at the elbow (reference position of 10° vs 60° away from a start position) in both ipsilateral and contralateral

matching tasks. Absolute angular errors ranged from 1.15° to 2.73° for the ipsilateral matching task and from 2.2° to 3.4° for the contralateral matching task, respectively. Furthermore, Gurari and colleagues (2018) demonstrated that matching errors decreased when the position of the reference arm was in a more flexed position compared to an extended position. This is in line with previous studies that have suggested improved limb position sense in a flexed position is related to limb geometry such that participants have been found to overestimate extended positions to prevent injury (Fuentes & Bastian, 2010; van Beers et al., 1998; Wilson et al., 2010).

Taken together, factors that influence performance on laboratory based proprioceptive matching tasks are the manner in which the reference limb is placed into position (i.e., reference position is actively attained by the participant versus passively), task type (i.e., ipsilateral or contralateral matching task), the limb being examined (i.e., upper vs. lower limb) and the location of the reference position (i.e., near vs. far relative to the body and flexed vs. extended position). These experimental design factors are important to consider when interpreting results, as certain manipulations can inflate errors, leading to inaccurate conclusions regarding proprioceptive acuity.

2.51 Movement Analysis Using Proprioceptive Matching Tasks

In addition to establishing proprioceptive acuity, proprioceptive matching tasks provide the opportunity to examine processes underlying goal directed movements to proprioceptive targets. Performance of goal directed movements is typically evaluated with respect to movement planning (offline) and control (online) processes (Ternes et al., 2014; Woodworth, 1899). Movement planning reflects processes related to the preparation of a movement. The contribution of movement planning processes can be assessed by looking at initial reaching performance (e.g., prior to reach initiation and up to peak velocity (PV)), such that a greater

contribution of movement planning processes is indicated when there is a longer reaction time (RT), and/or greater time to PV (TTPV; Burkitt et al., 2013; Elliott et al., 2001; Hansen et al., 2006; Heath et al., 1998; Khan et al., 2003). Online control refers to processes engaged during movement execution in response to sensory feedback (e.g., proprioception). A greater contribution of online control processes is inferred when participants spend a longer time after PV (TAPV), there is a greater number of movement corrections (i.e., a less smooth movement), and movements are more accurate (Elliott et al., 2010, Elliott et al., 2017; Yadav & Sainburg, 2014)

2.6 Proprioception in Older Adults

There has been limited research systematically assessing proprioception using the clinical assessments outlined above (i.e., the superficial sensation, vibration sense and joint position sense tasks) in OA. Instead, studies have assessed the integrity of cutaneous receptors by variations of these tasks or using just a single task. For example, tactile threshold has been shown to increase in OA, (Wickremaratchi & Llewelyn, 2006), where tactile threshold is defined as the minimum amount of stimulus participants are able to detect and is commonly used to detect sensory loss (Perez et al., 2010). Since tactile threshold has been shown to increase with age, one would assume that OA would perform poorly on the superficial sensation task described above. Vibration sense has also been shown to deteriorate in OA (e.g., from 10.3 seconds to 7.5 seconds in the thumb; Temlett, 2009). To our knowledge only one study has looked at the ability of OA to detect direction of fine finger movements (Kokmen et al., 1978). The study found no differences in ability to discriminate direction of motion across groups. Based on this limited number of studies, we would expect OA to perform poorly on the superficial sensation and vibration sense tasks but have intact joint position sense.

In contrast to clinical assessments, laboratory based proprioceptive matching tasks are commonly used to assess proprioception in OA. The ipsilateral and contralateral matching tasks have been used to establish proprioceptive acuity in OA in the upper and lower limbs (Adamo et al., 2007; Goble, 2010; Herter et al., 2014; Kaplan et al., 1985; Petrella et al., 1997). In general, OA perform worse (i.e., have greater errors) compared to younger adults on both ipsilateral and contralateral matching tasks in the UL (Adamo et al., 2007; Goble, 2010; Herter et al., 2014) and the lower limb (Kaplan et al., 1985; Petrella et al., 1997). Specifically, Adamo and colleagues (2007) observed that OA had significantly greater matching errors (i.e., errors were 1° to 2° greater) than younger adults in both ipsilateral and contralateral matching tasks at the elbow joint regardless of the reference location relative to the body (i.e., 10°, 30° and 60° away from body; Adamo et al., 2007). Similar absolute error magnitude differences between older and younger adults at the elbow have been reported in studies by Goble and colleagues (2010; ipsilateral matching task) and Herter and colleagues (2014; contralateral matching task). Herter and colleagues (2014) employed a similar protocol to Adamo and colleagues (2007), in that they compared older and younger adults' performance on both ipsilateral and contralateral matching tasks using a robot manipulandum. In Herter's study, the robot used was a Kinarm exoskeleton robot (KINARM, Kingston, Ontario). The robot passively moved participants' arms to the reference location and then participants were instructed to actively mirror the position with the same arm (ipsilateral matching task), or the other arm (contralateral matching task). In agreement with previous studies (Adamo et al., 2007; Goble, 2010), OA were less accurate at reproducing the reference position than younger adults.

In the lower limb, Kaplan and colleagues (1985) reported greater absolute errors in OA compared to younger adults for both ipsilateral and contralateral matching tasks involving the

knee joint. Similarly, Petrella and colleagues (1997) found greater errors in OA compared to younger adults when asked to reproduce the reference position at the knee. However, in the study by Petrella and colleagues (1997), participants actively moved the reference limb into position, which differed from the study by Kaplan and colleagues (1985), in which the reference position was passively attained.

Similar to younger adults, OA typically have greater absolute errors in contralateral matching tasks compared to ipsilateral matching tasks (Adamo et al., 2009; Schaap et al., 2015). Moreover, it has been suggested that errors may be exacerbated in the contralateral matching tasks in OA compared to younger participants due to atrophy of the corpus callosum arising with age (Boisgontier et al., 2012; Hou & Pakkenberg, 2012; Ota et al., 2006).

In addition to age related accuracy deficits in matching tasks, OA do not move their limb as smoothly as younger adults (Adamo et al., 2007; Ketcham et al., 2002). Techniques to measure the smoothness of a movement include determining the number of velocity peaks within the movement, and/or the movement's jerk score. A velocity peak is a zero crossing in an acceleration profile (i.e., maximum velocity before deceleration phase). The number of velocity peaks is the amount of zero crossings (i.e., the number of times the acceleration profile crosses the x-axis) divided by two (Adamo et al., 2007; Goble et al., 2006). Jerk score reflects the change in acceleration over the course of a movement. Therefore, a lower number of velocity peaks and/or lower jerk score indicate a smoother movement trajectory (Adamo et al., 2007; Ketcham et al., 2002). Adamo and colleagues, (2007) examined velocity peaks within each movement of their testing limb and found OA had more velocity peaks than younger adults. Similar results were seen with respect to jerk scores, such that Ketcham and colleagues (2002) reported higher jerk scores for OA compared to younger adults during a speed accuracy task.

OA also tend to initiate and execute the movements more slowly compared to younger adults. RT is defined as the time to react to a stimulus (i.e., interval of time from stimulus presentation and movement onset). Generally, when reaching to visual targets, RT has been shown to be 26 ms to 48 ms longer in OA compared to younger adults (Haaland et al., 1993; Light et al., 1996). Movement slowness is a known consequence of aging characterized by a longer movement time (MT), decreased PV and increased TTPV during UL movements (Adamo et al., 2007; Fradet et al., 2008; Goggin & Meeuwsen, 1992; Ketcham et al., 2002). MT is the interval of time from movement onset to offset and has also been shown to be longer in OA than younger adults when moving the testing limb into position (Adamo et al., 2007). In fact, Adamo and colleagues (2007) reported that MT was approximately 1 to 2 seconds longer in OA compared to younger adults across ipsilateral and contralateral matching tasks. Interestingly, there was no difference in MT between ipsilateral and contralateral matching tasks for either OA or younger adults.

PV is the greatest resultant velocity of the limb during the movement and TTPV is the time within the movement that PV is achieved. Studies have shown that the PV achieved during goal directed movements tends to decrease with age (Fradet et al., 2008; Ketcham et al., 2002) but that TTPV is higher in OA than younger adults (Goggin & Meeuwsen, 1992). Although, these studies examined PV and TTPV in pointing tasks and a handwriting task on a computer screen respectively, similar results are expected in a matching task, as similar arm movements are required. As well, OA also tend to tend to spend more TAPV compared to younger adults (Goggin & Meeuwsen, 1992), and more TAPV than before PV (Cooke et al., 1989). This increased TAPV is thought to be a compensatory strategy employed by OA to reduce endpoint errors in goal directed reaches (Walker et al., 1997). Taken together, these results suggest that

OA tend to spend more time planning (i.e., offline control) their movements and also more time executing (i.e., online control) their movements than young controls.

To date, there has been no systematic investigation incorporating clinical assessments of proprioception in OA. However, one laboratory based study examining proprioception, incorporated clinical assessments such as the 9HPT to provide insight into UL performance (Wright et al., 2011). Most clinical studies are restricted to assessing UL function and utilize the 9HPT to assess manual dexterity. While, OA tend to take longer than young controls to complete the task, it is unclear if proprioceptive deficits underlie these changes in MT (Wang et al., 2015; Wright et al., 2011). Furthermore, results of clinical vs. laboratory based assessments of proprioception have not been compared. Thus, there is a need for a systematic investigation into proprioceptive performance across clinical and laboratory settings in OA, as these assessments might provide insight into how movements are performed and further implications for proprioceptive deficits.

2.7 Proprioception in People with Multiple Sclerosis

Proprioception is commonly assessed with PwMS using the sensory system score within the EDSS. Studies have reported PwMS have an overall EDSS score ranging from 2.5-3.5 (combined 7 functional system score) and median sensory system score of 2 across the three tasks (Jamali et al., 2017; Prosperini et al., 2010; Sbardella et al., 2013). A median sensory system score of 2 across the 3 tasks, indicates a mild decrease in touch or position sense.

That said, other studies have used variations of these tasks (i.e., superficial sensation, vibration sense and joint position sense) to assess sensory function in PwMS. Scherder and colleagues (2018) adapted the superficial sensation task such that they assessed participants' sensation of a piece of cotton wool on their hand, forearm and upper arm. It was reported that

23.9% of PwMS had sensory disturbances, as participants were unable to identify where the cotton wool was placed. Similar to the vibration sense task, Jamali and colleagues (2017) assessed vibration sense in PwMS and age-gender and body mass index controls using a tuning fork applied to the two bony landmarks at the foot and one at the wrist (total three trials). The PwMS included in the study had relapsing-remitting MS for on average 7.5+/-5 years and an EDSS score of 3.5+/-1.36. The average of the three trials was recorded and results indicated that PwMS felt the vibration for a significantly shorter time than control participants (28.6s vs 46.2s respectively). Khan and colleagues (2018) also assessed vibration sense in PwMS and healthy age and gender-matched controls using a vibration perception threshold task. Although the majority of PwMS included were diagnosed with relapsing-remitting MS (n = 48) and secondary progressive MS (n = 19), this study also included patients' diagnosed with clinically isolated syndrome but fulfilled the 2010 revised McDonald Criteria for a diagnosis of MS. PwMS had a disease duration of 7.72 +/- 3.97 years and EDSS score of 1.49 +/-1.82. Rather than identifying when the vibration ended, as done in the vibration sense task, participants were to identify when the vibration started. It was reported that PwMS took significantly longer to identify the vibration on their toe in comparison to controls in the foot (9.64 seconds compared to 3.55 seconds, respectively). These impairments reflect impaired sensory function with PwMS (Shakoor et al., 2008).

Similar to the joint position task outlined in Chapter 3, Pg. 32, the Rivermead Assessment of Somatosensory Performance protocol assesses one's ability to match the position of their elbow, wrist, thumb, ankle and big toe. The experimenter passively moves participants' limbs and proprioceptive acuity is assessed by participants' ability to detect movement onset and direction of movement. Jamali and colleagues (2017) conducted a cross-sectional study with 82

PwMS and 30 controls using this protocol (see Chapter 3, Pg. 57 for participant characteristics of this study). In comparison to controls, PwMS had significantly lower scores, indicating deficits in proprioceptive acuity (Jamali et al., 2017). Overall, PwMS display deficits on these clinical assessments than control participants, indicating sensory deficits with respect to proprioception.

Although the superficial sensation, vibration sense and joint position task are widely used to assess proprioception with PwMS, limited research has examined proprioception with PwMS using laboratory based matching tasks. In fact, we were able to find only two laboratory based matching studies published in peer-reviewed journals (Iandolo et al., 2020; Rahmani & Sadeghi, 2017). These studies were restricted to examining proprioceptive acuity in the lower limb. Recently, Iandolo et al., 2020 assessed proprioception of 24 PwMS and 24 age and gender matched controls using the ipsilateral and contralateral matching tasks with the right foot. PwMS had a disease duration of 38.17 months +/-24.77 and an EDSS score of 1.00 (0.00-3.60). In the ipsilateral matching task, the right foot was passively moved to one of four reference positions and then passively moved back. In the contralateral matching task, the left foot was passively moved to the same reference positions as in the ipsilateral matching task and remained there for the duration of the trial. Participants were then asked to match the reference position with the same foot (i.e., ipsilateral matching task) or opposite foot (i.e., contralateral matching task). Interestingly, PwMS demonstrated greater errors (by 2.51°) in the contralateral matching task but not the ipsilateral matching task (0.26° greater) compared to control participants. Similarly, a study by Rahmani & Sadeghi (2017) assessed proprioceptive acuity of the ankle and knee in 60 PwMS (EDSS score 1-10) using an ipsilateral matching task. Participants' ankles were passively moved in dorsiflexion, plantar flexion, inversion or eversion and the knee was extended. Participants were then instructed to actively reproduce the ankle or knee position and absolute

errors were measured. Proprioceptive acuity was reported to be worse (higher absolute errors by approximately 3°) in the ankle across movement directions compared to the knee. As well, differences between the affected and non-affected limbs were not reported but a trend towards greater absolute errors in the affected limb was seen.

To date, no study has assessed proprioceptive acuity in laboratory based matching tasks in the UL, and hence, evaluation of the moving limb has not been explored. However, goal directed reaches to visual targets have been assessed with PwMS. Studies have found that, in general, PwMS can take up to 940 ms longer to execute goal directed movements (MT) and produce less smooth movements (i.e., have a higher jerk score) compared to control participants (Carpinella et al., 2009; Pellegrino et al., 2018). In one study by Ternes et al (2014), goal directed movements were assessed using a touchscreen to draw uninterrupted lines between two targets. Interestingly, although PwMS movements achieved a lower PV, the time to achieve PV was similar as control participants. That said, PwMS spent more TAPV compared to sex-aged matched controls, presumably in order to correct their movements and reduce endpoint errors (Ternes et al., 2014). Other studies incorporating simple RT tasks (i.e., key presses/response button) have shown that PwMS take longer to initiate their movements compared to control participants (Jennekens-Schinkel et al., 1988; Reicker et al., 2007). In fact, one study found that PwMS took approximately 70 ms longer than controls to initiate their movements in response to a visual stimulus (Jennekens-Schinkel et al., 1988). Overall, similar to OA, PwMS have been shown to take longer to initiate and execute their movements compared to control participants, and their movements are less smooth. These movement characteristics indicate a greater contribution of movement planning (offline; longer RT) and control (online; i.e., less smooth movement and greater TAPV) processes compared to control participants.

Although we see deficits in these clinical tasks, including joint position-matching tasks, the literature regarding proprioception in PwMS in the UL is limited. In fact, most studies examining UL performance in PwMS have limited their investigation to using the 9HPT to assess manual dexterity (Feys et al., 2017; Yozbatıran et al., 2006), without systematically examining proprioception. While PwMS take significantly longer than control participants to complete the 9HPT (e.g., 23.9 seconds compared to 18.6 seconds respectively; Khan et al., 2018), it is unclear if proprioceptive deficits underlie these changes in MT. Based on the limited literature assessing proprioception through laboratory based matching tasks, proprioceptive acuity in the UL in PwMS remains to be determined, as well as the processes underlying goal directed actions to proprioceptive targets.

2.8 Purpose and Hypothesis

OA and PwMS experience similar changes to the CNS (Cole et al., 2019; Han et al., 2017; Høgestøl et al., 2019; Hou & Pakkenberg, 2012; Ota et al., 2006). Specifically, MS has been suggested to lead to brain aging, resulting in similar structural changes as seen in OA (Cole et al., 2019; Høgestøl et al., 2019). Moreover, OA and PwMS display proprioceptive deficits on clinical assessments and/or laboratory based proprioceptive matching tasks (Adamo et al., 2007; Goble, 2010; Herter et al., 2014; Iandolo et al., 2020; Jamali et al., 2017; Khan et al., 2018; Kokmen et al., 1978; Rahmani & Sadeghi, 2017; Scherder et al., 2018; Temlett, 2009; Wickremaratchi & Llewelyn, 2006). To date, proprioception in OA has typically been assessed via laboratory based matching tasks, whereas clinical assessments are used to assess proprioception with PwMS (Adamo et al., 2007; Goble, 2010; Herter et al., 2014; Jamali et al., 2017; Khan et al., 2018; Scherder et al., 2018). Thus, to our knowledge, there has been no study that has looked to evaluate and compare proprioception as determined by both clinical and

laboratory based assessments in OA and PwMS. The aim of this thesis is to determine if OA and PwMS demonstrate similar proprioceptive deficits on clinical assessments of proprioception and laboratory based proprioceptive matching tasks. Given that both OA and PwMS exhibit proprioceptive deficits on clinical and/or laboratory tasks and MS has been suggested to result in brain aging (Cole et al., 2019; Høgestøl et al., 2019), we hypothesize that OA and PwMS would perform similarly on the clinical and laboratory assessments. These results will provide insight into where proprioceptive deficits might lie and could be used in rehabilitation protocols targeting goal directed movements.

Chapter 3 Experiment

3.1 Introduction

Humans make goal directed reaches throughout the day, whether it be to grasp a coffee mug, tap a key on their keyboard, or reach for a book. These movements require the central nervous system (CNS) to know where one's limbs are in space. Proprioception refers to one's ability to sense limb position and/or body movement in the absence of vision (Gilman, 2002; Goble, Coxon, et al., 2012).

Proprioceptive deficits have been observed in older adults (OA; Schaap et al., 2015) and people with Multiple Sclerosis (PwMS; Jamali et al., 2017). In normal aging, declines in proprioceptive acuity have been suggested to arise due to changes in both the peripheral nervous system (PNS) and CNS (Goble et al., 2009; Lee et al., 2013). In the PNS, aging has been shown to lead to decreases in the number and sensitivity of mechanoreceptors (Aydoğ et al., 2006; Bolton et al., 1966; Geertsen et al., 2017; Iwasaki et al., 2003; Kararizou et al., 2005; Liu et al., 2005). In conjunction with alterations in the PNS, age-related changes within the CNS can impact proprioceptive processing. For example, aging has been associated with decreased grey matter (i.e., nerve cell bodies and dendrites) in the primary somatosensory cortex (S1; (Good et al., 2001; Quiton et al., 2007). As S1 is responsible for receiving and processing sensory inputs from mechanoreceptors, decreased grey matter could lead to insufficient processing of proprioceptive input (Yamada et al., 2016). Combined, these age-related changes in the PNS and CNS have been proposed to influence one's sense of proprioception and therefore impact motor performance of the upper limb (UL; Goble et al., 2009; Lee et al., 2013).

Similar to normal aging, multiple sclerosis (MS) results in life-altering impairments in motor and sensory systems (Jamali et al., 2017). MS is an immune mediated, chronic demyelinating condition of the CNS that has been shown to give rise to sensory impairments,

including proprioceptive deficits in the UL (Jamali et al., 2017). One's sense of proprioception is thought to be impaired with MS due to dysfunction in the transmission and processing of sensory input (Cameron et al., 2008; Feys et al., 2006; Fling et al., 2014). Specifically, proprioceptive input can be delayed or inaccurate, which could drive declines in proprioceptive acuity (Cameron et al., 2008; Feys et al., 2006). Furthermore, grey matter atrophy in the post central gyrus (where S1 is located) has been found with PwMS, which could lead to inadequate processing of proprioceptive input (Han et al., 2017). Given that OA and PwMS exhibit similar changes in the CNS, it is unsurprising that MS has been suggested to result in brain aging (Cole et al., 2019; Høgestøl et al., 2019). This raises the question whether OA and PwMS exhibit similar proprioceptive deficits in the UL.

Changes in proprioception in OA and PwMS credited to age and disease have been detected across clinical and laboratory settings. Typically, clinical assessments (e.g., the Expanded Disability Status Scale (EDSS) used with PwMS; (Şen, 2018)), use a number of tasks to evaluate sensory function, and hence provide an overall index of proprioception. These tasks include the superficial sensation task, vibration sense task and joint position sense task (at the finger), which together assess the integrity of mechanoreceptors (i.e., cutaneous receptors) and joint position sense. More specifically, the superficial sensation task and vibration sensation task examine the integrity of cutaneous receptors (Gilman, 2002; Wu et al., 1999), while, within the EDSS, the joint position sense task assesses joint position sense of fine (finger) movements. In conjunction with the clinical tasks described above, the 9-hole peg test (9HPT; Kellor et al., 1971) is often performed to assess UL function (Semenko et al., 2015), specifically to examine manual dexterity (i.e., the ability to make coordinated movements; Makofske, 2011).

To date, there has been limited research in OA which has looked to evaluate proprioception in the UL using standard clinical assessments. Specifically, to our knowledge, no study has used the superficial sensation task to assess integrity of cutaneous receptors in OA. However, other studies assessing integrity of cutaneous receptors have found that tactile threshold increases with age (Bruce, 1980; Stevens & Choo, 1996; Wickremaratchi & Llewelyn, 2006) and vibration sense declines (Temlett, 2009). Interestingly, Kokmen et al., 1978 found no differences in OA and younger participants when asked to detect direction of finger movements. Lastly, it has been shown that OA take longer than younger adults to complete the 9HPT task (Wang et al., 2015; Wright et al., 2011).

Similar to OA, PwMS demonstrate deficits on clinical assessments compared to control participants (Jamali et al., 2017; Khan et al., 2018; Scherder et al., 2018). Unfortunately, research with PwMS typically reports an overall disability score, as opposed to an index related to proprioceptive processing (e.g., one's overall score on the EDSS is reported, compared to their sensory system score), or performance outcomes on individual tasks. For example, one study reported a median sensory system score on the EDSS of 2 out of the 3 in PwMS across the 3 tasks (i.e., superficial sensation, vibration sense and joint position sense tasks), reflecting a mild decrease in proprioception (Prosperini et al., 2010). More specifically, PwMS have been shown to experience deficits in superficial sensation (Scherder et al., 2018), vibration sense (Jamali et al., 2017; Khan et al., 2018) and joint position sense (Jamali et al., 2017) compared to control participants. Similar to OA, PwMS take longer to complete the 9HPT compared to controls (Huertas-Hoyas et al., 2020; Khan et al., 2018; Yozbatıran et al., 2006).

The joint position sense tasks used in the clinic have participants indicate a direction of motion (e.g., did their finger move up or down). In laboratory settings, proprioceptive acuity is

assessed by having participants reproduce a reference position in a matching task. These matching tasks are more reflective of goal directed movements carried out in everyday life, in comparison to the detection of motion in the clinic, as they require a larger range of motion, and there is a target goal (as would be the case when reaching for a coffee mug). Within these laboratory matching tasks, a participant's limb is moved into a specific position, known as the reference position. This movement can be completed actively by the participant or passively, such that the experimenter/robotic device moves the participant's arm into position. After establishing the reference position, participants are to reproduce the position with the same (ipsilateral matching task) or opposite (contralateral matching task) arm. Deficits in proprioceptive acuity in matching tasks are determined by analyzing endpoint errors (Goble, 2010).

In general, OA tend to perform worse (i.e., have greater errors) compared to younger adults on both ipsilateral and contralateral matching tasks with the UL (Adamo et al., 2007; Goble, 2010; Herter et al., 2014). As well, similar to younger adults, OA typically have greater absolute errors in the contralateral matching tasks compared to ipsilateral matching tasks (Adamo & Martin, 2009; Schaap et al., 2015). It has been further proposed that errors in the contralateral matching task may be exacerbated with age due to atrophy of the corpus callosum (Hou & Pakkenberg, 2012; Ota et al., 2006), as the corpus callosum is imperative for interhemispheric communication required in the contralateral matching task (Boisgontier et al., 2012; Goble, 2010).

Although there is a plethora of literature involving clinical assessments of proprioception with PwMS, there is a limited number of studies assessing proprioceptive acuity using laboratory based proprioceptive matching tasks (i.e., Iandolo et al., 2020; Rahmani & Sadeghi, 2017). To

our knowledge, matching tasks conducted with PwMS have only examined proprioceptive acuity in the lower limb. Specifically, Iandolo et al., 2020 assessed position sense at the ankle using ipsilateral and contralateral matching tasks. During the ipsilateral matching task, PwMS and aged-matched controls had similar matching errors, whereas in the contralateral matching task the PwMS demonstrated higher matching errors than aged-matched controls. Therefore, similar to OA, PwMS demonstrate greater errors in the contralateral matching task compared to the ipsilateral matching task, which could be attributed to atrophy in the corpus callosum seen in PwMS (Han et al., 2017; Iandolo et al., 2020).

In addition to providing a measure of proprioceptive acuity, matching tasks are useful for providing insight into processes underlying goal directed movements to a proprioceptive target (i.e., the reference position). Studies examining movements in the laboratory (i.e., proprioceptive matching tasks, reaches to visual targets and pointing tasks) have demonstrated that OA carry out their matching movements differently compared to younger adults. In general, OA take longer to initiate and execute their movements and their movements are less smooth compared to younger participants (Adamo et al., 2007; Fradet et al., 2008; Ketcham et al., 2002; Light et al., 1996). To our knowledge no study has required PwMS to perform laboratory based proprioceptive matching tasks in the UL and therefore no analysis of movement parameters has been completed. However, goal directed reaches to visual targets have been examined with PwMS, with results indicating that PwMS take longer to execute goal directed movements compared to control participants and their movements are less smooth (Carpinella et al., 2009; Pellegrino et al., 2018). Other studies employing simple reaction time (RT) tasks have found PwMS take longer to initiate their movements in comparison to controls (Jennekens-Schinkel et al., 1988; Reicker et al., 2007). Interestingly, in a study by Ternes et al (2014), PwMS were found to achieve peak

velocity (PV) at a similar time as control participants. That said, PwMS spent more time after PV (TAPV) compared to controls, presumably in order to correct their movements and reduce endpoint errors as seen in OA. Together, these results suggest that both OA and PwMS demonstrate deficits in the planning (i.e., offline) and control (i.e., online execution) of goal directed movements compared to younger adults and control participants, respectively.

Based on the literature reported above, both OA and PwMS exhibit proprioceptive deficits on clinical and/or laboratory tasks assessing proprioception compared to younger and control participants, respectively (Adamo et al., 2007; Goble, 2010; Herter et al., 2014; Iandolo et al., 2020; Jamali et al., 2017; Khan et al., 2018; Kokmen et al., 1978; Rahmani & Sadeghi, 2017; Scherder et al., 2018; Temlett, 2009; Wickremaratchi & Llewelyn, 2006). However, from the literature outlined above, it is evident that the assessment of proprioception has not been consistent across OA and PwMS. Studies assessing proprioception in OA have generally used laboratory based proprioceptive matching tasks, rarely including standard clinical assessments. On the contrary, studies with PwMS have primarily relied on clinical assessments to provide insight into proprioception. Thus, the purpose of this study was to systematically assess and compare proprioception as established via clinical and laboratory based assessments in OA and PwMS. Given that MS has been suggested to result in brain aging (Cole et al., 2019; Høgestøl et al., 2019) and OA and PwMS exhibit proprioceptive deficits, we hypothesized that OA and PwMS would show similar performance on the clinical assessments and proprioceptive matching tasks.

3.2 Methodology

3.2.1 Participants and Demographics

Twenty-four participants (70+ years old) from the Ottawa community were recruited to take part in this study following a telephone screening. The attached screening packet (Appendix A) was read to participants over the telephone to describe the study purpose and participant involvement. Eligible individuals had normal or corrected-to-normal vision, and self-reported no history of neurological, musculoskeletal/orthopedic or any other diagnosed condition that might affect upper extremity function. Upon arriving at the lab, participants provided written informed consent, as well as completed a series of self-report questionnaires. These questionnaires established information regarding the participants' characteristics (i.e., disease duration, MS subtype, age and sex), and hand dominance (Oldfield, 1971; see Appendix B1). Height and weight were also measured in the laboratory, using a scale with a stadiometer (Detecto, Webb City, MO.) and reported in Table 1. All ethical standards and safety monitoring procedures were followed according to the University of Ottawa's Faculty of Health Sciences and Science Research Ethics Board. Participation was completely voluntary, and participants were free to withdraw at any point without consequence. Participants were compensated $20 per session (i.e., $40 in total).

The analyses and results presented below also include data from twenty right-handed participants, which were collected previously as part of a larger project looking at UL function with PwMS. These participants have lived with MS on average for 14.6 years +/8.71. 13 of them (65%) have relapsing-remitting multiple sclerosis (RRMS) and the remaining 7 participants (35%) have progressive multiple sclerosis (PMS). More information on the participants (i.e., OA and PwMS) can be found in Table 1.

3.2.2 Experimental Paradigm

Position sense (i.e., proprioception) was evaluated using clinical assessments and laboratory based proprioceptive matching tasks. Participants had the option to complete the clinical assessments and laboratory based proprioceptive matching tasks on the same day or two days separated by a week (13 PwMS completed the tasks on separate days). Clinical assessments evaluated sensitivity of cutaneous receptors in the fingers and arms (i.e., superficial sensation and vibration sense) and position sense using the standard tasks included in the EDSS and Fugl-Meyer (Fugl-Meyer et al., 1975) assessments. Clinical assessments also included a manual dexterity examination via the 9HPT (Feys et al., 2017; Kellor et al., 1971), assessment of grip strength and endurance measured using a dynamometer, determination of manual ability using the ABILHAND questionnaire (Penta et al., 2001) and measurement of cognitive processing speed using the symbol-digit modalities test (SDMT; Aaron, 1982). Proprioceptive matching tasks were completed in the laboratory using a 2-joint robot manipulandum (Kinarm End-Point Lab, KINARM technologies).

The order in which the clinical and laboratory sessions were completed was counterbalanced across participants, and there was a minimum break of 10 minutes between sessions. Participants could choose to complete the clinical assessments and laboratory based proprioceptive matching tasks on the same or different days. Total testing time took approximately 1 hour and 10 minutes (30 minutes for the clinical assessments, plus a 10 minute break followed by 30 minutes for the laboratory proprioceptive matching task).

3.2.3 Clinical Procedure

3.2.3.1 Experimental Apparatus and Setup for Clinical Assessments

The superficial sensation, vibration sense and joint position sense at the finger tasks were administered by a neurostatus certified assessor to determine sensory function (Şen, 2018). These tasks form part of a subset of the EDSS which was administered in its entirety to get an overall evaluation of disability (as established via the EDSS total score). Similarly, shoulder position sense task, which is part of the Fugl-Meyer assessment, was conducted to determine clinically defined UL position sense at the shoulder. The superficial sensation task consisted of an assessor pressing a neurological pin on 8 random locations on participants' hands. Participants informed the assessor if they felt the dull or sharp side and received scores out of 5 that indicated their accuracy. For the vibration sensation task, an assessor hit a tuning fork which was then placed on the knuckle of a participant's middle finger of their left or right hand. Participants completed 2 trials, 1 for each hand. They then received a score out of 3 based on their ability to sense when the vibration on their hand had stopped. During the position sense task for the finger (i.e., EDSS) and shoulder (i.e., Fugl-Meyer), the assessor moved the finger or limb up or down, respectively. After the movement was complete, participants reported the direction of the movement (performance was scored out of 3 for the EDSS and 2 for the Fugl-Meyer). Performance on the superficial sensation, vibration sense and finger position sense tasks were combined to make up a sensory score within the EDSS known as the EDSS sensory score, which is scored out of 6. More detailed information on the superficial sensation, vibration sense and joint position sense task for the finger (i.e., EDSS) and shoulder (Fugl-Meyer) can be found in Appendix C and D. Other clinical assessments included were the ABILHAND questionnaire and SDMT. Manual ability was assessed using the ABILHAND questionnaire (Penta, Tesio, Arnould, Zancan, &

Thonnard, 2001; see Appendix B2). Cognitive processing speed was analyzed using the SDMT, in which participants were required to substitute geometric symbols for numbers using a response key and the number of symbols completed out of 110 were recorded (Aaron, 1982).

UL dexterity, strength and endurance were assessed using the 9HPT, grip strength and grip endurance assessments respectively. In the 9HPT, participants first picked up the 9 pegs, 1 at a time, and placed them individually in the holes on the board. Once the board was full, participants then removed the pegs 1 at a time (Kellor et al., 1971). The 9HPT was completed 4 times in total, 2 times with each hand. The average amount of time to complete the 9HPT with each hand was determined. During the grip strength task, participants squeezed a dynamometer as hard as they could (Haidar et al., 2017). 3 trials were completed with the dominant hand, followed by 3 trials with the non-dominant hand. Grip strength was defined for each hand as the maximum value exerted across the three trials (Haidar et al., 2017). In the grip endurance task, participants squeezed a dynamometer as hard as they could for 1 minute. Grip endurance was determined by changes in performance in force over the duration of the trial. Specifically, the ratio of force at the end of the trial/force at the start of the trial was calculated for each hand (Nicolay & Walker, 2005). Although the Fugl-Meyer assessment was used in this study, it was not included during data collection with PwMS. Please see Appendix C and D for additional details regarding these clinical assessments and evaluation of performance (i.e., scoring performance).

3.2.3.2 Data Analysis

Scores for these tasks (i.e., superficial sensation task, vibration sensation task, joint position sense task at the finger (separated by each hand), total EDSS score, EDSS sensory score, and ABILHAND questionnaire score) were compared between OA and PwMS using a Mann-

Whitney-U test. To determine if the time to complete the 9HPT (s), grip strength (kg) and grip endurance (ratio) differed across groups of participants (i.e., OA and PwMS) and hand (right vs. left), a 2 Group x 2 Hand mixed analysis of variance (ANOVA) with repeated measures (RM) on the last factor was conducted for each variable. Lastly, to assess differences in SDMT scores between groups (i.e., OA and PwMs), a t-test was conducted.

3.2.4 Robotic Procedure

3.2.4.1 Experimental Apparatus and Setup for Laboratory based Proprioceptive Matching Tasks

The laboratory matching tasks took place in a secluded testing room using a two-joint robot manipulandum (KINARM End-Point Lab, KINARM, Kingston, Canada). The experimental set-up consisted of a downward facing monitor (EzSign model 47LD452B, LG. Seoul, South Korea; refresh rate = 60 Hz), which was located 20.5 cm above a reflective surface and 41.0 cm above 2 robotic handles (Figure 1A). Thus, visual stimuli presented on the monitor and reflected by the surface appeared to lie in the same horizontal plane as the robot handles. Participants sat in a height-adjustable chair and grasped either both handles or a single handle of the two-joint robot with their left and/or right hands (Figure 1A). Once participants were comfortably seated, the chair was locked in place and the lights were turned off. Participants' view of their hands was obstructed by the reflective surface and a black cloth draped between their shoulders and the experimental apparatus. The location of the robotic handles (i.e., participants' hands) was tracked at 1000 Hz, with a spatial accuracy of 0.1 mm.

3.2.4.2 Laboratory Based Proprioceptive Matching Tasks

Proprioceptive acuity was assessed in ipsilateral and contralateral matching tasks, in which participants were to match a reference hand with their testing hand. In the ipsilateral

matching task, the reference and testing hand were the same, while, in the contralateral matching task, the reference and testing hands differed. Participants completed both the ipsilateral and the contralateral matching tasks with both hands. An example trial sequence for the ipsilateral and contralateral matching tasks is displayed in Figure 1C. In the example shown, participants completed 12 trials of the ipsilateral matching task (3 practice trials followed by 9 matching trials), followed by 12 trials of the contralateral matching task (3 practice trials followed by 9 matching trials) with their right hand as the reference hand. The participant then completed 12 trials of the ipsilateral matching task (3 practice trials) and 12 trials of the contralateral matching task (3 practice trials) with the left hand as the reference hand. Participants completed 48 trials in total.

At the beginning of each trial, the robot passively moved the reference hand to a white circular home position (1 cm in diameter), located approximately 20 cm in front of the participant (see Figure 2). In the contralateral task, two home positions for the left and right hands, separated by 20 cm, were displayed on the reflective surface. Participants were instructed to stay still, maintaining their hand(s) within the home position(s). If participants attempted to move outside the home position, the robot passively moved their hand back to the home position. Following 500 ms at the home position, the robot handle passively moved the participant's left or right reference hand to one of the three reference locations at a distance of 5 cm (near), 7.7 cm (middle) or 9.4 cm (far) from the home position at an angle of 75°, 65° and 44° from the horizontal, respectively (Figure 1B). The robot moved the hand to the reference location along an indirect path in a movement time (MT) of 1500 ms. Specifically, the hand was moved around the reference location either two or three times before stopping at the final location (refer to Figures 2a, box (ii) and 2b, box (ii)). This was the reference position participants needed to match with

the same hand (i.e., in the ipsilateral matching task) or opposite hand (i.e., in the contralateral matching task). In the ipsilateral task, the robot handle was positioned at the reference position for 1000 ms (Figure 2a, box (iii)) before being passively returned to the home position (MT = 1500 ms; Figure 2a, box (iv)). In the contralateral matching task, the robot was held at the reference position for the duration of trial. After a delay (500 ms in the ipsilateral matching task and 1000 ms in the contralateral matching task; Figure 2b, box (iv)), the home position of the testing hand changed colour from white to magenta (Figure 2a, box (vi) and Figure 2b, box (iv)). This colour change was participants' cue to reproduce the reference position with their testing hand. At the end of the trial, participants' hand(s) were brought back to the home position passively by the robot manipulandum (MT = 1500 ms; Figure 2a, box (viii) and Figure b, box (vi)). These tasks were counter-balanced across participants by hand (i.e., right vs. left testing hand first) and task (i.e., ipsilateral matching task first vs. contralateral matching task first).

3.2.4.3 Data Analysis

Position, velocity and acceleration data were analyzed using custom written MATLAB scripts (Matlab 2013, The Mathworks Inc.). The active movement portion of each trial (i.e., when the participant moved the testing hand into position) was the focus of our analysis. Movement onset of the testing hand was defined as the first increase in velocity greater than 0.01 m/s for 50 consecutive recording samples (i.e., 50 ms). The trial was considered complete when the velocity of the arm fell below 0.01 m/s. Performance related to the variables described below was determined for each participant, for both the ipsilateral and contralateral matching tasks for both hands (i.e., left and right testing hands) at all reference locations.

3.2.4.4 Assessment of Limb Motion

To analyze limb motion, we assessed mean performance with respect to movement accuracy, as well as planning and execution measures. Accuracy was assessed using endpoint errors, which reflect the position of the testing hand in relation to the reference position. Planning measures were analyzed to gain insight into how participants planned their movement (i.e., offline control). Lastly, execution measures were included to assess how movements were executed (i.e., online control).

To assess final position accuracy, we determined (1) resultant error, (2) absolute angular error, and (3) absolute errors in both the x and y directions. The resultant error (R-Error) was defined as the distance between the final position of the testing hand and the reference position. The absolute end point angular error (|EPAE|) was defined as the absolute value of the angular difference between the movement vector (i.e., vector joining the home position to the testing hand's end position) and reference vector (i.e., vector joining the home position to the reference location. Absolute error on the other hand does not account for direction and was defined as the deviation of the testing hand's end position from the target in the x (horizontal) and y (vertical) directions. In addition to calculating mean errors, variability of errors across trials was calculated.

Movement planning measures of the testing hand included RT, proportional time to peak velocity (pTTPV), PV in the resultant direction and absolute angular error at PV (|PVAE|). RT was defined as the interval of time between the onset of the go signal (i.e., home position of the testing hand changed colour to magenta) to movement initiation. pTTPV was defined as the time within the movement that PV (i.e., the greatest resultant velocity of the hand during the movement) was achieved divided by the interval of time from movement onset to offset. Lastly,

|PVAE| was defined as the absolute value of the angular difference between the movement vector (i.e., vector joining the home position to the hand at PV) and reference vector (i.e., vector joining the home position to the reference location). The means and variability for all aforementioned variables were calculated.

Movement execution measures related to the testing hand included MT, path length, proportional time after peak velocity (pTAPV) and jerk score. MT was defined as interval of time from movement onset to offset. Path length was defined as the distance the testing hand moved from the home position to the final testing hand position. Proportional time after peak velocity (pTAPV) was defined as the TAPV was achieved to the end of the movement divided by MT. Lastly, jerk score was defined as the change in acceleration over the course of a movement, such that jerk score was calculated according to the following formula:=

$$\text{jerk score} = \text{sqrt}\left(\frac{\text{ssJerk}}{2} \text{ x } \frac{\text{MT}^5}{\left(\frac{\text{Jerk}_{\text{VoltsRange}}}{1000}\right)^2}\right)$$

in which SSJerk represents the sum of the squared jerk across the trajectory, MT represents movement time in seconds, and $\text{Jerk}_{\text{VoltsRange}}$ represents the difference between the maximum and minimum jerks recorded from the acceleration profile across a trajectory. A higher jerk score indicates a less smooth movement. Means and variability of means (i.e., standard deviation) were calculated for all aforementioned variables (i.e., MT, path length, PTAPV, jerk score).

To assess group differences in performance on the ipsilateral and contralateral matching tasks, we submitted the dependent variables described above (i.e., means and standard deviations of accuracy measures: resultant errors, |EPAE|, absolute errors in both the x (i.e., AEX errors) and y (i.e., AEX errors) directions; planning measures: RT, pTTPV, PV, |PVAE|; execution

Measures: MT, path length, pTAPV, jerk score) to a 2 Group (OA and PwMS) x 2 Hand (left vs. right hand) x 3 reference location (5 cm vs. 7.7 cm vs. 9.4 cm) mixed ANOVA with RM on the last 2 factors. Statistical tests were run separately for the 2 tasks (ipsilateral and contralateral matching tasks).

Finally, we compared performance on the ipsilateral and contralateral matching tasks within groups for variables that demonstrated group differences in the analysis above. Specifically, accuracy measures (i.e., |EPAE| and AEX error), planning measures (i.e., RT, PV, pTTPV, and |PVAE|), and execution measures (i.e., pTAPV, and MT) were analyzed in a 2 Task (ipsilateral vs. contralateral matching task) x 2 Hand (left vs. right hand) RM ANOVA. Statistical tests were run separately for the two groups (OA and PwMS). The significance value for all statistical tests performed was set at $p < 0.05$, and Bonferonni post-hoc tests corrected for multiple comparisons were used to find the locus of significant effects.

3.3 Results

3.3.1 Clinical Assessments

In Table 2 we report scores achieved on our clinical assessments. As expected, OA and PwMS showed differences in performance for most clinical measures (e.g., EDSS, Sensory Score, Abilhand questionnaire, SDMT, 9HPT and Grip Endurance). The overall EDSS score for OA was significantly lower than for PwMS ($U = 26.00$, $Z = -5.231$, $p < 0.001$). More important to our research question, analysis of the EDSS sensory score revealed a lower score for OA compared to PwMS ($U = 64.5$, $Z = -4.616$, $p < 0.001$). The median sensory score for PwMS was 1.00, which indicates a proprioceptive deficit for PwMS in comparison to OA (Median = 00.00). Similarly, analysis of the three tasks (i.e., superficial sensation, vibration sense and joint position sense) that make up the sensory score indicated that PwMS displayed deficits in comparison to

OA for both the left and right hands (Superficial sensation: Left hand: U = 152.000, Z= -2.765, p = 0.006; Right hand: U = 177.500, Z = -2.320, p = 0.020; Vibration sense: Left hand: U = 142.000, Z = -3.181, $p < 0.001$; Right hand: U = 168.000, Z = -2.850, p = 0.004; Joint position sense: Left hand: U = 180.000, Z = -2.572, p = 0.010; Right hand: U = 180.000, Z = -2.572, p = 0.010). OA also demonstrated intact position sense at the shoulder, receiving a perfect score of 2.00 overall on the Fugl-Meyer assessment. In accordance with the EDSS results, the Abilhand questionnaire revealed that PwMS reported lower manual ability than OA (U = 359.00, Z = 2.928, p = 0.003). The SDMT revealed that OA had slower cognitive processing speed in comparison to PwMS ($t(1,42) = 2.839$, p = 0.007).

Analysis of the time to complete the 9HPT revealed a main effect of Group ($F(1,42) = 11.827$, p = 0.001, $\eta^2 = 0.220$) and Hand ($F(1,42) = 10.548$, p = 0.002, $\eta^2 = 0.201$), as well as a significant interaction between Group x Hand ($F(1,42) = 5.002$, p = 0.031, $\eta^2 = 0.106$). As shown in Table 2, post hoc analysis revealed that the time to complete the 9HPT with the right and left hands was longer in PwMS than OA (Right hand: p = 0.013; Left hand: p = 0.001). ANOVA also revealed that PwMS took longer to complete the 9HPT with their left hand compared to their right hand (p = 0.001). On average, grip strength was 23.39 kg, which did not differ between Groups ($F(1,42) = 2.906$, p = 0.096, $\eta^2 = 0.065$), nor across Hands ($F(1,42) = 3.056$, p = 0.088, $\eta^2 = 0.068$). However, in assessing grip endurance, ANOVA revealed main effects of Group ($F(1,42) = 10.699$, p = 0.002, $\eta^2 = 0.203$) and Hand ($F(1,42) = 5.885$, p = 0.020, $\eta^2 = 0.123$), as well as a significant interaction between Group x Hand ($F(1,42) = 4.592$, p = 0.038, $\eta^2 = 0.099$). Post hoc analysis revealed that grip strength could be maintained longer in the left hand of OA compared to the left hand of PwMS ($p < 0.001$). There was no difference in

grip endurance in the right hand between OA and PwMS ($p = 0.065$). However, PwMS demonstrated greater grip endurance in their right hand compared to their left hand ($p = 0.004$).

Overall, clinical assessment of UL performance indicated that PwMS displayed UL dysfunction (i.e., poorer performance on the 9HPT, and deficits with respect to grip endurance in the left hand), including underlying proprioceptive deficits (i.e., lower scores on all sensory tests), in comparison to OA. However, OA exhibited greater cognitive deficits than PwMS, as indicated by the SDMT.

3.3.2 Laboratory Based Proprioceptive Matching Tasks

Below we report results from the laboratory based proprioceptive matching tasks. Specifically, main effects of Group and Hand, significant Group x Hand and Group x Hand x Target interactions with respect to mean performance on our accuracy, planning and execution measures are reported. Variability related to the measures reported below are provided in Tables 3 and 4 and are only discussed in the text if analyses revealed a significant difference between groups. Furthermore, given differences in performance with respect to reference position were as expected (e.g., with respect to pTTPV, MT, path length, etc.), and that analyses did not reveal any significant interactions between Group x Target, significant main effects of Target and Target x Hand interactions are reported in the supplementary file in order to streamline our results.

3.3.2.1 Ipsilateral Matching Task

3.3.2.1.1 Accuracy

In Figure 3, we show mean absolute positions in the ipsilateral and contralateral matching tasks for OA and PwMS for the three reference positions. Starting with the ipsilateral matching task in Table 3, we see that, in general, participants did not match the reference position

accurately, such that the average R-Error across all reference positions was 2.94 cm (SD = 1.04; see Table 3). That said, analysis of mean R-Error did not reveal a main effect of Group ($F(1,42) = 3.010$, $p = 0.090$, $\eta^2 = 0.067$). ANOVA revealed a significant interaction between Group and Hand with respect to R-Error variability ($F(1,42) = 4.842$, $p = 0.033$, $\eta^2 = 0.103$). However, post hoc analyses failed to reveal any group differences between the left ($p = 0.053$) and right hands ($p = 0.253$).

When examining directional errors, we did find group differences as displayed in Figure 4a. Group differences with respect to performance accuracy were seen in |EPAE| ($F(1,42) = 6.772$, $p = 0.013$, $\eta^2 = 0.139$), such that OA were less accurate than PwMS across both hands (i.e., ANOVA revealed no main effect of Hand and no significant Group x Hand interaction, both $p > 0.05$). Similar to |EPAE|, analysis of mean absolute errors in the x direction (i.e., AEX) revealed a main effect of Group ($F(1,42) = 5.110$, $p = 0.029$, $\eta^2 = 0.108$), such that OA had horizontal errors that were 0.54 cm greater on average than errors seen in PwMS. There was no difference between groups with respect to absolute errors in the vertical direction (i.e., AEY; $F(1,42) = 1.668$, $p = 0.204$, $\eta^2 = 0.038$). While analysis of AEY variability indicated a significant Group x Hand interaction ($F(2,42) = 6.571$, $p = 0.014$, $\eta^2 = 0.135$), post hoc analysis revealed that there were no differences between OA and PwMS in the left ($p = 0.081$) or right ($p = 0.120$) hands. However, variability of AEY for the left hand in OA was significantly greater than for their right hand ($p = 0.007$). Together, these results suggest OA were less accurate at matching the reference position compared to PwMS, while both groups displayed similar consistency in their endpoints.

3.3.2.1.2 Movement Planning

In Table 3, mean and variability of RT are presented. As seen in Figure 5a ANOVA revealed a main effect of Group ($F(1,42) = 4.933$, $p = 0.032$, $\eta^2 = 0.105$), and significant interaction between Group x Hand ($F(1,42) = 13.019$, $p = 0.001$, $\eta^2 = 0.237$) with respect to RT. Post hoc analysis indicated that PwMS took longer to initiate their movements with their right hand compared to OA ($p = 0.002$). RT for the left hand did not differ between Groups ($p = 0.553$). OA initiated their movements earlier with their right hand compared to their left hand ($p = 0.002$). Analysis of RT variability also revealed a significant Group x Hand interaction ($F(1,42) = 6.536$, $p = 0.014$, $\eta^2 = 0.135$), such that PwMS were more variable when initiating movements with their right hand compared to their left hand ($p = 0.025$).

When evaluating performance at PV, analyses revealed that the proportional time that PV was achieved (pTTPV), magnitude of PV, and errors at PV differed between groups. PwMS spent a greater proportion of their movement achieving PV than OA ($F(1,42) = 7.372$, $p = 0.010$, $\eta^2 = 0.148$), and achieved a lower PV ($F(1,42) = 5.872$, $p = 0.020$, $\eta^2 = 0.123$). However, OA were less accurate than PwMS at PV ($F(1,42) = 4.464$, $p = 0.041$, $\eta^2 = 0.096$), regardless of hand (Group x Hand interaction ($F(1,42) = 0.001$, $p = 0.981$, $\eta^2 < 0.001$). Therefore, although PwMS took longer to achieve PV, they were more accurate at PV compared to OA. With respect to variability, analysis of PV variability revealed a significant Group x Hand x Target interaction ($F(1,42) = 1.190$, $p = 0.309$, $\eta^2 = 0.028$). Post hoc analysis indicated that when matching the reference position with the left hand, PV variability was greater in OA than PwMS for the middle ($p = 0.030$) and far targets ($p = 0.003$). On the other hand, when matching the reference position with the right hand, PV variability was greater in PwMS than OA for the middle target ($p = 0.022$). From these results, it is evident that there are group differences with respect to

movement planning, such that PwMS took longer to initiate their movements in the right hand (i.e., RT), and took longer to achieve a lower PV compared to OA. As well, PwMS were more accurate at PV compared to OA.

4.3.2.1.3 Movement Execution

Although OA and PwMS differed with respect to endpoint accuracy and planning of their movements, there were few differences between groups with respect to how movements were executed (i.e., controlled online). There were no differences between Groups with respect to MT ($F(1,42) = 0.325$, $p = 0.572$, $\eta^2 = 0.008$), and path length ($F(1,42) = 3.187$, $p = 0.081$, $\eta^2 = 0.071$; see Table 3). However, path length did differ between hands for both groups ($F(1,42) = 6.301$, $p = 0.016$, $\eta^2 = 0.130$), such that the left hand moved a greater distance compared to the right hand (Left hand: M = 11.88 cm, SD = 2.37; Right hand: M = 11.13 cm, SD = 2.13).

Although OA and PwMS reached in a similar MT and reached a similar distance, the proportion of time spent after PV differed between groups. In accordance with the pTTPV results, ANOVA revealed that OA spent a greater proportion of their movement after PV compared to PwMS ($F(1,42) = 7.371$, $p = 0.010$, $\eta^2 = 0.149$). Therefore, OA spent a greater proportion of the movement in the online control phase compared to PwMS. Lastly, smoothness of movement did not differ between OA and PwMS groups ($F(1,42) = 0.238$, $p = 0.628$, $\eta^2 = 0.006$). Taken together, these results indicate that while OA spend more time in the online phase of their movements, they execute their movements in a similar manner to PwMS.

3.3.2.2 Contralateral Matching Task

3.3.2.2.1 Accuracy

Similar to results observed in the ipsilateral matching task, all participants displayed errors when trying to match the reference position in the contralateral matching task. Average R-

Error was 3.20 cm (SD = 1.02, see Table 4), which did not differ between Groups ($F(1,42) = 2.57$, $p = 0.116$, $\eta^2 = 0.058$). With respect to |EPAE|, group differences were about the same magnitude as seen in the ipsilateral matching task (e.g., OA vs PwMS: Ipsilateral matching task = 1.85 cm, Contralateral matching task = 1.76 cm), however, this group difference failed to reach significance in the contralateral matching task ($F(1,42) = 1.360$, $p = 0.250$, $\eta^2 = 0.031$). We did find significantly larger horizontal errors in OA compared to PwMS (AEX: $F(1,42) = 4.218$, $p = 0.046$, $\eta^2 = 0.091$ see Table 4, Figure 4b), Similar to the ipsilateral matching task, analysis revealed no group differences with respect to AEY ($F(1,42) = 0.137$, $p = 0.713$, $\eta^2 = 0.003$). Therefore, similar to the ipsilateral matching task, we find that OA had greater directional errors than PwMS, specifically in the horizontal direction.

3.3.2.2.2 Movement Planning

In contrast to the ipsilateral matching task, there were few group differences observed with respect to our planning measures in the contralateral matching task. As seen in Table 4, there was no main effect of Group with respect to RT ($F(1,42) = 3.763$, $p = 0.059$, $\eta^2 = 0.082$). Similar to the ipsilateral matching task, analysis of pTTPV revealed a main effect of Group ($F(1,42) = 5.901$, $p = 0.019$, $\eta^2 = 0.123$) as seen in Figure 5b. Thus, PwMS spent a greater proportion of their movement achieving PV, regardless of hand used ($F(1,42) = 0.042$, $p = 0.838$, $\eta^2 = 0.001$). However, unlike the ipsilateral matching task, both groups achieved a similar PV ($F(1,42) = 1.711$, $p = 0.198$, $\eta^2 = 0.039$) and had similar errors at PV ($F(1,42) = 0.402$, $p = 0.529$, $\eta^2 = 0.009$). Therefore, all participants initiated their movements within a similar amount of time and achieved a similar PV. While PwMS took a longer time to achieve PV compared to OA, all participants demonstrated similar errors at PV.

3.3.2.2.3 Movement Execution

Similar to the ipsilateral matching task, OA and PwMS executed their movements in a similar manner with respect to MT and path length. On average MT was 1081.59 ms across groups and did not differ between OA and PwMS ($F(1,42) = 1.173$, $p = 0.285$, $\eta^2 = 0.027$). As well, the distance the hand travelled was similar across groups ($F(1,42) = 0.837$, $p = 0.365$, $\eta^2 = 0.020$). However, similar to the ipsilateral matching task, the proportion of the movement spent after PV differed between groups, with OA demonstrating a greater pTAPV compared to PwMS ($F(1,42) = 0.5897$, $p = 0.020$, $\eta^2 = 0.123$). Therefore, similar to the ipsilateral matching task, OA spent a greater proportion of the movement in the online control phase compared to PwMS. Lastly, smoothness of movement did not differ between OA and PwMS groups ($F(1,42) = 0.481$, $p = 0.492$, $\eta^2 = 0.011$). Taken together these results indicate that once again OA and PwMS executed their movements in a similar manner.

3.3.2.3 Ipsilateral vs. Contralateral Matching Tasks

Final analyses looked to compare performance across tasks for both groups. We found a significant main effect of Task with respect to |EPAE| for both OA ($F(1,46) = 35.204$, $p < 0.001$, $\eta^2 = 0.434$) and PwMS ($F(1,38) = 74.738$, $p < 0.001$, $\eta^2 = 0.663$). ANOVA revealed that greater errors were seen in the contralateral matching task compared to the ipsilateral matching task for OA (Ipsilateral matching task: M = 6.35°, SD = 3.47; Contralateral matching task: M = 14.07°, SD = 6.81) and PwMS (Ipsilateral matching task: M = 4.50°, SD = 2.22; Contralateral matching task: M = 12.31°, SD = 5.30). Similarly, there was a main effect of Task with respect to AEX for both OA ($F(1,46) = 7.332$, $p = 0.009$, $\eta^2 = 0.137$) and PwMS ($F(1,38) = 19.285$, $p < 0.001$, $\eta^2 = 0.337$). Findings related to AEX were similar as those obtained for |EPAE|, in that greater errors were seen in the contralateral matching task compared to ipsilateral matching task for OA

(Ipsilateral matching task: M = 1.84 cm, SD = 1.10; Contralateral matching task: M = 2.64 cm, SD = 1.31) and PwMS (Ipsilateral matching task: M = 1.30 cm, SD = 0.61; Contralateral matching task: M = 2.08 cm, SD = 0.84).

Planning and execution measures revealed similar performance between tasks for OA and PwMS. Specifically, RT was similar across tasks for OA ($F(1,46) = 0.051$, $p = 0.823$, $\eta^2 = 0.001$) and PwMS: $F(1,38) = 0.313$, $p = 0.579$, $\eta^2 = 0.008$). The pTTPV was also similar across tasks for OA ($F(1,46) = 0.086$, $p = 0.771$, $\eta^2 = 0.002$) and PwMS: ($F(1,38) = 1.449$, $p = 0.236$, $\eta^2 = 0.037$), as was the magnitude of PV achieved (OA: $F(1,46) = 3.240$, $p = 0.078$, $\eta^2 = 0.066$; PwMS: $F(1,38) = 0.950$, $p = 0.336$, $\eta^2 = 0.024$). Consistent with the accuracy measures reported above, errors at PV differed between tasks for OA ($F(1,46) = 16.318$, $p < 0.001$, $\eta^2 = 0.262$) and PwMS ($F(1,38) = 41.342$, $p < 0.001$, $\eta^2 = 0.521$). ANOVA revealed greater errors in the contralateral matching task compared to the ipsilateral matching task for OA (Ipsilateral matching task: M = 8.58°, SD = 5.13; Contralateral matching task: M = 16.33°, SD = 9.84) and PwMS (Ipsilateral matching task: M = 6.40°, SD = 3.55; Contralateral matching task: M = 14.91°, SD = 7.93). There was no main effect of Task with respect to MT for OA ($F(1,46) = 1.185$, $p = 0.282$, $\eta^2 = 0.025$) or PwMS ($F(1,38) = 0.104$, $p = 0.748$, $\eta^2 = 0.003$) or pTAPV (OA: $F(1,46) = 0.085$, $p = 0.772$, $\eta^2 = 0.002$; PwMS: $F(1,38) = 1.445$, $p = 0.237$, $\eta^2 = 0.037$). Thus, as expected participants had greater errors in the contralateral matching task in comparison to ipsilateral matching task at both PV and movement endpoint but demonstrated similar movement planning and execution across tasks with respect to other performance variables.

3.5 Discussion

Proprioception plays an important role in UL function such that proprioceptive deficits have been suggested to contribute to impairments in one's ability to perform activities of daily

living (ADL; Goble, Mousigian, et al., 2012; Hughes et al., 2015; Lee et al., 2013). Thus, identifying deficits in proprioception in the UL is essential in order to prevent further deterioration and guide future rehabilitation. OA and PwMS have both been shown to exhibit deficits in proprioception in their UL, across clinical assessments and/or laboratory based matching tasks (Adamo et al., 2007; Goble, 2010; Herter et al., 2014; Iandolo et al., 2020; Jamali et al., 2017; Khan et al., 2018; Kokmen et al., 1978; Rahmani & Sadeghi, 2017; Scherder et al., 2018; Temlett, 2009; Wickremaratchi & Llewelyn, 2006). Moreover, it has been suggested that MS leads to brain aging, resulting in similar structural changes as seen in OA (Cole et al., 2019; Høgestøl et al., 2019). In the current study, we asked if proprioceptive deficits are similar between OA and PwMS across both clinical and laboratory assessments.

3.5.1 Proprioception as Evaluated by Clinical Assessments

In general, typical assessments carried out in a clinical setting are quick to administer and score, providing an overall picture of the somatosensory system (or proprioception) through a composite score. For example, PwMS are administered the EDSS, in which the function of the sensory system is evaluated by combining scores across the superficial sensation, vibration sense and joint position sense tasks. These tasks are taken to reflect one's sense of proprioception through assessment of mechanoreceptor integrity (i.e., cutaneous receptors) and joint position sense. The superficial sensation task and vibration sensation task examine the integrity of cutaneous receptors (Gilman, 2002; Wu et al., 1999), while the joint position sense task assesses joint position sense of fine movements (i.e., the finger). While these clinical assessments are typically conducted with PwMS, similar standardized assessments have not been carried out with OA. Instead, OA have undergone variations of these tasks (e.g., sensitivity to touch; Bruce, 1980) and vibration sense tested at the thumb (Temlett, 2009). In general, findings reported

demonstrate that PwMS and OA have greater deficits than control and younger participants respectively with respect to superficial sensation (Bruce, 1980; Scherder et al., 2018) and vibration sense (Jamali et al., 2017; Temlett, 2009). However, only PwMS, not OA have been found to perform worse on joint position sense tasks (Jamali et al., 2017; Kokmen et al., 1978).

Our study sought to examine if OA and PwMS performed similarly on these tasks. Contrary to our expectations, PwMS did not perform as well as OA on these clinical assessments used to assess proprioception and additional clinical assessments used to evaluate UL function. Interestingly, OA scored perfectly on the superficial sensation, vibration sense, and joint position tasks examining finger and shoulder position, indicating intact proprioception. In contrast, PwMS had an average sensory score of 1.5, which indicates a mild to moderate decrease in vibration or mild decrease in touch or position sense (Şen, 2018). Based on these results we expected PwMS to have greater errors on the laboratory based proprioceptive matching tasks compared to OA.

3.5.2 Proprioception as Evaluated by Laboratory Based Proprioceptive Matching Tasks

Laboratory based proprioceptive matching tasks are more reflective of goal directed reaches used in ADL than clinical assessments. Goal directed reaches require gross movements actively generated by participants in order to reach a target, in comparison to the fine movements assessed in the clinical tasks. The laboratory based proprioceptive matching tasks provide insight into both proprioceptive acuity (i.e., errors experienced when trying to match a reference position), and underlying motor control processes related to movement planning and execution. In the current study, participants completed the two most common laboratory based proprioceptive matching tasks, the ipsilateral and contralateral matching tasks. These tasks assess limb position sense in the same (ipsilateral matching task) and opposite arm (contralateral

matching task). The purpose of the contralateral matching task was to determine if there were differences between groups in a task involving interhemispheric communication.

Although previous research has examined performance of OA on laboratory based proprioceptive matching tasks, limited work has been done with PwMS and none investigating performance of the UL. In general, OA have been shown to have greater absolute errors than younger adults in both the ipsilateral and contralateral matching tasks with the UL (Adamo et al., 2007; Herter et al., 2014). In the current study, we also found that OA were not able to match the reference position accurately across either task (i.e., errors of approximately 6.35° and 14.07° in the ipsilateral and contralateral matching tasks, respectively). In the ipsilateral matching task, absolute angular errors and errors in the horizontal direction were significantly larger in OA than PwMS. In the contralateral matching task, similar to the ipsilateral matching task we see larger errors in the horizontal direction in OA compared to PwMS, but there was no difference in absolute angular errors between groups. For both groups, as demonstrated in young participants (Adamo & Martin, 2009; Goble, 2010), errors were larger in the contralateral vs. ipsilateral matching task. These results are not surprising, as both OA and PwMS demonstrate atrophy of the corpus collosum, which is imperative for the interhemispheric communication required in the contralateral matching task (Han et al., 2017; Hou & Pakkenberg, 2012; Iandolo et al., 2020; Ota et al., 2006).

The decreased accuracy in OA compared to PwMS was not expected, especially given the improved performance of PwMS on the clinical assessments discussed above. Therefore, our results reveal that performance on clinical assessments differed from performance on matching tasks that are more reflective of ADL. Perhaps the group differences between the ipsilateral and contralateral matching tasks and clinical assessments are not surprising given that the clinical

assessments require participants to evaluate fine movements at the joints, whereas the laboratory based proprioceptive matching tasks assess the accuracy of goal-directed, gross movements to proprioceptive targets. Chen and colleagues (2007) found that PwMS felt that tasks that required controlled fine movements were more difficult to perform than other movements. Given the role of proprioception in fine movements, it is reasonable to assume that these motor deficits detected by clinical assessments reflect proprioceptive impairment. Similarly, proprioception plays an important role in gross movements but PwMS have the opportunity to employ compensatory strategies to get to a desired endpoint (Pellegrino et al., 2018). In previous work examining goal directed movements, these strategies included reaching with a slower speed, spending more TAPV and reaching with an overall longer movement duration to reduce endpoint errors compared to controls (Carpinella et al., 2009; Pellegrino et al., 2018; Ternes et al., 2014). Employing these strategies enables participants to utilize proprioceptive feedback for a longer period of time to reach the desired endpoint.

While, OA have been found to use similar compensatory strategies during goal directed reaches to visual and proprioceptive targets compared to younger participants (Adamo et al., 2007; Cooke et al., 1989; Kitchen, 2018), our results indicate that OA were less accurate than PwMS on the laboratory based matching tasks indicating proprioceptive impairment.

3.5.3 Proprioceptive Guidance of Movement

Performance of goal directed movements is typically evaluated with respect to the contribution of movement planning (offline) and control (online) processes (Ternes et al., 2014; Woodworth, 1899). Movement planning refers to movement preparation and is evaluated based on initial movement performance (i.e., prior to reach initiation and up to PV). In contrast, the control of a movement is proposed to involve online changes in the movement in response to

sensory feedback (e.g., proprioception) to reach a desired endpoint. A greater contribution of movement planning processes is reflected by increased RT, and time to peak velocity (TTPV; Burkitt et al., 2013; Elliott et al., 2001; Hansen et al., 2006; Heath et al., 1998; Khan et al., 2003), while a greater contribution of movement execution processes is reflected by longer time spent after PV (TAPV), greater number of movement corrections (i.e., a less smooth movement), and movements are more accurate (Elliott et al., 2010, Elliott et al., 2017; Yadav & Sainburg, 2014)

This is the first study to compare processes underlying goal directed movements between OA and PwMS, and in fact one of the few studies to examine how PwMS carry out goal-directed movements to proprioceptive targets. We found group differences within the ipsilateral matching tasks with regards to movement planning measures. In particular, we found that PwMS took longer to initiate their movements (in the right hand) and spent a greater time (proportion of the movement) to achieve a lower PV compared to OA. That said, PwMS were more accurate at PV (i.e., |PVAE|) than OA, perhaps reflecting a speed-accuracy trade-off (Fitts, 1954). While both OA and PwMS have been found to emphasise accuracy over speed when reaching to visual targets (Goggin & Meeuwsen, 1992; Ternes et al., 2014), our results suggest that PwMS prioritize accuracy more than OA. In the contralateral matching task, we again see that PwMS engaged in more planning processes than OA, such that they spent a longer proportion of the movement achieving PV. Therefore, although in the literature both OA and PwMS initiate movements later and achieve a lower PV compared to younger and control participants (Fradet et al., 2008; Jennekens-Schinkel et al., 1988; Ketcham et al., 2002; Light et al., 1996; Reicker et al., 2007; Ternes et al., 2014), our results indicate that there is a greater contribution of planning processes to movements made by PwMS compared to OA.

Interestingly, both OA and PwMS have been shown to spend more time in the second portion of the movement (i.e., longer TAPV) than controls (Goggin & Meeuwsen, 1992; Ternes et al., 2014). In the current study, we found that OA spent a greater proportion of their movement after PV compared to PwMS, presumably to correct their movements (Ternes et al., 2014). Spending more TAPV is thought to be a compensatory strategy to achieve similar endpoint errors to controls (Fradet et al., 2008; Ternes et al., 2014). This strategy proved to be ineffective, as OA were less accurate at matching the reference position compared to PwMS. Consistent with previous findings tasks (Adamo et al., 2007; Adamo & Martin, 2009) we found no differences in how movements were executed between ipsilateral and contralateral matching tasks. Furthermore, although OA and PwMS differed in endpoint accuracy and the contribution of movement planning processes, all participants executed their movements in a similar way, across both the ipsilateral and contralateral matching tasks. Lastly, OA and PwMS demonstrated similar consistency in performance across the majority of variables analyzed (note the groups did differ with respect to PV variability).

3.5.4 Clinical Assessments Movement Characteristics

We included additional tests in this study (e.g., 9HPT, SDMT, Abilhand) that are typically used in clinical settings with OA and PwMS to provide an overview of overall UL function. The mean scores on the 9HPT task in the current experiment are consistent with previous values reported for OA (Dominant hand: 24.9 s; Non-dominant hand: 26.5 s; Wang et al., 2015) and PwMS (Dominant hand: 23.6 s; Non-dominant hand: 28.0 s; Huertas-Hoyas et al., 2020). A common way to establish abnormal scores is to take a participant's age and sex normative values + 1SD (Johansson et al., 2007). Based on this criteria, scores for PwMS scores were higher than normative values in the dominant and non-dominant hand (Grice et al., 2003).

A similar trend was not seen in OA. While, the 9HPT provides a measure of dexterity, it can also provide insight into how movements are carried out. The longer to complete the 9HPT suggests slower movements and thus, in our study, PwMS demonstrated overall slower movements than OA. This slowness in reaching is consistent with the lower PV (in the right hand) seen with PwMS compared to OA in the matching tasks. These results confirm that PwMS prioritize accuracy over speed, which may have translated to lower errors in the laboratory based proprioceptive matching tasks.

The SDMT provides insight into information processing speed (Drake et al., 2010). It has been used as a screening tool for cognitive impairment, such that participants with scores below one standard deviation of the normative mean are designated as impaired (Charvet et al., 2014). The average scores found in our study are consistent with the literature in OA (45.9; Wolinsky et al., 2013) and PwMS (51.4; Brenton et al., 2019) and indicate that neither OA nor PwMS display cognitive impairment. However, we found that our OA participants had a significantly lower mean SDMT score than PwMS. Even though OA do not show cognitive impairment based on normative means, the lower score indicates slower information processing speed. This finding is surprising given that slowing in information processing speed is thought to be the primary cognitive deficit associated with MS (Hughes et al., 2011; Reicker et al., 2007). That said, the lower processing speed in OA compared to PwMS may explain why OA limited their engagement of online processes in the matching tasks (i.e., took less time to prepare their movements and spent a greater proportion of the movement after PV). However, this strategy provided to be ineffective, as OA exhibited greater errors than PwMS. Furthermore, processing speed has been found to be a predictor of cognitive decline and people that need help with ADL (Benedict et al., 2017; Hsiao et al., 2019). Based on this, it would be expected that the group with

the lower SDMT score would translate to a feeling of functional limitations when performing ADL (assessed by Abilhand score). Contrary to expectations, in our study, we found that PwMS reported lower scores on the Abilhand questionnaire compared to OA, indicating feelings of functional limitations in the UL when performing ADL. Thus, although OA perform less accurately than PwMS on the laboratory based proprioceptive matching tasks, they don't perceive limitations in everyday activities. Overall, based on these clinical assessments, PwMS exhibited greater UL deficits in comparison to OA. However, it is difficult to conclude that these UL deficits are due to proprioception deficits, as in the matching tasks PwMS performed better than OA. Taken together, the addition of these clinical assessments provide insight into movement performance and should be considered in future studies examining the processes underlying goal directed movements.

3.5.5 Conclusion

The objective of this study was to assess if proprioception is similar between OA and PwMS based on clinical and laboratory assessments. Our results indicate that OA and PwMS do not perform similarly on either clinical assessments or laboratory based proprioceptive matching tasks. In fact, OA performed better on the clinical assessments, while PwMS performed better on the laboratory matching tasks with respect to accuracy. Thus, proprioceptive deficits established are dependent on the assessment used. It is important to keep in mind that clinical assessments do not reflect proprioceptive acuity in everyday tasks. Therefore, this raises concern regarding diagnoses that are based on deficits that might not manifest in everyday tasks. Furthermore, within the laboratory matching tasks, movement analysis revealed that PwMS spent more time in the initial, planning stage of the movement compared to OA, who spent more time in the

execution stage of the movement. Future research should seek to explore why discrepancies across assessments of proprioception to better diagnosis deficits.

3.6 Tables

Table 1. Demographic outcomes of OA and PwMS. Values are reported as mean (SD), unless otherwise specified.

Outcome	**OA (n=24)**	**PwMS (n=20)**	**P-Value**
Age, yrs	76.13 (4.22)	48.70 (10.14)	< 0.001*
Sex, n			
Female	14 (58.3%)	13 (65%)	-
Male	10 (41.7%)	7 (35%)	-
Height, cm	165.28 (9.62)	167.57 (9.81)	-
Weight (kg)	71.17(15.46)	72.88 (12.01)	-
BMI, kg/m^2	25.99 (4.97)	25.83 (2.59)	-
Disease Duration, yrs	-	14.55(8.71)	-
Type of MS, n			
RRMS	-	13 (65%)	-
PMS	-	7 (35%)	-

* Denotes significant difference between the OA and PwMS ($p < 0.05$)

Table 2. Clinical outcomes of OA and PwMS. EDSS, sensory score, superficial sensation, vibration sense and joint position sense scores are reported as median (interquartile range). All other values are reported as mean (SD). * denotes differences between groups. + denotes differences between hands within a group.

Outcome	OA (n=24)	PwMS (n=20)	P-Value
EDSS	1.50 (1.50 - 1.00)	3.75 (2.50 - 5.63)	< 0.001*
Sensory Score	0.00 (0.00 - 0.00)	1.00 (2.25 - 1.00)	< 0.001*
Superficial Sensation			
Left Hand	0.00 (0.00 - 0.00)	0.00 (0.00 - 1.00)	0.006*
Right Hand	0.00 (0.00 - 0.00)	0.00 (0.00 - 1.00)	0.02*
Vibration Sensation			
Left Hand	0.00 (0.00 - 0.00)	1.00 (0.00 - 1.00)	0.001*
Right Hand	0.00 (0.00 - 0.00)	0.50 (0.00 - 1.00)	0.004*
Joint Position Sense			
Left Hand	0.00 (0.00 - 0.00)	0.00 (0.00 - 0.25)	0.01*
Right Hand	0.00 (0.00 - 0.00)	0.00 (0.00 - 0.25)	0.01*
Fugl-Meyer	2.0 (0.00)	-	-
Abilhand	44.17 (4.38)	37.10 (9.82)	0.003*
SDMT	46.00 (7.25)	53.45 (10.12)	0.007*
9HPT, sec			
Left Hand	22.14 (2.91)	30.14 (10.49)	0.001*
Right Hand	21.31 (2.39)	25.63 (7.77)	0.013*
Grip Strength (kg)			
Left Hand	24.58 (7.55)	20.35 (6.47)	n.s
Right Hand	25.63 (7.04)	23.00 (8.84)	n.s
Grip Endurance Δ%			
Left Hand	43.58 (12.75)	28.28 (12.26) +	< 0.001*
Right Hand	44.18 (14.31)	36.39 (13.08)	n.s

Table 3. Accuracy, planning and execution measures of OA and PwMS during the ipsilateral matching task, separated by hand. Values are reported as mean (SD). * denotes differences between groups. + denotes differences between hands within a group.

Variable	OA: Left Hand	OA: Right Hand	PwMS: Left Hand	PwMS: Right Hand
Accuracy Measures				
|EPAE| (degrees)				
Mean	6.35 (2.84) *	6.35 (4.10) *	4.73 (2.03)	4.27 (2.40)
Variability	4.09 (3.49)	3.54 (2.58)	2.65 (0.99)	3.16 (3.07)
R-Error (cm)				
Mean	3.59 (1.85)	3.00 (2.07)	2.53 (1.02)	2.48 (1.14)
Variability	1.29 (0.96)	0.95 (0.48)	0.83 (0.40)	1.04 (0.71)
AE_X (cm)				
Mean	2.03 (1.12) *	1.66 (1.09) *	1.40 (0.61)	1.20 (0.61)
Variability	1.03 (0.77)	0.87 (0.55)	0.65 (0.29)	0.76 (0.51)
AE_Y (cm)				
Mean	2.24 (1.74)	2.70 (1.56)	1.93 (0.93)	2.00 (1.07)
Variability	0.67 (0.30) +	1.06 (0.75)	0.77 (0.32)	0.90 (0.52)
Planning Measures				
RT (ms)				
Mean	603.24 (255.55) +	445.96 (196.78) *	651.95 (284.33)	744.61 (367.16)
Variability	255.57 (206.28)	197.31 (187.74)	203.43 (126.82) +	395.53 (288.47)
pTTPV (%)				
Mean	47.14 (9.65) *	45.75 (10.43) *	53.11 (6.32)	53.24 (8.48)
Variability	8.39 (3.19)	10.48 (5.06)	6.98 (2.64)	9.40 (5.28)
PV (cm/s)				
Mean	19.90 (3.98) *	19.47 (5.04) *	16.82 (3.45)	16.70 (4.43)
Variability	3.15 (1.56)	2.30 (0.84)	2.08 (0.79)	2.65 (1.29)
|PVAE|(degrees)				
Mean	9.09 (4.48) *	8.07 (5.78) *	6.89 (4.10)	5.91 (3.01)
Variability	5.87 (3.88)	4.58 (2.73)	4.12 (3.76)	4.10 (2.83)
Execution Measures				
MT (ms)				
Mean	1122.74 (166.40)	1083.61 (237.59)	1135.38 (202.57)	1134.06 (234.04)

Variability	206.26(138.39)	179.91 (83.56)	144.61 (81.02)	182.33 (98.01)
Path Length (cm)				
Mean	12.58 (2.77) +	10.69 (1.72)	11.56 (2.53) +	11.18 (1.96)
Variability	2.20 (1.88)	1.25 (0.77)	1.21 (0.60)	1.30 (1.25)
pTAPV (%)				
Mean	52.86 (12.70) *	54.25 (12.43) *	46.89 (8.54)	46.76 (9.85)
Variability	8.39 (5.14)	10.48 (6.94)	6.98 (4.56)	9.40 (6.28)
Jerk Score				
Mean	4463.89 (2559.39)	4196.56 (3379.12)	4576.84 (2475.18)	4798.30 (2821.43)
Variability	2491.60 (2856.14)	2150.44 (2204.70)	1825.42 (1770.74)	2388.65 (2252.41)

Table 4. Accuracy, planning and execution measures of OA and PwMS during the contralateral matching task, separated by hand. Values are reported as mean (SD). * denotes differences between groups. + denotes differences between hands within a group.

Variable	OA: Left Hand	OA: Right Hand	PwMS: Left Hand	PwMS: Right Hand
Accuracy Measures				
|EPAE| (degrees)				
Mean	13.55 (5.72)	14.53 (7.86)	12.43 (5.70)	12.19 (4.91)
Variability	5.77 (2.19)	4.21 (1.66)	5.97 (3.07)	6.18 (3.43)
R-Error (cm)				
Mean	3.19 (0.94)	3.68 (1.63)	2.87 (0.88)	2.98 (0.98)
Variability	1.05 (0.40)	0.92 (0.53)	1.04 (0.59)	1.16 (0.56)
AE_X (cm)				
Mean	2.51 (0.95) *	2.78 (1.68) *	2.00 (0.71)	2.16 (0.97)
Variability	1.04 (0.31)	0.91 (0.50)	0.99 (0.57)	1.08 (0.51)
AE_Y (cm)				
Mean	1.56 (0.58)	1.90 (0.87)	1.63 (0.81)	1.69 (0.72)
Variability	0.74 (0.45)	0.65 (0.28)	0.76 (0.38)	0.82 (0.50)
Planning Measures				
RT (ms)				
Mean	482.02 (226.49)	539.61 (287.70)	643.49 (272.46)	653.13 (275.81)
Variability	170.36 (83.92)	214.48 (180.19)	225.58 (175.50)	244.35 (153.07)
pTTPV (%)				
Mean	44.04 (11.50) *	47.28 (8.03) *	49.75 (8.52)	51.58 (7.00)
Variability	10.54 (4.38)	11.11 (4.38)	9.60 (4.28)	10.96 (5.27)
PV (cm/s)				
Mean	16.87 (6.04)	17.82 (5.19)	15.60 (5.62)	15.65 (3.64)
Variability	2.29 (0.93)	2.65 (1.38)	2.32 (0.99)	2.23 (0.78)
|PVAE|(degrees)				
Mean	14.49 (6.78)	18.11 (12.90)	14.14 (5.39)	15.68 (10.47)
Variability	7.51 (3.44)	6.81 (4.00)	7.10 (3.01)	8.12 (5.49)
Execution Measures				

MT (ms)				
Mean	1043.31 (286.48)	1049.31 (200.14)	1094.05 (250.10)	1132.74 (266.20)
Variability	164.16 (102.68)	191.70 (87.59)	169.44 (96.98)	179.64 (111.55)
Path Length (cm)				
Mean	10.31 (5.22)	10.48 (2.52)	9.25 (1.82)	10.14 (2.06)
Variability	1.37 (1.15)	1.32 (0.63)	1.50 (0.93)	1.44 (0.84)
pTAPV (%)				
Mean	52.86 (9.65) *	54.25 (10.43) *	50.25 (8.52)	46.89 (6.32)
Variability	8.39 (3.19)	10.48 (5.06)	9.60 (4.28)	6.98 (2.64)
Jerk Score				
Mean	4209.06 (5429.16)	3758.25 (2092.63)	4472.38 (3027.37)	4657.33 (3120.21)
Variability	1792.66 (2388.41)	1979.01 (1479.01)	1992.79 (1872.73)	2493.48 (2952.81)

3.7 Figures

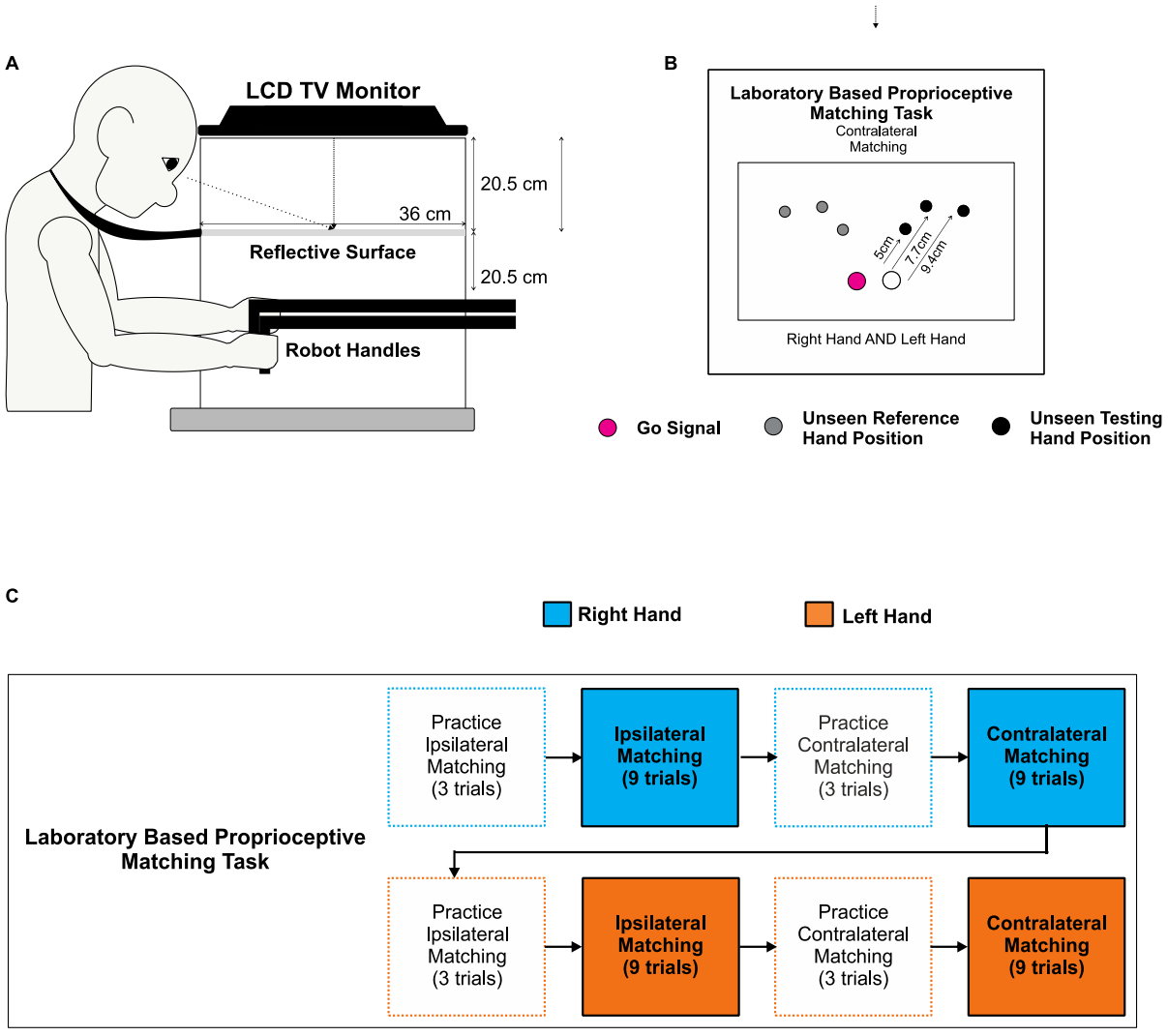

Figure 1. Experimental Apparatus, Robotic Tasks and Trial Sequence
(A): Experimental apparatus for the robotic matching tasks. Participants were instructed to grasp the robot handles with their left or right hand (i.e., ipsilateral matching task) or both hands (i.e., contralateral matching task). (B) Top view of the contralateral matching task, displaying the three potential reference locations (grey circles) participants were to match with the testing hand (black circles) following the go signal (i.e., home position turning to magenta). The reference locations were the same for both the ipsilateral and contralateral matching tasks. (C) An example trial sequence that was completed by a participant using their right (blue) and left (orange) hands. Tasks outlined by a solid black line indicate trials that were included in our analyses, whereas dotted lines represent practice trials that were not analyzed. These tasks were counter-balanced by hand (i.e., right vs. left testing hand first) and task (i.e., ipsilateral matching first vs. contralateral matching first)

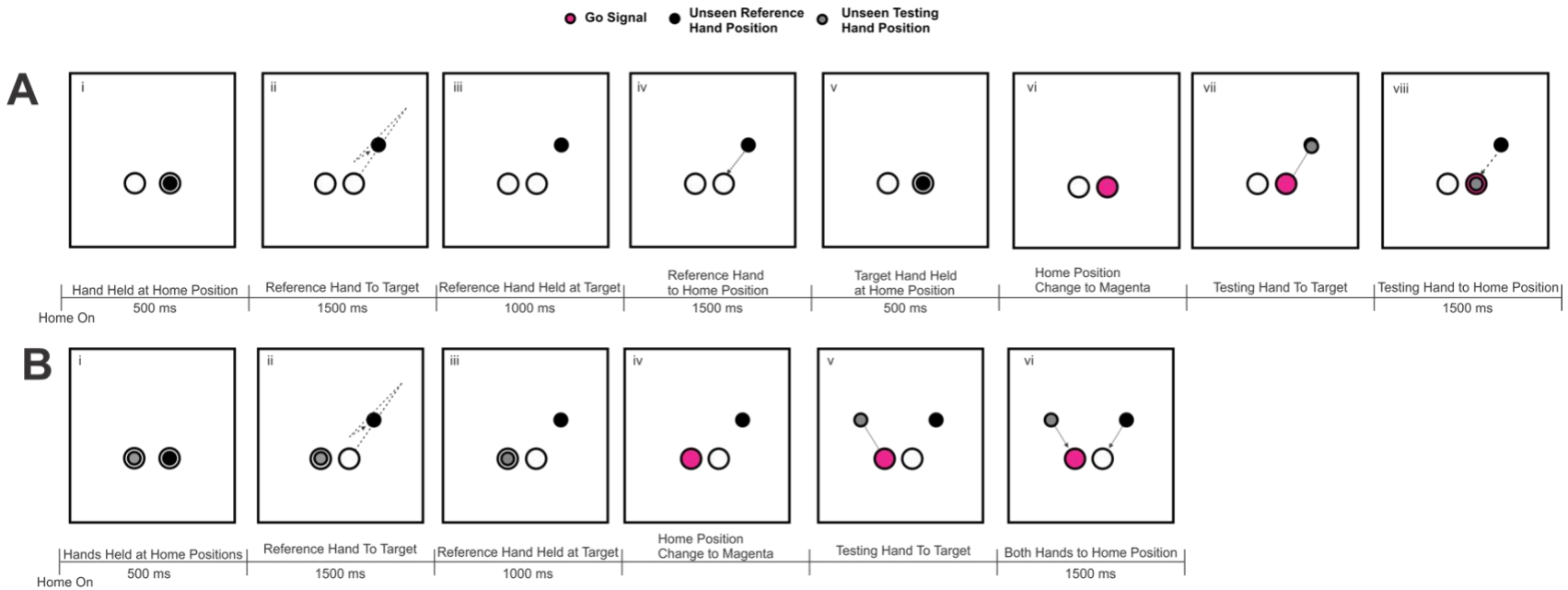

Figure 2. Timeline of events within a trial for the (A) Ipsilateral and (B) Contralateral Matching Tasks
(A) The ipsilateral arm-matching task commenced with the reference hand held at the home position for 500 ms (box i). The robot then passively moved the reference hand out to the reference position in a MT of 1500 ms, with two or three reversals around the unseen reference location (box ii). The reference hand was held at the reference location for 1000 ms (box iii), before being passively moved back to the home position in a MT of 1500 ms (box iv). Once back at the home position, the hand was held at the home position for 500 ms (box v). Following this time, the home position changed to magenta (box vi), which signalled to the participant to actively reproduce the reference location with the same arm (box vii). (B) The contralateral matching task commenced with the two hands held at their corresponding home positions (20 cm apart) for 500 ms (box i). The robot then passively moved the reference arm for 1500 ms to the unseen reference position. The robot moved along a path with two or three reversals around the reference position before it stopped at the final reference location (box ii). The reference hand stayed in the reference position for the duration of the trial. After 1000 ms, the home position of the testing hand changed to magenta (box iv), which signalled the participant to actively reproduce the final position in the opposite testing arm (box v). Once the final position of the testing hand was determined, both hands were brought passively back to the home positions in a MT of 1500 ms (Figure 2A box viii and Figure 2B box vi).

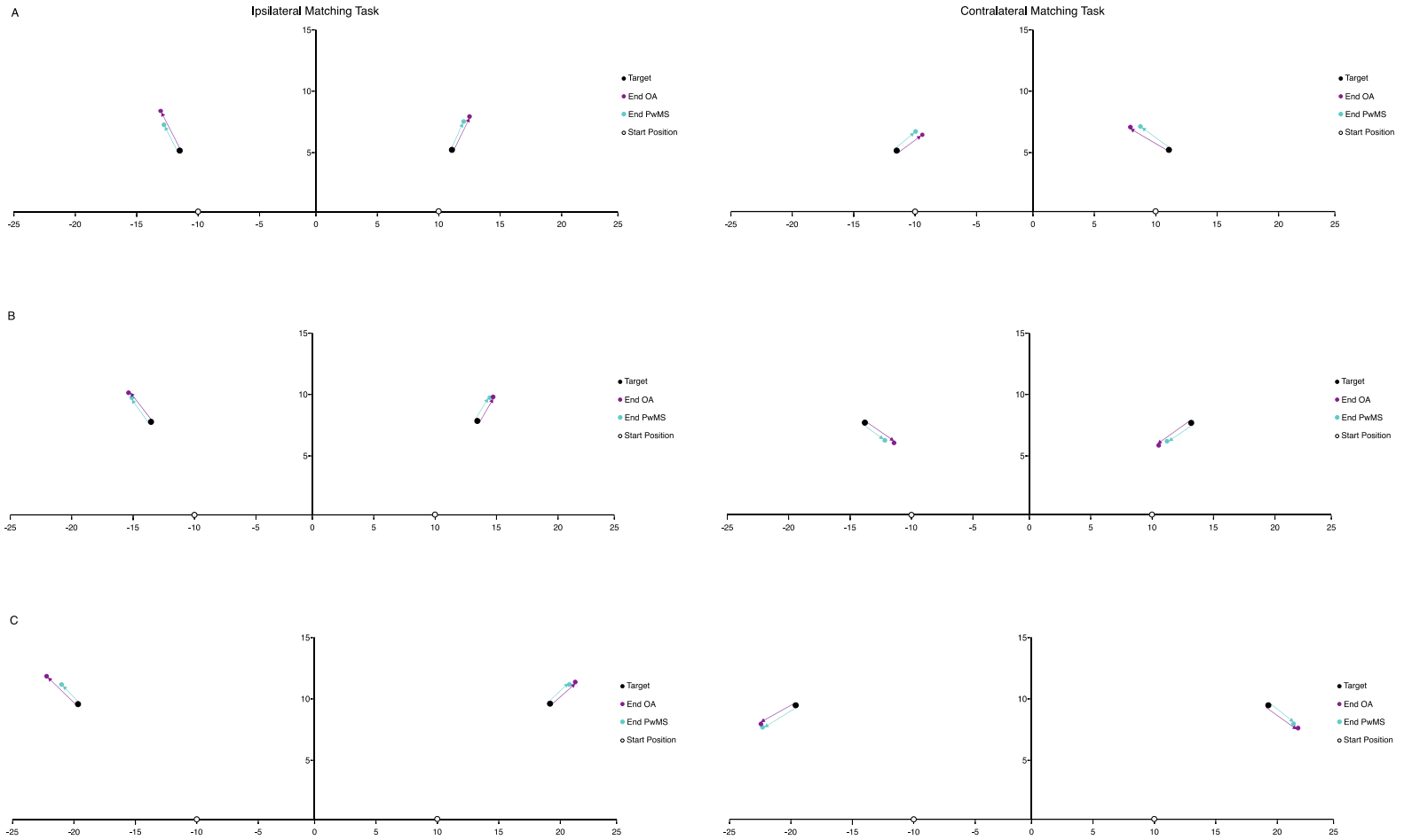

Figure 3. Mean absolute positions at reach endpoint for OA (purple) and PwMS (turquoise) for the ipsilateral (left) and contralateral (right) matching tasks for the near target (A), the middle target (B) and the far target (C).

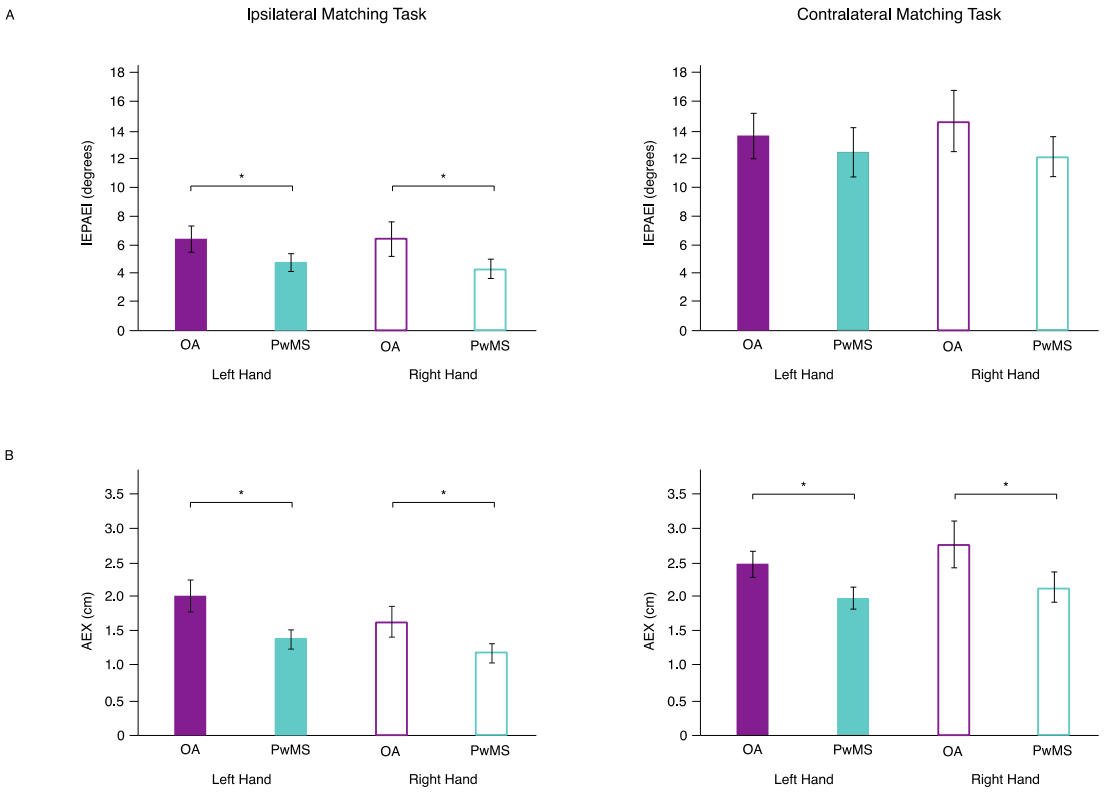

Figure 4. Accuracy Measures. (A) Absolute Endpoint Angular Errors (°) for the ipsilateral (left) and contralateral (right) matching tasks. (B) Absolute errors (cm) in the horizontal direction for the ipsilateral (left) and contralateral (right) matching tasks. OA are represented by purple bars and PwMS by turquoise bars. Trials in which participants' left hand was the matching hand are represented by filled bars, while trials in which participants' right hand was the matching hand are represented by unfilled bars. Error bars denote standard error of the mean. * Indicates significance between groups.

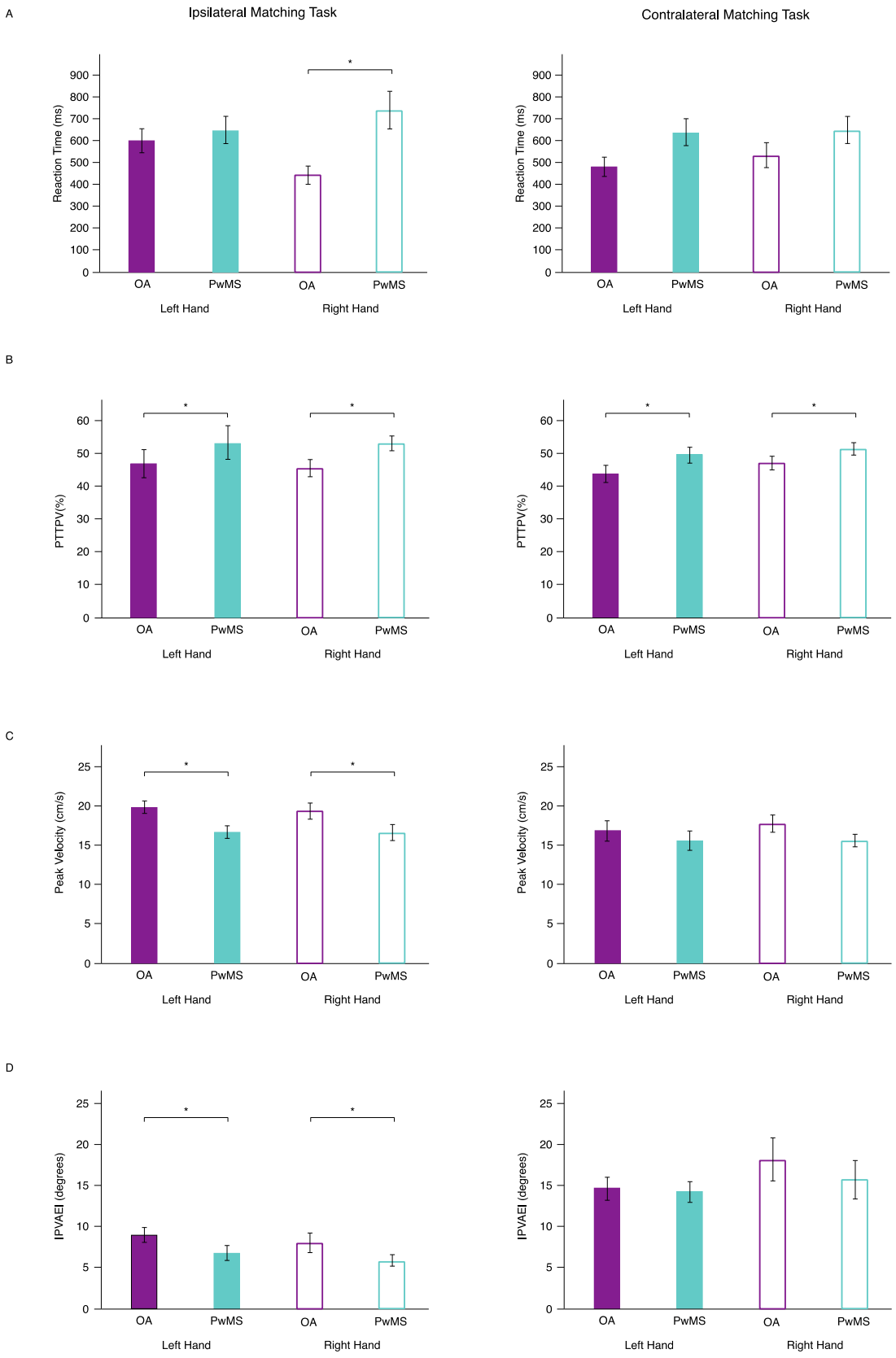
A
Ipsilateral Matching Task
Contralateral Matching Task
Reaction Time (ms)
B
PTTPV(%)
C
Peak Velocity (cm/s)
D
IPVAEI (degrees)
OA
PwMS
Left Hand
Right Hand
*

Figure 5. Planning Measures. (A) Reaction time (ms) for the ipsilateral (left) and contralateral (right) matching tasks. (B) Proportional time to peak velocity (%) for the ipsilateral (left) and contralateral (right) matching task. (C) Peak velocity (cm/s) for the ipsilateral (left) and contralateral (right) matching task. (D) Absolute peak velocity angular errors (°) for the ipsilateral (left) and contralateral (right) matching tasks. OA are represented by purple bars and PwMS by turquoise bars. Trials in which participants' left hand was the matching hand are represented by filled bars, while trials in which participants' right hand was the matching hand are represented by unfilled bars. Error bars denote standard error of the mean. * Indicates significance between groups.

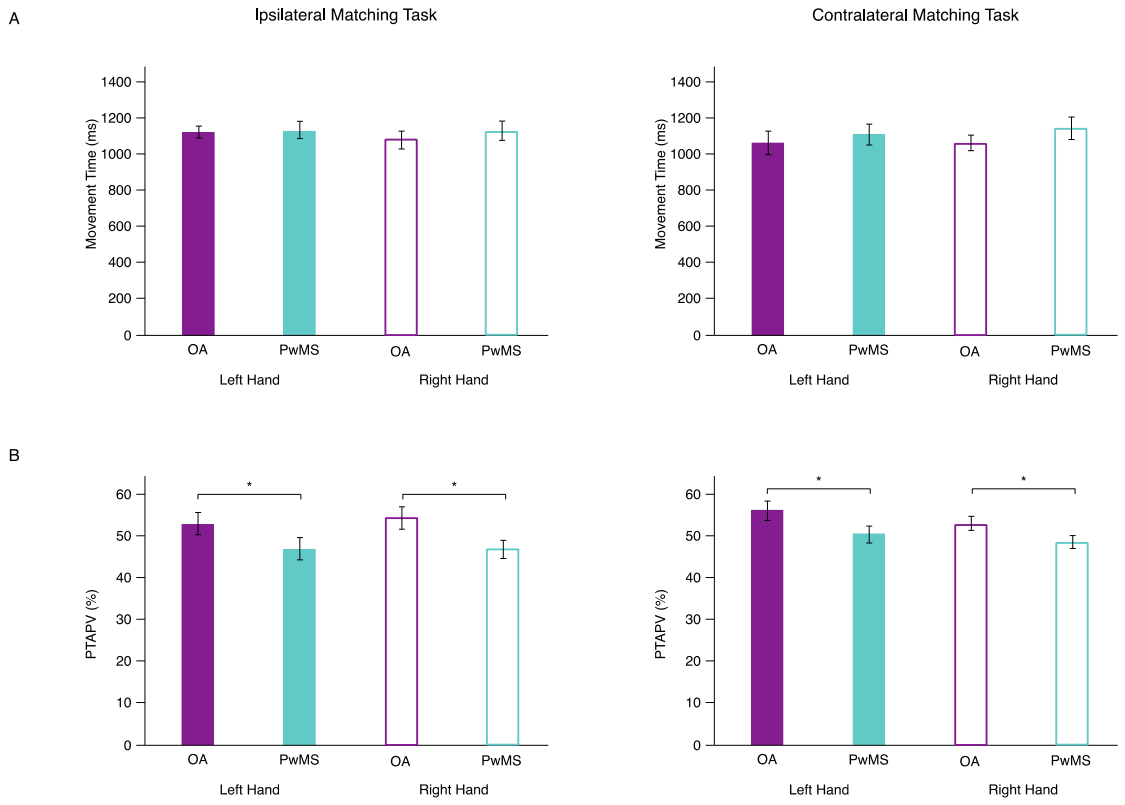

Figure 6. Execution Measures. (A) Movement time (ms) for the ipsilateral (left) and contralateral (right) matching tasks. (B) Proportional time after peak velocity (%) for the ipsilateral (left) and contralateral (right) matching task. OA are represented by purple bars and PwMS by turquoise bars. Trials in which participants' left hand was the matching hand are represented by filled bars, while trials in which participants' right hand was the matching hand are represented by unfilled bars. Error bars denote standard error of the mean. * Indicates significance between groups.

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Chapter 4 General Discussion

The objective of this thesis was to determine if proprioceptive performance evaluated using clinical and laboratory based proprioceptive matching tasks is similar across older adults (OA) and people with multiple sclerosis. We found that performance between OA and PwMS differed across both tasks. Specifically, PwMS performed worse on the clinical assessments, while OA performed worse on the laboratory based proprioceptive matching tasks. Furthermore, within the laboratory tasks, analysis of movement performance revealed that PwMS spent more time in the initial, planning stage of the movement compared to OA, who spent more time in the execution stage of the movement.

One of the initial goals of the thesis was to determine if performance on clinical assessments reflects proprioceptive acuity as established via laboratory based matching tasks. Given that OA received perfect scores on their clinical assessments of proprioception, we were unable to address this research question. Instead, we focused our analyses and results on our second research goal, comparing proprioceptive assessments between OA and PwMS and examining how goal directed actions are carried out in laboratory based proprioceptive matching tasks.

We recruited OA that were over 70 years old to take part in our study, as opposed to 60 years, as typically seen in the literature (Light et al., 1996; Petrella et al., 1997). These older participants allowed us to compare the influence of age with MS (who ranged in age from 31 to 61 years of age), as all OA were older than our participants with MS. Based on our findings, OA performed better on clinical assessments of proprioception and upper limb (UL) function compared to PwMS, while PwMS performed better on laboratory based proprioceptive matching tasks. Given the nature of these tasks, our results might not be surprising. Specifically, the laboratory based proprioceptive matching tasks require gross movements actively generated by

participants in order to reach to a target, in comparison to the fine movements assessed in the clinical tasks.

Given that clinical assessments only examine fine movements rather than gross movements seen in everyday activities, perhaps misdiagnosis of deficits in proprioception can arise. The implication of diagnosing someone with a deficit when there isn't one can be detrimental, as treatments for UL impairments and proprioceptive deficits can be invasive (e.g., include magnetic stimulation; Pollock et al., 2014; Schabrun & Hillier, 2009). Furthermore, in our sample of PwMS, participants performed well on the laboratory based proprioceptive matching tasks, however if they were informed of their UL deficits on the clinical tasks this could impact performance on the matching tasks. Studies have shown that OA, when told of negative stereotypes associated with age (i.e., memory loss), performed worse on memory tasks (Chasteen et al., 2005; Hess et al., 2003). Therefore, misdiagnosing an individual with an UL impairment could result in poorer performance on subsequent tasks. Results from our study indicate that it may be beneficial to include more assessments in the clinic to determine where proprioceptive deficits might lie and what that means for functional ability. We recommend inclusion of the Fugl-Meyer assessment to assess proprioception using both fine and gross movements. Other factors to consider when conducting clinical assessments and laboratory based proprioceptive matching tasks with OA and PwMS are the clinical assessments used, testing instructions and the relationship between proprioceptive deficits and falls.

4.1 Consideration of Clinical Assessments

Proprioception plays an important role in UL function such that proprioceptive deficits have been suggested to contribute to impairments in one's ability to perform activities of daily living (ADL; Goble, Mousigian, et al., 2012; Hughes et al., 2015; Lee et al., 2013). Therefore, other clinical assessments looking at UL function were included to provide an overview of UL

function in OA and PwMS. Since we screened for neurological, musculoskeletal/orthopedic conditions in OA, as expected, the Expanded Disability Status Scale (EDSS; Şen, 2018) score for OA was significantly lower than for PwMS. However, OA had a median EDSS score of 1.50, which was driven by a decline in the visual system, which is not unexpected with age (Saftari & Kwon, 2018). Although the clinical assessments assessing proprioception and laboratory based proprioceptive matching tasks did not require vision (i.e., participants made judgements or reached to a felt position in the absence of vision), the written symbol-digit modalities test (SDMT) task did. Future studies should consider utilizing the auditory rather than the written version of the SDMT task when assessing OA.

Consistent with previous studies, PwMS had a median EDSS score of 3.75, indicating significant disability (Lamers & Feys, 2014; Prosperini et al., 2010). They also displayed elevated scores on evaluation of all functional systems (visual, brainstem, pyramidal, cerebellar, sensory, bowel and bladder and cerebral systems), indicating greater disability than OA. In line with these impairments, PwMS took longer to complete the 9-hole peg test (9HPT), had a lower Abilhand score and less grip endurance (left hand). Interestingly, these clinical assessments, like the EDSS, also tend to assess fine movements rather than gross movements seen in ADL. For example, the majority of questions in the Abilhand questionnaire ask about fine movements (i.e., threading a needle, taking a cap off a bottle and sharpening a pencil). Similarly, the 9HPT primarily assesses finger dexterity (fine movements) rather than gross movements required in the laboratory based proprioceptive matching tasks. This calls into question if the Abilhand questionnaire and 9HPT should be considered reliably assessments of UL function (Lamers et al., 2013; Luijten et al., 2018). Based on our results we do not think these assessments provide an accurate overview of upper extremity function, specifically with respect to proprioception. Therefore, clinicians should consider including other assessments to provide a better overview of UL function. For example,

the Fugl-Meyer assessment which assesses joint position sense at the finger and shoulder thus utilizing fine and gross movements.

Another consideration is hand asymmetry in the clinical assessments. We found that when using the non-dominant hand, PwMS performed worse than when using their dominant hand on the 9HPT and grip endurance. These results suggest asymmetry across the hands and has been demonstrated previously (Farrell et al., 2020; Lamers et al., 2013). Although we did not report which side was more impaired in PwMS, in the literature it has been suggested that the more affected limb tends to be the non-dominant arm in PwMS (Lamers et al., 2013; Severijns et al., 2015). Interestingly, we did not see any differences between hands for the superficial sensation, vibration sense or joint position sense task. Future studies should consider which side is impaired when reporting clinical measures to gain insight into asymmetries of movement. Taken together these clinical assessments provide an overview of UL function however, whether decline in function can be attributed to deficits in proprioception is unclear.

4.2 Understanding of Instructions

Another factor to consider when testing is ensuring participants understand the task instructions. The biggest challenge in the current experiment when testing OA was their understanding of the ipsilateral and contralateral matching tasks. Even though participants were instructed to either match the reference position with their same (ipsilateral matching task) or opposite (contralateral matching task) arm, they continuously tried to replicate the movement trajectory of the robot rather than reach directly to the endpoint. Our robot moved their arm around the reference location either two or three times before stopping at the final location (known as the reference position), in order to prevent participants from remembering the movement as opposed to the final position. Therefore, some of the participants' reaching trajectories resembled a circle, as they tried to replicate the robot's movements. On trials in which the reaching trajectory

resembled a circle, end positions were established but reaching performance on these trials was not able to be assessed. In attempt to promote understanding of the task, participants were shown the task with full view of their limbs during a demonstration trial. Participants next completed three practice trials with each arm to gain familiarity with the task. In some cases, we included even more practice trials (e.g., up to 9 practice trials).

In order to promote understanding of the task, we used a consistent script to instruct all participants on the tasks. Unfortunately, OA still tended to have a harder time understanding the task compared to PwMS. Moreover, the OA were not forthcoming in admitting their confusion about the task and/or instructions. Instead they attempted to complete the task without asking for clarification or help (i.e., completed movement trajectories resembling a circle). In order to avoid participants from completing the task without understanding task instructions in the future, studies can look to manipulate how practice trials are carried out. For example, future studies should seek to determine if there is a benefit in the instructor demonstrating the skill compared to participant trying the skill with verbal instruction. Previous research has found that learning a new motor skill is beneficial if participants have the opportunity to both observe and practice a skill (Shea et al., 2000).

4.3 Motor Aspects

A limitation of our study was that we didn't measure motor deficits outside the scope of the study. Therefore, underlying motor deficits might contribute to some of the differences between groups. However, as both groups were able to perform the matching tasks and had similar movement smoothness, the contribution of underlying motor deficits to group differences might be minimal. If we included PwMS with longer disease duration (14+ years) or older participants (80+) these motor deficits might be more apparent. Therefore, although we found group differences in the clinical and laboratory based proprioceptive matching task, this might not be the

case with different disease durations and/or subtypes of MS when compared to older adults. There might be an MS group with a certain disease duration or subtype that is similar to OA. This is the first study that has looked at proprioception in OA and PwMS. Future studies should look to see if there are differences and compare older populations to longer duration/different subtypes of MS.

4.4 Conclusion

OA and PwMS have both been shown to exhibit deficits in proprioception in their UL, across clinical assessments and laboratory based matching tasks (Adamo et al., 2007; Goble, 2010; Herter et al., 2014; Iandolo et al., 2020; Jamali et al., 2017; Khan et al., 2018; Kokmen et al., 1978; Rahmani & Sadeghi, 2017; Scherder et al., 2018; Temlett, 2009; Wickremaratchi & Llewelyn, 2006). Moreover, it has been suggested that MS leads to brain aging, resulting in similar structural changes as seen in older adults (Cole et al., 2019; Høgestøl et al., 2019). In the current test we asked if proprioception was similar between OA and PwMS based on clinical assessments and laboratory based proprioceptive matching tasks. However, our results indicate that OA and PwMS do not perform similarly on proprioceptive assessments in either clinical or laboratory based settings. We found that OA performed better on clinical assessments and PwMS were more accurate on the laboratory based proprioceptive matching tasks. In the analysis of movement within the laboratory based proprioceptive matching tasks we found that PwMS spent more time in the initial, planning stage of the movement compared to OA who spent more time in the execution stage of the movement. Our results call into question the relationship between clinical assessments and laboratory based proprioceptive matching tasks. Future research should seek to explore why discrepancies across these tests exists and their link to proprioceptive deficits.

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Appendix A
Screening Script

Hello, may I please speak with "person's name?" This is "name of research assistant" and I am calling from the Clinical Exercise Physiology Laboratory at the University of Ottawa regarding a study on upper body function in people with multiple sclerosis. I'd like to first describe the study to you and then run you through a screening process if you are interested. It may take several minutes, is that okay?

- ☐ Yes. Okay great.
- ☐ No. When would be a good time to call back? _____ (date/time)

Before we begin, I want to let you know that any information that you provide today will be kept confidential and will only be used to determine your eligibility for participation in this study.

First, let me tell you a little about our study. The purpose of this study is to learn more about upper body function in people with multiple sclerosis (MS). We are recruiting people with MS who notice problems with their upper body function, as well as those who do not. We are also recruiting people without MS. If you are eligible to participate, we will ask you to come into the lab for 2 testing sessions at the University of Ottawa campus. The two testing days will be separated by about 1 week.

Do you have any questions at this point?

The first testing session will take place at Lees Campus and your will be asked to undergo resting blood pressure measurement, neurological tests, upper body coordination tasks, upper body strength and endurance tests, and three thinking tasks. The second session will take place on main campus and you will be asked to complete a series of upper body reaching tasks while holding onto robotic handles and then complete several questionnaires about yourself. Each session will take about 1 hour to complete. All procedures and equipment used in this protocol are routinely used in research settings involving human participants. If you choose to participate in this study, you will receive compensation of $20 per testing session ($40 in total for the whole study).

Do you have any questions?

Does this project sound like something you would be interested in volunteering for?

- ☐ Yes. (Proceed with screening checklist and PAR-Q)-All participants passed PAR-Q and therefore results will not be discussed in detail.
- ☐ No. Okay, thank you for your time today.

Before we can enroll you in the study, I need to run you through a screening process to see if you are eligible to participate. This consists of a series of questions which may take about 5 minutes. Is that okay?

- ☐ Yes. Okay great. (Proceed with screening questions)
- ☐ No. When would be a good time to call back? _____ (date/time)

To start, I have a few quick questions:

Simple Checklist of Requirements

All prospective participants:

1. Are you between 18 and 65 years of age? Y N
2. Are you willing to come to the University of Ottawa to complete two testing sessions separated by about 1 week? Y N
3. Are you able to read and answer questions in English? For example, a questionnaire in English about your ability to perform everyday tasks. Y N

(Prospective participants with MS)

1. Have you been diagnosed with MS? Y N
2. Have you had a relapse within the last 30 days? Y N
3. Have you had any changes to your disease-modifying therapies within the past 6 months? Y N

If participant satisfies all criteria above, undertake PAR-Q screening.

If participants does not satisfy criteria, proceed to '**Not Qualified**' section.

Get Active Questionnaire (GAQ)

Now I'm going to ask you a few questions about your health. Please answer each question honestly by responding "yes" or "no".

YES	NO		
☐	☐	**1.**	Have you experienced ANY of the following (A to F) within the past six months?
☐	☐	*A*	A diagnosis of/treatment for heart disease or stroke, or pain/discomfort/pressure in your chest during activities of daily living or during physical activity?
☐	☐	*B*	A diagnosis of/treatment for high blood pressure (BP), or a resting BP of 160/90 mmHg or higher?
☐	☐	*C*	Dizziness or lightheadedness during physical activity?
☐	☐	*D*	Shortness of breath at rest?
☐	☐	*E*	Loss of consciousness/fainting for any reason?
☐	☐	*F*	Concussion?
☐	☐	**2.**	Do you currently have pain or swelling in any part of your body (such as from an injury, acute flare-up of arthritis, or back pain) that affects your ability to be physically active?
☐	☐	**3.**	Has a health care provider told you that you should avoid or modify certain types of physical activity?
☐	☐	**4.**	Do you have any other medical or physical condition (such as diabetes, cancer, osteoporosis, asthma, spinal cord injury) that may affect your ability to be physically active?

Answer the following questions to assess how active you are now.

1. During a typical week, on how many days do you do moderate- to vigorous-intensity aerobic physical activity (such as brisk walking, cycling or jogging)? ☐ **Days/Week**

2. On days that you do at least moderate-intensity aerobic physical activity (e.g., brisk walking), for how many minutes do you do this activity? ☐ **Minutes/Day**

For adults, please multiply your average number of days/week by the average number of minutes/day: ☐ **Minutes/Week**

QUALIFIED? Y N

Qualified: Based on your answers, you are qualified to participate in our study at this time. We will need to measure your blood pressure in person to confirm your final eligibility to participate. We will do this at the first scheduled session. Please be aware that if your blood pressure is too high on that day, it might not be safe for you to participate in this study.

We will now send you a copy of the consent form by email or postal mail for you to review. May I please have your contact information (recorded on next page)?

(MS only) For the purpose of organizing people into study groups, do you currently experience any upper limb (i.e., hand or arm) problems due to your MS?

- ☐ Yes
- ☐ No

We can now schedule you for your testing sessions with us. Would you like to do this now, or would you prefer to schedule this at another time?

- ☐ Yes. Okay great. (Proceed with scheduling)
- ☐ No. When would be a good time to call back? _____ (date/time)

Do you have any final questions today?

Would you like our contact information in case you have any questions or concerns?

Lab phone: 613-562-5800 x3274
E-mail: clinicalexercisephyslab@gmail.com

We look forward to meeting you, and thank you for your time today. Have a great day!

Not Qualified: If participant is not qualified, then briefly explain the goal of the project, if interested, and thank the individual for their interest in participation. Ask them if they are interested in being contacted regarding other research studies that they may qualify for, and record their contact information.

Are you interested in being contacted about other research studies in people with MS?

- ☐ Yes. Great, may I please have your contact information (recorded on next page)?
- ☐ No. Thank you for your time today. All identifying information that you have provided today will be destroyed.

CONTACT INFORMATION

Name _____

E-mail _____

Phone _____ h

_____ c

Preferred method for delivery of study information:

- ☐ E-mail
- ☐ Postal mail

Mailing Address _____

Apt _____

City _____

Province _____ Postal Code _____

Appendix B
Self Reported Questionnaires

B1 Edinburg Handedness Inventory

Edinburg Handedness Inventory

Please **indicate with a number (1 or 2)** your preference in using your left or right hand in the following tasks.

Where the preference is so strong you would never use the other hand, unless absolutely forced to, put the number 2.

Where there is a general preference that you are more likely to use the one hand over the other, put the number 1.

If you are indifferent, put a 1 in each column (1 | 1).

Some of the activities require both hands. In each case, the part of the task or object for which hand preference is wanted is indicated in parentheses.

Task/Object	Left Hand	Right Hand
1. Writing		
2. Drawing		
3. Throwing		
4. Scissors		
5. Toothbrush		
6. Knife		
7. Spoon		
8. Broom (upper hand)		
9. Striking a Match (match)		
10. Opening a box (lid)		
Total Checks:	LH =	RH =

Modified from:
Oldfield, R. C. (1971). The assessment and analysis of handedness: The Edinburgh inventory. Neuropsychologia, 9, 97-113.

Participants will not see the below section.
Handedness will be determined using the following equation(s):

Cumulative Total:	CT = LH + RH =
Difference:	D = RH – LH =
Result:	R = (D/CT) x 100 =
Interpretation: (Left Handed: R < -40) (Ambidextrous: -40 ≤ R ≤ +40) (Right Handed: R > +40)	

ABILHAND Questionnaire

Instructions

The activities given below normally use both hands, and we would like to know if you can do them. For each question please indicate whether you can do the activity using your hands:

N/A = not an activity you attempt
0 = Not at all
1 = Only partially or with great difficulty and slowly
2 = Fully and easily

Can you:	N/A	0	1	2	Weight
Hammer a nail					1.72
Thread a needle					1.68
Peel potatoes					1.53
Cut all your finger nails					1.49
Wrap up gifts					1.28
File all your finger nails					1.12
Cut up meat					1.11
Peel onions					0.73
Shell nuts					0.47
Open a jar					0.28
Fasten a zip on a jacket					0.22
Open a packet of crisps					0.11
Button up a shirt					-0.18
Sharpen a pencil					-0.33
Spread butter on bread					-0.71
Fasten a snap					-0.72
Button up trousers					-0.72
Take the cap off a bottle					-0.75
Open an envelope					-1.33
Squeeze toothpaste out of tube					-1.58
Zip up trouser zip					-1.59
Unwrap a bar of chocolate					-1.63
Wash both hands					-2.18

References:

Penta et al, 2001; Penta et al, 1998

Comment

This recently published questionnaire-based assessment of manual ability for use with patients after stroke has yet to be tested in widespread use, but has a thorough psychometric pedigree. The developers started with 57 activities, but many could be undertaken using one hand, and this group was selected on the basis that two hands were necessary and that the activities fitted a hierarchical scale. Some of the activities are presumably specific to certain countries (not many people in Britain shell hazel nuts), but the scale is hierarchical and so a score can be deduced using the highest scoring item marked. The weights given in the right column are logits, derived from Rasch analysis, and could be used as a score. Reliability and utility in a research or clinical setting has yet to be established.

Appendix C
EDSS Sensory System Assessments

In this section the instructions for the superficial sensation, vibration sense and finger position sense tasks within the EDSS will be described in detail. All the scores were reported on the EDSS scoring sheet displayed in this section.

Superficial Sensation

In the superficial sensation task, participants were shown a neurological pin that consists of a dull and sharp side. The assessor pressed the pin down on the participant's index finger, demonstrating what both sides of the pin felt like before commencing the experiment. Following this, the participant closed their eyes and the assessor interchanged between pressing the pin into the palm and back of the hand, testing 8 random locations per hand. The possible press locations included the knuckles and metacarpals of the thumb, index finger, middle finger, ring finger and pinky, as well as the purlicue. Participants informed the assessor if they felt the dull or sharp side. Performance with respect to each hand was recorded. A score of 0 was given if participants had no incorrect responses out of 8. A score of 1 was given if the participant had one incorrect response (indicating slightly diminished sensation). A score of 2 was given if the participant reported two to five incorrect responses but was unaware of impairment (indicating mild impairment). A score of 3 was given if the participants reported two to five incorrect responses but was aware of impairment (indicating impaired discrimination). If the participant could not discriminate between the sharp/dull pin on 6 or more trials, then a score of 4 was given (indicating moderate impairment). The number of correct responses for each hand and corresponding score was documented on the EDSS scoring sheet (refer to Appendix C).

Vibration Sense

Vibration sensation was assessed using a tuning fork and was conducted with participants' eyes closed. The assessor demonstrated what the tuning fork felt like by hitting one of the two prongs of the tuning fork and placing the opposite side of the tuning fork on the participant's middle finger. The participant was then asked to indicate when the vibration stopped. The tuning fork vibrated for approximately 15-20 seconds, depending on how hard the assessor had hit it. Following this, the assessor placed the tuning fork on the knuckles of the participant's middle finger on the left or right hand, one after the other (total 2 trials). Participants were scored on their ability to sense when the vibration on their hand had stopped. A score of 0 was given if there was no discrepancy in the vibration duration between the assessor and participant. If the participant detected that the vibration continued for more than 10 seconds but less than the assessor, they received a score of 1 (mild deficit). A score of 2 was given if they detect between 2 to 10 seconds of vibration (moderate deficit). If participants did not detect the vibration, they received a score of 3 (marked deficit). The scores of both hands were documented on the EDSS scoring sheet (see below)

Position Sense

Within the last two clinical tasks, position sense of the upper limb was assessed. The EDSS examined position sense during fine movements (finger movements) while the Fugl-Meyer examined position sense during gross movements (shoulder movements). The EDSS task required participants to close their eyes with their palms facing down, slightly above their lap. The assessor pinched their right index finger and move it up or down approximately 5°. The participant then told the assessor which way they think their finger moved. One practice trial was completed using each hand in order to familiarize participants with the task. The task was completed 5 times using both the right and left index fingers (total 10 trials). The number of correct directions reported was

documented on the EDSS scoring sheet. If there were no incorrect responses, then the participant received a score of 0 (normal). A score of 1 (mild deficit) was given if the participant had one to two incorrect responses. This indicated proprioceptive deficits at the distal joints. However, if the participant missed three to four movements, a score of 2 was reported (moderate deficit), indicating proprioceptive deficits at the proximal joints. Lastly, if there was no perception of movement (almost or all responses are incorrect), participants received a score of 3 (marked deficit). The scores were recorded on the EDSS scoring sheet (see below)

5 SENSORY FUNCTIONS

SUPERFICIAL SENSATION (LIGHT TOUCH AND PAIN)
0 normal
1 signs only: slightly diminished sensation (temperature, figure-writing) on formal testing of which patient is not aware
2 mild: patient is aware of impaired light touch or pain, but is able to discriminate sharp/dull
3 moderate: impaired discrimination of sharp/dull
4 marked: unable to discriminate between sharp/dull and/or unable to feel light touch
5 complete loss: anaesthesia

VIBRATION SENSE (AT THE MOST DISTAL JOINT)
0 normal
1 mild: graded tuning fork 5–7 of 8; alternatively, detects more than 10 seconds but less than the examiner
2 moderate: graded tuning fork 1–4 of 8; alternatively, detects between 2 and 10 sec.
3 marked: complete loss of vibration sense

POSITION SENSE
0 normal
1 mild: 1–2 incorrect responses, only distal joints affected
2 moderate: misses many movements of fingers or toes; proximal joints affected
3 marked: no perception of movement, astasia

*LHERMITTE'S SIGN
Does not contribute to the Sensory FS score
0 negative
1 positive

*PARAESTHESIAE (TINGLING)
Does not contribute to the Sensory FS score
0 none
1 present

FUNCTIONAL SYSTEM SCORE
0 normal
1 mild vibration or figure-writing or temperature decrease only in one or two limbs
2 mild decrease in touch or pain or position sense or moderate decrease in vibration in one or two limbs;
and/or mild vibration or figure-writing or temperature decrease alone in more than two limbs
3 moderate decrease in touch or pain or position sense or marked reduction of vibration in one or two limbs;
and/or mild decrease in touch or pain or moderate decrease in all proprioceptive tests in more than two limbs
4 marked decrease in touch or pain in one or two limbs;
and/or moderate decrease in touch or pain and/or marked reduction of proprioception in more than two limbs
5 loss: essentially of sensation in one or two limbs;
and/or moderate decrease in touch or pain and/or marked reduction of proprioception for most of the body below the head
6 sensation essentially lost below the head

Appendix D

Fugl-Meyer Assessment

Within the Fugl-Meyer task, participants closed their eyes, and raised their arms to shoulder height with their palms facing down. The assessor moved the participant's arm approximately 10° up or down at the shoulder. Following this movement, participants verbally indicated which direction they felt their arm move. One practice trial was completed with each arm to familiarize participants with the task. The task was completed four times in each limb, moving the limb in a random direction (i.e., up or down), for a total of 8 trials. A score of 2 was given if the participant had 0 or 1 incorrect response. However, if the person missed 2 to 4 of the 8 trials, a score of 1 was given. Lastly, a score of zero was given to participants who misidentified the direction of the limbs 5 or more times. The number of correct responses for each limb separately (i.e., 4 trials per limb) and both arms together (i.e., total of 8 trials) were recorded on the back of the EDSS scoring sheet (see Appendix C) and followed scoring listed below.

		less than 3/4 correct or absence	3/4 correct or considerable difference	correct 100%, little or no difference
Position small alterations in the position	Shoulder	0	1	2

Appendix E

Laboratory Based Proprioceptive Matching Task Instructions

Preliminary Records

Thank you for coming today and agreeing to participate. First thing I will get you to do is to get seated in the chair and make the proper adjustments for comfort (while grasping the handle). Before we begin I will quickly take some measurements of your position.

- Take measurements

General Description of Tasks

In this experiment, you will be performing reaches using your right, left or both hands to control the robot handles of the KINARM. Your hand will be represented on the screen as a small circle (like a cursor) or a line (like a rod). Your task will be to make movements by control the robot handle to interact with the visual information on the screen.

Testing will be separated by 3 tasks with 5-min breaks between each task, but you are welcome to take breaks at any time throughout the experiment.

Task 1: Visual Guided Reaching Task (VGRT)

Depending on order; could be done after PAT.

In this task, you will be reaching to 8 targets. You will first start at a visible home position (i.e., a white circle). Your cue to move is when you see a target appear. Targets will be yellow circles, similar in size to the home position. Once you get within half a cm of the target, the trial will end and your hand will be passively brought back to the home position. Your hand will be held there for half a second and then the trial begins again when another target appears.

Task 2: Proprioceptive Acuity Task (PAT)

Depending on order; could be done before VGRT.

In this task, you will be matching the position of your right or left arm using only proprioceptive information.

Ipsilateral Matching. You will grasp both the left and right robot handle and start at a visible home position. The robot handle with move your right or left hand around the workspace and then finally stop at a position for half a second. The robot will passively bring your hand back to home position. The home position will change colour from white to magenta, which is your cue to match the position where your hand was held. Once you have completed the matching task your hand will be passively brought back to the home position and in order to start the next trial.

Contralateral Matching. You will grasp both the left and right robot handle and start at a visible home position. The robot handle with move your right hand around the workspace and then finally stop. The home position at your left hand will change colour from white to magenta, which is your cue to mirror-match the position of where your right hand is being held. Once you have completed the matching task your hand will be passively brought back to the home position and in order to start the next trial.

Task 3: Object Hit Task (OHT)

In this task, you will be controlling the robot handle with your right, left or both hands to "hit" targets, which will be red circles that are falling from the top of the workspace. Your hand will be represented by horizontal lines (rods) that you will control to hit the targets. Your task is to hit as many targets as you can as they fall.

Supplementary file

In this section we report results for which ANOVA revealed a significant main effect of Target or interaction involving the factor of Target in the ipsilateral and contralateral laboratory based matching tasks. Variability related to the measures reported below are provided in Tables S1 and S2 and will not be discussed further. In the ipsilateral matching task, a main effect of target was found for angular errors at movement endpoint (i.e., |EPAE|; $F(1.714,72.007) = 4.962$, $p = 0.013$, $\eta^2 = 0.106$) and absolute error in both the x ($F(1.679,70.527) = 9.056$, $p = 0.001$, $\eta^2 = 0.177$) and y ($F(1.220,51.234) = 8.963$, $p = 0.003$, $\eta^2 = 0.176$) directions. Post hoc analysis with respect to angular errors at movement endpoint revealed larger errors at the near target (target 1) compared to the middle target (target 2; $p = 0.029$) and far targets (target 3, $p = 0.031$). However, there was no significant difference between targets 2 and 3 ($p = 1.000$). Analysis with respect to absolute error in the x direction indicated that the errors at target 3 were larger than at target 1 ($p = 0.012$) and target 2 ($p = 0.003$). On the other hand, post hoc analysis of absolute error in the y direction revealed that errors at target 1 were greater than at both target 2 ($p = 0.028$) and target 3 ($p = 0.008$). Similarly, greater errors were seen at target 2 than target 3 ($p = 0.038$). Thus, participants tended to overshoot the near target, and reached with a greater lateral error to the far target.

In terms of movement planning, a significant interaction between Hand x Target was found for PV ($F(2,84) = 9.451$, $p < 0.001$, $\eta^2 = 0.184$) and a main effect of Target was found for errors at PV ($F(1.488,62.489) = 9.510$, $p = 0.001$, $\eta^2 = 0.185$). Post hoc analysis for PV revealed that when reaching with the right hand, PV was less when reaching to target 1 compared to when reaching to target 2 ($p < 0.001$) and target 3 ($p < 0.001$). As well, PV was less when reaching to target 2 than target 3 ($p < 0.001$). Similarly, when reaching with the left hand, PV was less when reaching to target 1 than both target 2 ($p < 0.001$) and target 3 ($p < 0.001$). As well, PV was less when reaching to target 2 than target 3 ($p < 0.001$). When reaching to target 3, a lower PV was achieved

when reaching with the right versus left hand ($p = 0.013$). Analysis of errors at PV revealed greater initial direction errors when reaching to target 1 compared to target 2 ($p = 0.003$) and target 3 ($p = 0.006$), but no significant difference when reaching to targets 2 and 3 ($p = 0.706$). Together, these results indicate that participants achieved the highest PV when reaching to the far target, and again demonstrated greater errors at the near target.

With respect to movement execution, it was expected that the further the target, the longer the movement would be (i.e., MT). As well, path length was expected to be greater and movements less smooth when reaching to the far target compared to the near targets. In accordance with these expectations, analysis of MT revealed a significant interaction between Hand x Target ($F(1.670,70.126) = 5.253$ $p = 0.011$, $\eta^2 = 0.111$). When reaching to target 1 post hoc analysis revealed a significant difference between hands, such that reaches with the right hand were completed in a shorter MT compared to when reaching with the left hand ($p = 0.017$). Moreover, reaches with the right hand were completed in a shorter MT when reaching to target 1 than both target 2 ($p < 0.001$) and target 3 ($p < 0.001$). Similarly, participants took less time to reach to target 2 than target 3 ($p < 0.001$).When reaching with the left hand, participants took less time to complete the movement when reaching to target 1 than both target 2 ($p = 0.036$) and target 3 ($p < 0.001$). Similarly, participants took less time to reach target 2 than target 3 ($p = 0.014$). In regards to path length, analysis revealed a main effect of target ($F(1.715,72.009) = 212.628$, $p < 0.001$, $\eta^2 = 0.835$), such that one reached with a greater path length when moving to 3 compared to target 2 ($p < 0.001$) and target 1 ($p < 0.001$). Similarly, reaches to target 2 resulted in a greater path length than reaches to target 1 ($p < 0.001$). As displayed in Table S1, ANOVA revealed a main effect of target for jerk score ($F(2,84) = 19.159$, $p < 0.001$, $\eta^2 = 0.313$). Post hoc analysis revealed that reaches to target 3 had a higher jerk score than reaches to target 2 ($p = 0.001$) and target 1 ($p <$

0.001). Taken together these results indicate participants took longer to complete their reach, moved further and less smoothly to targets further away.

Table S1. Accuracy, planning and execution measures of OA and PwMS during the ipsilateral matching task, separated by hand and target. Values are reported as mean (SD). * denotes differences between targets such that all targets differ from each other. **denotes differences between targets such that reaches to targets 1 (near target) and 3 (far target) are significantly different $^{+}$ denotes differences between targets such that reaches to target 1 are different than reaches to both target 2 and 3. $^{++}$ denotes differences between targets such that reaches to target 3 are different than reaches to both targets 2 and 1.

Measure	OA: Left Hand	OA: Right Hand	PwMS: Left Hand	PwMS: Right Hand
Accuracy Measures				
|EPAE| (degrees)				
Mean T1	7.16 (3.79) $^{+}$	7.63 (7.16) $^{+}$	6.06 (3.46) $^{+}$	5.26 (2.43) $^{+}$
Variability T1	4.72 (5.61)	3.24 (2.93)	3.46 (1.80)	3.54 (2.18)
Mean T2	6.58 (4.91)	5.55 (3.47)	5.03 (3.41)	3.54 (2.66)
Variability T2	3.79 (5.64)	3.65 (2.08)	2.84 (1.91)	2.77 (2.82)
Mean T3	5.31 (4.96)	5.87 (7.22)	3.10 (1.42)	4.02 (3.81)
Variability T3	3.77 (6.28)	3.72 (5.70)	1.65 (0.92)	3.17 (5.91)
R-Error (cm)				
Mean T1	3.80 (2.83)	3.33 (2.72)	2.63 (1.44)	2.69 (1.83)
Variability T1	1.15 (1.24)	0.79 (0.37)	0.96 (0.62)	1.18 (1.14)
Mean T2	3.25 (1.52)	2.66 (1.83)	2.69 (1.40)	2.34 (1.01)
Variability T2	1.31 (1.29)	0.85 (0.53)	0.82 (0.57)	0.82 (0.69)
Mean T3	3.72 (1.95)	3.00 (2.37)	2.28 (0.89)	2.40 (1.22)
Variability T3	1.41 (1.70)	1.23 (1.07)	0.72 (0.44)	1.14 (1.27)
AE X (cm)				
Mean T1	1.57 (1.15) $^{++}$	1.52 (1.26) $^{++}$	1.25 (0.61) $^{++}$	0.98 (0.83) $^{++}$
Variability T1	0.93 (1.00) **	0.61 (0.48) **	0.51 (0.29) **	0.61 (0.56) **
Mean T2	1.89 (1.06)	1.33 (0.93)	1.59 (0.99)	1.04 (0.60)
Variability T2	0.89 (0.91)	0.75 (0.51)	0.80 (0.80)	0.74 (0.43)
Mean T3	2.62 (1.74)	2.11 (1.99)	1.37 (0.86)	1.59 (1.02)

Variability T3	1.28 (1.43)	1.26 (1.18)	0.64 (0.24)	0.91 (1.10)
AE Y (cm)				
Mean T1	3.33 (2.66) *	2.82 (2.52) *	2.15 (1.48) *	2.38 (1.74) *
Variability T1	1.02 (0.92)	0.74 (0.24)	0.98 (0.62)	1.12 (1.05)
Mean T2	2.44 (1.39)	2.09 (1.74)	1.99 (1.12)	2.00 (0.91)
Variability T2	1.16 (0.99)	0.71 (0.57)	0.63 (0.37)	0.70 (0.52)
Mean T3	2.33 (1.26)	1.82 (1.50)	1.64 (0.65)	1.60 (0.95)
Variability T3	0.99 (1.24)	0.57 (0.43)	0.71 (0.42)	0.87 (0.69)
Planning Measures				
RT (ms)				
Mean T1	578.38 (281.72)	435.96 (204.61)	677.35 (325.15)	843.47 (571.58)
Variability T1	223.51 (196.78)	200.44 (181.52)	213.24 (168.11)	351.23 (476.35)
Mean T2	627.17 (304.82)	410.28 (175.82)	627.20 (310.02)	693.62 (369.55)
Variability T2	282.10 (301.78)	154.87 (109.40)	193.61 (146.23)	281.31 (347.72)
Mean T3	604.17 (347.52)	491.65 (336.54)	651.31 (293.24)	696.75 (387.77)
Variability T3	261.09 (315.46)	236.60 (430.64)	203.43 (170.17)	334.12 (372.13)
PV (cm/s)				
Mean T1	15.41 (4.56) *	16.49 (7.03) *	12.61 (3.54) *	14.25 (4.84) *
Variability T1	1.98 (1.52) **	2.40 (1.53) **	2.12 (1.35) **	2.26 (1.54) **
Mean T2	19.10 (5.63)	18.61 (6.12)	16.74 (3.61)	16.41 (4.02)
Variability T2	3.55 (2.99)	1.92 (1.38)	1.92 (1.42)	3.14 (2.02)
Mean T3	25.19 (4.38)	23.29 (4.87)	21.11 (4.43)	19.46 (5.24)
Variability T3	3.91 (2.24)	2.58 (1.15)	2.19 (1.18)	2.54 (1.64)
|PVAE| (degrees)				
Mean T1	12.73 (11.92) +	11.37 (10.81) +	8.94 (7.46) +	6.60 (4.20) +
Variability T1	8.10 (7.85) +	5.92 (4.70)	6.83 (9.51)	4.61 (2.79)
Mean T2	7.84 (5.45)	6.98 (6.30)	6.48 (4.14)	5.64 (3.82)
Variability T2	5.03 (6.45)	3.76 (4.18)	3.45 (2.23)	4.16 (4.15)
Mean T3	6.70 (4.56)	5.86 (6.36)	5.25 (3.36)	5.50 (5.65)
Variability T3	4.47 (5.69)	4.05 (4.56)	2.08 (1.27)	3.53 (5.20)

pTTPV (%)				
Mean T1	48.17 (14.10)	45.09 (13.41)	56.24 (9.84)	54.33 (9.29)
Variability T1	10.14 (6.68)	10.36 (6.10)	7.68 (5.81)	8.08 (4.64)
Mean T2	46.22 (13.47)	47.58 (13.78)	51.39 (8.02)	53.73 (9.16)
Variability T2	8.10 (5.47)	8.74 (6.31)	6.48 (3.83)	10.81 (6.84)
Mean T3	47.03 (10.53)	44.58 (10.10)	51.71 (7.77)	51.67 (11.09)
Variability T3	6.94 (3.26)	12.34 (8.41)	6.77 (4.03)	9.31 (7.35)
Execution Measures				
MT (ms)				
Mean T1	1064.19 (171.97) *	934.44 (223.10) *	1046.83 (231.79) *	984.80 (245.54) *
Variability T1	178.98 (122.58)	148.41 (89.17)	162.75 (168.88)	170.45 (125.35)
Mean T2	1114.03 (214.85)	1100.08 (321.85)	1122.25 (210.72)	1128.18 (237.45)
Variability T2	230.24 (254.63)	169.74 (136.28)	137.71 (90.16)	155.73 (98.06)
Mean T3	1189.99 (222.31)	1216.32 (255.24)	1237.04 (235.05)	1289.21 (277.22)
Variability T3	209.57 (155.31)	221.58 (94.41)	133.39 (69.89)	220.82 (137.37)
Path Length (cm)				
Mean T1	9.31 (2.95) *	8.50 (2.94) *	8.00 (3.23) *	7.75 (2.17) *
Variability T1	1.75 (1.43)	1.05 (0.61)	1.87 (3.66)	1.44 (1.23)
Mean T2	11.84 (4.26)	11.15 (3.24)	10.72 (1.91)	10.26 (1.52)
Variability T2	2.88 (4.41)	1.20 (1.06)	0.96 (0.70)	1.15 (0.96)
Mean T3	16.60 (2.72)	15.03 (2.58)	14.83 (1.73)	14.07 (2.36)
Variability T3	1.98 (1.80)	1.37 (0.64)	1.07 (0.69)	1.17 (1.16)
TAPV (%)				
Mean T1	51.83 (14.10)	54.91 (13.41)	43.76 (9.84)	45.67 (9.29)
Variability T1	10.14 (6.68)	10.36 (6.10)	7.68 (5.81)	8.08 (4.64)
Mean T2	53.78 (13.47)	52.42 (13.78)	48.61 (8.02)	46.27 (9.16)
Variability T2	8.10 (5.47)	8.74 (6.31)	6.48 (3.83)	10.81 (6.84)
Mean T3	52.97 (10.53)	55.42 (10.10)	48.29 (7.77)	48.33 (11.09)
Variability T3	6.94 (3.26)	12.34 (8.41)	6.77 (4.03)	9.31 (7.35)
Jerk Score				

Mean T1	3584.15 (1933.12) ++	2707.45 (2232.42) ++	3876.09 (3301.66) ++	3924.34 (3410.42) ++
Variability T1	1753.60 (1946.33)	1419.98 (1537.10)	2370.60 (4500.82)	2272.02 (3287.63)
Mean T2	4550.83 (4326.76)	4494.27 (5521.85)	4291.35 (2291.75)	4197.68 (2502.73)
Variability T2	2951.73 (6185.09)	2228.03 (3592.34)	1522.69 (1180.26)	1717.98 (1494.12)
Mean T3	5256.68 (3718.73)	5387.95 (3341.81)	5563.08 (2952.17)	6272.89 (3592.36)
Variability T3	2769.46 (2993.56)	2803.31 (2510.74)	1582.97(1074.79)	3175.96 (3234.10)

In the contralateral matching task, we also found a main effect of target when analyzing angular errors at movement endpoint (i.e., |EPAE|; $F(1.412, 59.292) = 28.814$, $p < 0.001$, $\eta^2 = 0.407$). Post hoc analysis with respect to angular errors at movement endpoint revealed larger errors at the near target (target 1) compared to the middle target (target 2; $p < 0.001$) and far target (target 3, $p < 0.001$). Similarly, target 2 had a greater error than target 3 ($p < 0.001$). As well, a significant interaction between Hand x Target was found for absolute error in the horizontal direction (i.e., AEX ($F(1.699,71.356) = 6.153$, $p = 0.005$, $\eta^2 = 0.128$), with post hoc analysis indicating that when reaching to the near target, the right hand had greater error than the left hand.

In terms of movement planning, a significant interaction between Hand x Target interaction was found for PV ($F(2,84) = 135.328$, $p < 0.001$, $\eta^2 = 0.763$) and a main effect of Target was found for errors at PV ($F(1.661,69.750) = 17.555$, $p < 0.001$, $\eta^2 = 0.295$). Post hoc analysis for PV revealed that when reaching with the right hand, PV was less when reaching to target 1 compared to when reaching to target 2 ($p < 0.001$) and target 3 ($p < 0.001$). As well, PV was less when reaching to target 2 than target 3 ($p < 0.001$). Similarly, when reaching with the left hand, PV was less when reaching to target 1 than when reaching to target 2 ($p < 0.001$) and target 3 ($p < 0.001$). As well, PV was less when reaching to target 2 than target 3 ($p < 0.001$). When reaching to target 3, a lower PV was achieved when reaching with the left versus the right hand ($p = 0.036$). Analysis of errors at PV revealed greater initial direction errors when reaching to target 1 compared to target 2 ($p < 0.001$) and target 3 ($p < 0.001$). As well, initial direction errors were greater when reaching to target 2 than target 3 ($p = 0.037$). Together, these results indicate that participants achieved the highest PV when reaching to the far target, and again demonstrated greater errors at the near target.

With respect to movement execution, similar to the ipsilateral task we expected the further the target, the longer the movement (i.e., MT), greater path length and less smooth movements. In accordance with these expectations, analysis of MT revealed a main effect of Target ($F(2,84) = 28.255$, $p < 0.001$, $\eta^2 = 0.402$), such that reaching to target 1 took less time than when reaching to target 2 ($p < 0.001$) and target 3 ($p < 0.001$). As well, reaching to target 2 took less time than target 3 ($p = 0.002$). With regard to path length, analysis revealed a significant interaction between Hand x Target ($F(2,84) = 4.540$, $p = 0.013$, $\eta^2 = 0.098$). When reaching to target 1, post hoc analysis revealed a significant difference between hands, such that reaches with the left hand had a greater path length compared to when reaching with the right hand ($p = 0.048$). Moreover, reaches with the right hand were completed with a shorter path length when reaching to target 1 than target 2 ($p < 0.001$) and target 3 ($p < 0.001$). Similarly, reaches to target 2 resulted in a shorter path length than target 3 ($p < 0.001$). When reaching with the left hand, reaches were completed with a shorter path length when reaching to target 1 compared to target 2 ($p < 0.001$) and target 3 ($p < 0.001$). Similarly, reaches to target 2 resulted in a shorter path length than target 3 ($p < 0.001$). As displayed in Table S2, there was a main effect of Target ($F(2,84) = 9.849$, $p < 0.001$, $\eta^2 = 0.190$) with respect to jerk score. Post hoc analysis revealed that target 1 had a lower jerk score than both target 2 ($p = 0.049$) and target 3 ($p < 0.001$). Taken together these results indicate participants took longer to reach, moved further and less smoothly to targets further away.

Table S2. Accuracy, planning and execution measures of OA and PwMS during the contralateral matching task, separated by hand and target. Values are reported as mean (SD). * denotes differences between targets such that all targets differ from each other. **denotes differences between targets such that reaches to targets 1 (near target) and 3 (far target) are significantly different $^{+}$ denotes differences between targets such that reaches to target 1 are different than reaches to both target 2 and 3. $^{++}$ denotes differences between targets such that reaches to target 3 are different than reaches to both targets 2 and 1.

Measure	OA: Left Hand	OA: Right Hand	PwMS: Left Hand	PwMS: Right Hand
Accuracy Measures				
|EPAE| (degrees)				
Mean T1	17.69 (11.58) *	20.80 (14.77) *	15.15 (8.04) *	17.00 (7.84) *
Variability T1	7.26 (4.50) $^{++}$	4.80 (3.03) $^{++}$	7.47 (5.17) $^{++}$	7.78 (5.38) $^{++}$
Mean T2	14.79 (7.25)	13.62 (9.21)	12.06 (7.78)	12.42 (5.83)
Variability T2	5.61 (3.85)	5.22 (3.00)	5.80 (4.93)	6.62 (4.23)
Mean T3	8.17 (4.68)	9.17 (8.50)	10.09 (8.11)	7.14 (5.17)
Variability T3	4.42 (2.27)	2.59 (1.56)	4.64 (4.62)	4.13 (4.60)
R-Error (cm)				
Mean T1	2.89 (1.84)	3.95 (2.39)	2.53 (1.28)	3.30 (1.49)
Variability T1	1.04 (0.96)	1.02 (1.04)	0.86 (0.65)	1.27 (0.93)
Mean T2	3.19 (1.12)	3.56 (2.21)	2.55 (0.89)	2.75 (1.26)
Variability T2	1.11 (0.84)	0.92 (0.55)	1.01 (0.67)	1.07 (0.80)
Mean T3	3.49 (1.54)	3.53 (1.91)	3.53 (1.72)	2.89 (1.26)
Variability T3	0.99 (0.52)	0.82 (0.47)	1.26 (1.14)	1.15 (0.92)
AE X (cm)				
Mean T1	2.21 (1.80)	3.15 (2.42)	1.61 (0.88)	2.32 (1.42)
Variability T1	0.84 (0.51)	0.94 (1.04)	0.75 (0.70)	1.02 (0.64)
Mean T2	2.41 (1.30)	2.68 (2.35)	1.68 (1.11)	2.02 (1.24)
Variability T2	1.27 (0.87)	0.96 (0.52)	1.04 (0.73)	1.11 (0.78)
Mean T3	2.90 (1.48)	2.52 (2.08)	2.70 (1.76)	2.15 (1.25)

Variability T3	1.00 (0.49)	0.85 (0.60)	1.17 (1.08)	1.11 (1.02)
AE Y (cm)				
Mean T1	1.41 (1.08)	1.91 (1.33)	1.56 (1.37)	1.96 (1.02)
Variability T1	0.78 (1.08)	0.65 (0.42)	0.72 (0.58)	1.13 (1.06)
Mean T2	1.66 (0.65)	1.84 (1.05)	1.46 (0.76)	1.54 (0.86)
Variability T2	0.78 (0.43)	0.72 (0.46)	0.71 (0.46)	0.63 (0.50)
Mean T3	1.61 (1.02)	1.96 (1.09)	1.87 (1.08)	1.58 (0.94)
Variability T3	0.67 (0.41)	0.59 (0.32)	0.85 (0.55)	0.71 (0.39)
Planning Measures				
RT (ms)				
Mean T1	448.88 (202.81)	464.56 (212.90)	590.18 (224.39)	663.57 (346.77)
Variability T1	126.32 (78.74)	149.07 (122.60)	218.74 (182.05)	249.66 (277.57)
Mean T2	468.00 (262.51)	596.60 (422.26)	626.67 (307.58)	687.41 (401.85)
Variability T2	164.50 (110.97)	302.82 (449.63)	182.82 (131.16)	293.73 (355.97)
Mean T3	529.18 (291.22)	557.66 (315.85)	713.63 (382.93)	608.42 (264.63)
Variability T3	220.25 (162.30)	191.33 (124.08)	275.17 (345.74)	189.67 (116.72)
PV (cm/s)				
Mean T1	13.04 (4.93) *	15.63 (5.74) *	11.91 (4.74) *	12.80 (3.46) *
Variability T1	2.07 (1.21)	2.71 (2.15)	1.75 (1.13)	2.50 (1.13)
Mean T2	17.09 (7.12)	17.71 (6.82)	15.00 (6.03)	15.48 (4.05)
Variability T2	2.52 (1.83)	2.89 (3.34)	2.46 (2.39)	2.18 (1.64)
Mean T3	20.46 (6.81)	20.12 (4.63)	19.90 (6.96)	18.66 (4.23)
Variability T3	2.28 (1.35)	2.35 (1.21)	2.74 (1.92)	2.01 (1.20)
|PVAE| (degrees)				
Mean T1	19.22 (11.79) *	22.22 (17.44) *	16.91 (7.80) *	20.55 (12.76) *
Variability T1	9.63 (7.34)	8.02 (4.57)	10.34 (5.65)	8.83 (6.11)
Mean T2	13.93 (8.42)	19.44 (18.26)	12.94 (7.26)	15.23 (13.29)
Variability T2	7.34 (4.25)	7.91 (9.19)	5.88 (3.84)	9.01 (8.03)
Mean T3	10.32 (6.04)	12.67 (10.07)	12.58 (8.71)	11.26 (9.30)
Variability T3	5.57 (3.96)	4.48 (2.11)	5.07 (4.10)	6.51 (6.13)

pTTPV (%)				
Mean T1	45.13 (13.90)	48.90 (10.17)	48.78 (11.28)	52.03 (8.15)
Variability T1	12.71 (8.98) +	13.96 (7.50) +	10.98 (6.94) +	13.57 (6.39) +
Mean T2	44.43 (13.22)	47.05 (11.67)	50.05 (9.70)	50.63 (9.73)
Variability T2	11.12 (7.13)	10.89 (6.51)	8.59 (4.84)	9.68 (6.77)
Mean T3	42.56 (11.16)	45.90 (9.92)	50.41 (11.32)	52.02 (9.02)
Variability T3	7.79 (3.62)	8.47 (5.53)	9.22 (6.64)	9.64 (7.22)
Execution Measures				
MT (ms)				
Mean T1	937.44 (266.15) *	960.61 (273.08) *	982.33 (242.23) *	1047.80 (306.06) *
Variability T1	152.10 (157.97)	186.09 (134.33)	164.17 (153.66)	163.59 (113.46)
Mean T2	1024.14 (364.61)	1045.69 (191.63)	1126.54 (303.59)	1106.93 (298.34)
Variability T2	167.66 (96.44)	213.96 (143.57)	144.79 (106.02)	181.74 (182.55)
Mean T3	1168.34 (291.95)	1141.64 (210.97)	1173.28 (314.20)	1243.51 (322.98)
Variability T3	172.71 (133.12)	175.06 (107.81)	199.37 (153.35)	193.59 (185.67)
Path Length (cm)				
Mean T1	7.32 (4.25) *	8.18 (2.63) *	6.41 (2.14) *	7.84 (2.67) *
Variability T1	0.96 (0.80)	1.47 (0.96)	1.61 (1.67)	1.79 (1.35)
Mean T2	10.06 (5.77)	10.33 (3.18)	9.14 (2.14)	9.61 (2.31)
Variability T2	1.84 (2.31)	1.61 (1.40)	1.37 (0.85)	1.34 (1.18)
Mean T3	13.54 (5.88)	12.92 (2.58)	12.20 (2.04)	12.96 (1.98)
Variability T3	1.31 (1.08)	0.89 (0.56)	1.51 (0.98)	1.21 (0.84)
TAPV (%)				
Mean T1	54.87 (13.90)	51.10 (10.17)	51.22 (11.28)	47.92(8.15)
Variability T1	12.71 (8.98) +	13.96 (7.50) +	10.98 (6.94) +	13.57 (6.39) +
Mean T2	55.57 (13.22)	52.95 (11.67)	49.95 (9.70)	49.37 (9.73)
Variability T2	11.12 (7.13)	10.89 (6.51)	8.59 (4.84)	9.68 (6.77)
Mean T3	57.44 (11.16)	54.10 (9.92)	49.59 (11.32)	47.98 (9.02)
Variability T3	10.84 (14.36)	8.47 (5.53)	9.22 (6.64)	9.64 (7.22)

Jerk score				
Mean T1	3584.15 (1933.12) +	3076.65 (2473.35) +	3310.36(2234.28) +	3267.63 (2174.02) +
Variability T1	1753.60 (1946.33)	1582.42 (1445.49)	1640.50(1989.01)	1848.41 (2522.95)
Mean T2	4550.83 (4326.76)	3646.77 (2165.22)	4814.67(4242.98)	4772.36 (6469.86)
Variability T2	2951.73 (6185.09)	2304.56 (2578.95)	1900.23(2446.31)	2973.76 (7331.02)
Mean T3	5256.68 (3718.73)	4551.31 (2512.67)	5292.10 (4533.77)	5932.00 (5095.56)
Variability T3	2769.46 (2993.56)	2050.05 (1868.16)	2437.64 (3205.76)	2658.25 (4231.11)