AN INVESTIGATION OF THE KINESTHETIC ABILITY AND EFFECTS OF BIMANUAL COORDINATION IN PATIENTS WITH MULTIPLE SCLEROSIS

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ABSTRACT

AN INVESTIGATION OF THE KINESTHETIC ABILITY
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Previous research has shown that balance and proprioception of the lower limbs are impaired in patients with multiple sclerosis (MS). The extent of kinesthetic impairment in the upper limb for this population is not well known. This study identifies the kinesthetic impairment in the upper limb in MS patients and determines if this performance can be modulated by simultaneous utilization of the contralateral limb. Patients with MS, aged 32-61 with mild to moderate severity and diagnosed within the last ten years, as well as age- and gender-matched healthy controls, performed center-out movements by controlling a cursor on a horizontally positioned computer screen with a joystick underneath so the hand was not visible. This task was performed unimanually and bimanually under visual and kinesthetic control. Results show that kinesthetically guided movements of MS patients in both unimanual and bimanual conditions are slower, less linear, and less accurate compared to controls. They improved movement linearity in the dominant kinesthetically guided arm when utilizing bimanual coordination compared to unimanual. However, the overall kinesthetic performance of MS patients did not improve with visual guidance from the contralateral limb, nor did it get worse. Patients with MS have impaired visual integration and kinesthetic ability. Damage to the corpus callosum might be an indicator of this. Simultaneous use of the upper limbs does not seem to improve fine motor functions or aid kinesthesia.

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KEY TO ABBREVIATIONS

ADL – Activities of Daily Living

ANOVA – Analysis of Variance

CC – Corpus Callosum

CNS – Central Nervous System

CP – Cerebral Palsy

DTI – Diffusion Tensor Imaging

EPE – Absolute End Point Error

EP_{ort} – Orthogonal End Point Error

EP_{par} – Parallel End Point Error

LCD – Liquid Crystal Display

MRI – Magnetic Resonance Imaging

MS – Multiple Sclerosis

MT – Movement Time

NHPT – Nine Hole Peg Test

PD – Parkinson's disease

RMSE – Root Mean Squared Error

CHAPTER 1
Introduction

Multiple sclerosis (MS) is an autoimmune disorder of increasing prevalence in the United States and Europe that includes inflammation and demyelination of the neurons in the central nervous system (CNS) (Lassmann, Brück, & Lucchinetti, 2007; Tullman, 2013). Typically this disease becomes clinically apparent when there are lesions in the brain or spinal cord visible by magnetic resonance imaging (MRI), but it has recently been found to include injury of the normal appearing white matter, such as diffusion of the tissue that cannot be seen by MRI (Lassmann et al., 2007).

Clinical diagnosis of MS may be challenging as the symptoms can vary widely, including muscle weakness, fatigue, numbness, impaired balance, and vertigo (Lassmann et al., 2007; Tullman, 2013). These symptoms were commonly found to be detrimental to a patient's quality of life and activities of daily living (ADL) (Einarsson, Gottberg, Fredrikson, Koch, & Holmqvist, 2006). An increased risk of falling in affected individuals has been a noted concern and an important topic of past research. Most studies have focused on the contributing factors to falls, which include proprioception, kinesthesia, and muscle weakness (Hoang, Cameron, Gandevia, & Lord, 2014; Nilsagård, Denison, Gunnarsson, & Boström, 2009a; Prosperini, Leonardi, De Carli, Mannocchi, & Pozzilli, 2010). Proprioception is influential in falls, thus it has mainly been studied in the lower limbs or torso as it relates to balance, posture, and gait (Cameron, Horak, Herndon, & Bourdette, 2008; Cattaneo et al., 2014; Fjeldstad, Pardo, Bemben, & Bemben, 2011; Frzovic, Morris, & Vowels, 2000; Hebert & Corboy, 2013; Huisinga, St George, Spain, Overs, & Horak, 2014; Rougier et al., 2007; Thoumie, 2002).

Proprioception is defined as the ability to determine limb location in the absence of vision based on peripherally and centrally based mechanisms (Fortier & Basset, 2012). Adequate balance requires proprioception, and it has been found that functional reach is impaired before there were any differences observed in balance control of stance or stride (Frzovic et al., 2000). This means that there could be more apparent proprioceptive problems in the upper limb before there are any issues evident in balance. Additionally, there were many ADLs that were found to be difficult for patients including the use of the upper limbs, but there was little research on how the upper limbs are functionally affected by MS (Einarsson et al., 2006). The nine-hole peg test (NHPT) is a clinical tool for assessing upper limb function and has a high level of predictability for activity limitations (Kierkegaard, Einarsson, Gottberg, Koch, & Holmqvist, 2012). It has yet to be exhibited across various modalities how proprioception and kinesthesia are utilized in the upper limb in individuals with MS. Differences in proprioceptive abilities could be detected earlier in the upper limb as there was evidence toward proprioception being more distinguished and accurate in the arm compared to the leg (Paschalis et al., 2010) in addition to its affect on daily functioning. It was important to define the level of upper limb function and how it was altered in those with MS compared to their healthy peers. This information could lead to a greater understanding of the mechanisms underlying proprioception and kinesthesia in individuals with MS, outside of the coping mechanisms and neural activity. This additional knowledge could inform us of the possible rehabilitation techniques to positively influence their quality of life and ADLs.

Multiple different tools have been used to assess upper limb impairment in MS. The NHPT has been one test that has greatly benefited both rehabilitation techniques and research. It allows for the assessment of movement efficiency and manipulation techniques. It has shown that movements were slower, less smooth, less straight, and with a decreased manipulation ability in those with MS compared to healthy controls (Carpinella, Cattaneo, & Ferrarin, 2014; Lambercy et al., 2013; Nociti et al., 2008). In addition to the NHPT, hand grip strength has also been a common measure used in many studies focusing on the upper limb function in those with MS (Lamers, Kelchtermans, Baert, & Feys, 2014). Grip strength was irregular in patients with MS because they tended to utilize an increased grip strength compared to their healthy peers and have issues with coordinating that strength to the load required (Gorniak, Plow, McDaniel, & Alberts, 2014; Krishnan & Jaric, 2008; Krishnan, de Freitas, & Jaric, 2008; Marwaha, Hall, Knight, & Jaric, 2006). This unusual response was expected when movements of the upper limb were known to be variable due to a lack of sensation and decreased strength, and the individuals had a difficult time adapting to new tasks or outside forces, had a decreased processing speed, or had less control over their movements (Basteris et al., 2011; Benedict et al., 2011; Casadio, Sanguineti, Morasso, & Solaro, 2008; Guclu-Gunduz, Citaker, Nazliel, & Irkec, 2012; Leocani et al., 2007; Llufriu et al., 2012; Longstaff & Heath, 2006).

Functional adaptations, learning strategies, and processing speed were difficulties faced while completing tasks that contribute to an increased cognitive effort during upper limb movements, especially in the use of the nondominant arm (Tacchino et al., 2013). These impaired movements of the upper limb were not exclusive to gross motor movements as some fine motor movements and manipulations had the same results. Those with MS showed impaired manual dexterity with characteristics such as slower movement times, which affected their ability to manipulate small objects or write (Schenk, Walther, &

Mai, 2000; Scherer, Bauer, & Baum, 1997). This impaired movement performance in the upper limb was found to be related to the amount of axonal loss found in the CNS (Solaro et al., 2007).

As previously mentioned, the number of lesions in the CNS is not the only factor that is related to motor impairment in patients with MS, as other neural tissue injuries can be a factor. The research on upper limb function has led to the study of brain and neural structures to determine how they were associated with upper limb movement. There were severe cases where the two arms were disconnected from one another. Characteristics included one non-responsive limb, spontaneous activity of one arm when the opposite arm moved, or loss of kinesthesia (Hamada, Okamoto, & Okuda, 2005; Hashimoto, Kanho, Fujimoto, & Tanaka, 1997; Kurne, Cakmakli, & Karabudak, 2008). These symptoms have been linked to lesions on the posterior cervical spinal cord, but were more commonly associated with lesions or disconnection of the corpus callosum (CC) (Hamada et al., 2005; Lunardelli, Sartori, Mengotti, Rumiati, & Pesavento, 2014; Moroni, Belin, Haguenau, & Salama, 2004). Other structures of the CNS have been thought to play an important role in the control of upper limb movements and are related to the duration and complexity of the task being completed, such as the cerebellum, motor insula, mirror neurons, motor cortex, and spinal cord (Anderson et al., 2011; Meyenburg et al., 2013; Pantano et al., 2011; Prosperini et al., 2014; Rocca et al., 2009; 2008; White, Lee, Light, & Light, 2009). The CC has been a subject of many studies in those looking at function in MS and was shown to have a strong relationship to the upper limb function. There was atrophy and a decreased volume of white matter in the CC which correlated to the level of disability observed in those with MS (Audoin et al., 2007; L. N. Brown, Zhang, Mitchell, Zabad, & Metz, 2010;

Evangelou et al., 2000b; Sbardella et al., 2013). More specifically than just atrophy and injury to white matter in the CC, there was an increased diffusivity in the CC that preceded atrophy and visible damage to the white matter and was a better marker for fine motor skills as assessed by clinical tests such as the NHPT (Kern, Sarcona, Montag, Giesser, & Sicotte, 2011; Lenzi et al., 2007; Ozturk et al., 2010; Ranjeva et al., 2003). When it came to simultaneous movement of the two arms and hands, the lack of coordination stemmed from the lack of interhemispheric transfer and lack of transcallosal inhibition; there was further evidence that the anterior part of the CC was responsible for influencing the bimanual fine motor movements in the fingers (Bonzano et al., 2008; L. N. Brown et al., 2010; Lenzi et al., 2007; Manson et al., 2008; Pelletier et al., 1993).

Bimanual coordination of fine motor movements is important to daily living and was found to be impaired in those with MS compared to their healthy peers measured by the time it took to complete the task or the length of their reaction time (Bonzano et al., 2013; Larson, Burnison, & Brown, 2002). Other studies that focused on the bimanual coordination in patients with MS were not entirely measuring coordination of the movements. Rather, they were frequently measuring the coordination of grip and force utilized to manipulate an object (Gorniak et al., 2014; Krishnan et al., 2008; Krishnan & Jaric, 2008). Bimanual coordination impairments were not solely based on the coupling of grip and load force, it also included sensorimotor control and deficits in the case of patients with MS (Marwaha et al., 2006).

These sensorimotor deficits point back to the lack of interhemispheric transfer in the CC, and possibly proprioception and kinesthesia. Difficulties in moving the arm in patients with MS was influenced by proprioception and the group I spindle afferents because when proprioception was inhibited, the tremors in movement were decreased (Quintern et al., 1999). There were few studies that investigated the proprioceptive influences in the fine motor skills of the upper limb in those with MS. Those that have done so focused on the static position sense in the fingers (Beckmann, Çiftçi, & Ertekin, 2013; Fukutake, Kuwabara, Kaneko, Kojima, & Hattori, 1998). This limited the scope of the proprioceptive influence, as one digit of the hand did not provide adequate information on how fine motor movements involved proprioception. Furthermore, there was evidence that kinesthesia was more important to movements of the upper limb. There was a decreased accuracy and speed in those with MS compared to healthy controls when they attempted to visualize the movements of their hands (Tabrizi et al., 2013). It was even more important that the motions in rehabilitation were active rather than passive in order to maintain their bimanual coordination, which pointed to the involvement of kinesthesia (Bonzano et al., 2014).

Past research on the upper limb, especially involving kinesthesia, in the healthy adult population was not entirely comprehensive. The available information was predictive of what to expect in those lacking complete coordination of their upper limbs. Other studies showed that bimanual tasks were performed more accurately than unimanual (Blinch et al., 2014; Gorman & Crites, 2013), and movement variability within a given limb improved when completing a bimanual task compared to being used unimanually (Helmuth & Ivry, 1996). There was even some variability in the type of bimanual movements. Mirror movements were typically found to be more accurate and synchronous than isodirectional movements (Cohen, 1971; Li, Levin, Forner-Cordero, & Swinnen, 2005), which was explained by the use of homologous rather than non-homologous muscles in the limb.

Additionally, isodirectional movements showed decreased accuracy and multi-joint, intralimb coordination (Li et al., 2005). Isodirectional as well as unimanual movements also showed an increased interhemispheric connectivity due to their need for communication between the two limbs or lack there of, respectively (Grefkes, Eickhoff, Nowak, Dafotakis, & Fink, 2008; Serrien, 2008). In addition, the nondominant limb was found to be more accurate in a unimanual task (Han, Waddington, Adams, & Anson, 2013), especially when utilizing proprioception (Goble & Brown, 2010). These findings supported the notion that movements in either arm had separate, specialized, and complementary control mechanisms (Mutha, Haaland, & Sainburg, 2013). When having to rely on proprioception or kinesthesia, both bimanual and unimanual coordination was negatively impacted – reaction and movement time increased and accuracy decreased (Cardoso de Oliveira & Barthelemy, 2005; Gooijers & Swinnen, 2014). However, it was found that losing visual feedback from one limb during a bimanual task is preferable when losing visual feedback on the limb during a unimanual task because the limb relying on kinesthesia was more accurate when coupled with the visible, contralateral limb (Kagerer, 2014). These findings shaped the present study.

There was little research conducted on the dynamic movement perceptions in the upper limb including bimanual coordination in patients with MS, it was a goal of this study to investigate the relationship between kinesthesia and bimanual coordination and define how this relationship was affected in those with MS compared to the healthy population. The main measures for kinesthesia in this study was end point error (EPE), its directional characteristics, and linearity of the movement trajectory by root mean squared error (RMSE). The characterization of kinesthesia in this way with the assistance of a visible contralateral limb has not been done in this patient population, but would provide valuable insight into possible rehabilitation techniques, interhemispheric communication, or integration of multisensory feedback. The present study maintained the hypothesis that the movements in those with MS would be more variable in their trajectories, or less linear, and less accurate compared to the healthy controls. When visual feedback for the trajectory of movement was taken away, the movements of MS patients would be less linear and less accurate than when visual feedback was available in both the unimanual and mixed bimanual conditions. This would also be true when compared to healthy controls. It was also hypothesized that when visual feedback was taken away for the trajectory of movement for one hand, that it would still be functionally accurate with the assistance of the simultaneous movement of the opposite hand when compared to unimanual use, but that it would be less accurate in MS patients than when compared to their healthy controls. This expected result was important because it could be useful for rehabilitation or ADLs. However, if the kinesthetic movement aided by a contralateral visual movement was not improved in MS patients, then it could be concluded that MS patients had a more severe inhibition of kinesthesia compared to the healthy population. It was expected that the nondominant arm would be more accurate than the dominant one in the kinesthetic condition across all participants.

CHAPTER 2
Literature Review

In order to understand how movements of the upper limb and kinesthesia are affected in patients with MS, normal movements in the healthy population had to be assessed. Understanding the unimanual and bimanual performances of the healthy population would help to see any abnormalities in the MS population. Studying the characteristics of the disease, the influence on the patient's activities of daily living, and identifying the areas of the brain most affected would assist in understanding MS and how their movements and kinesthetic ability would be affected. Proprioceptive ability in patients with MS has been looked at and provided insight as to how kinesthetic ability would be similarly affected. The clinical tests assessing upper limb movement and other research on other areas of upper limb ability showed that there were deficits in MS patients, and these findings helped to characterize dysfunction in MS but also identified the gaps in research.

Upper limb performance in the healthy population, specifically on unimanual tasks, showed that connections to the contralateral primary motor cortex caused activation while the ipsilateral motor areas were simultaneously inhibited (Grefkes et al., 2008). With reference to proprioception, there have been similar results from various methods. After task performance from passive movements, angle matching tasks and pointing to visual targets revealed that the nondominant arm had fewer errors in the angle matching task, but the dominant arm had fewer errors in the visual pointing task (Goble & Brown, 2008). The nondominant arm showed an advantage in static proprioceptive position matching conditions from another study, but it also showed a larger movement amplitude (Goble, Lewis, & Brown, 2006). This same finding was also seen in a dynamic position sense task when the previously passively set angle had to be determined during continuous passive movement (Goble & Brown, 2010).

Bimanual movements in healthy people also showed activation in the primary and sensory motor areas, but it also revealed an increased interhemispheric connectivity (Grefkes et al., 2008). Bimanual movements were found to be more accurate when compared to unimanual movements with reference to movement velocity and movement variability, which was explained to be from transitioning from a simple to a more complex task (Gorman & Crites, 2013). This result was also found when measuring proprioception with active bimanual movements, and the non dominant hand was only found to be advantageous in the unimanual condition (Han et al., 2013). The decrease in movement variability within a specific hand from unimanual to bimanual movements was due to coupling because there were timing mechanisms integrated prior to the execution of the movement (Helmuth & Ivry, 1996). This temporal and spatial coupling was unchanged with tasks that required moving a cursor on a screen with or without visual feedback, and the reaction times and movement amplitudes were increased in the conditions without visual feedback (Cardoso de Oliveira & Barthelemy, 2005). However, there were contrasting results. Another study found that bimanual coordination was worse without visual feedback but that movements were more accurate in the dominant hand only when both hands moved at the same temporal frequency, which directly correlated to the amount of the white matter in the CC (Gooijers et al., 2013). This was further characterized by the findings that only the spatial aspects of the grasp and not the reaching movement was affected by the amount of visual feedback (Bruyn & Mason, 2009). In addition, movements of only one hand without visual feedback under bimanual conditions were more accurate when paired with the contralateral hand movements that were under visual conditions compared to the unimanual movements (Kagerer, 2014). There were differences in how the hands responded to bimanual movements. The dominant hand was found to be able to move more accurately for a longer period of time that the nondominant hand without visual feedback. Although the dominant hand had a smoother trajectory, it needed vision for end point accuracy whereas the nondominant hand did not (Srinivasan & Martin, 2010). In a directed reaching task where the starting positions were shifted with reference to the targets after some time, the dominant arm adapted and maintained an accurate trajectory but the nondominant arm deviated back to the previously learned trajectory, which revealed that the dominant arm relied on predictive mechanisms while the nondominant arm relied on positional stability (Mutha et al., 2013).

The direction of movement also seemed to play a role in how bimanual coordination is modulated. There was a significant difference between bimanual performance in isodirectional and anisodirectional movements. There was a tendency to conform to anisodirectional movements rather than isodirectional. The switching from isodirectional movements to anisodirectional was not due to the preferred use of homologous muscles but was because of spatial and perceptual symmetry and coupling (Mechsner, Kerzel, Knoblich, & Prinz, 2001). There was found to be a cost of isodirectional movements compared to anisodirectional because it required more complex preparation and was due to the result of interference of interhemispheric connectivity (Blinch et al., 2014). There was increased hemispheric connectivity found for isodirectional and unimanual movements, which suggested that brain regions were flexible in coupling and decoupling to implement processing requirements for coordination (Serrien, 2008). The costs of isodirectional movements caused them to be more variable and less synchronous compared to anisodirectional movements, which supported the existence of a coupling mechanism for anisodirectional movements (Cohen, 1971). Contrastingly, anisodirectional movements were more coordinated and stable, and isodirectional coordination had a negative influence on the accuracy and stability of intralimb coordination as well as interlimb coordination (Li et al., 2005).

These patterns were also seen in continuous movements rather than just discrete reaching movements. When isodirectional and anisodirectional circle drawing was performed with differing temporal patterns, the dominant arm was more accurate in its trajectory, but it reversed movement from isodirectional to anisodirectional (Byblow, Summers, Semjen, Wuyts, & Carson, 1999). This bimanual continuous circle drawing was also performed while blindfolded. When vibration was applied to the tendons to inhibit any proprioceptive feedback, the circles lost their shape, became smaller, and caused drifting of the hands (Verschueren, Swinnen, Cordo, & Dounskaia, 1999a). In addition, the dominant hand increased its temporal lead over the nondominant hand (Verschueren, Swinnen, & Cordo, 1999b). This showed that proprioceptive feedback was necessary to movements that were performed without visual feedback.

Patients with multiple sclerosis suffer from many motor deficits, but those of the upper limb had not been characterized in their entirety. MS is a disease that affects much more than the motor system. It is primarily an autoimmune, inflammatory, and demyelinating disease that includes lesions and injury to the normal appearing white matter, and it can have different manifestations of the disease such as relapsing-remitting and progressive (Lassmann et al., 2007). It is increasing in prevalence, due to environmental and genetic factors, and has highly variable symptoms, which could lead to disability due to incomplete recovery from attacks (Tullman, 2013). Disability includes a variety of daily activities and safety precautions that must be taken to prevent further injury. It was found that the patients' social activities were maintained but independence was decreased by difficulty with daily activities such as dressing, household maintenance and cleaning, gardening, and transportation (Einarsson et al., 2006). Falling in MS patients, leading to physical injury, is common due to their disabilities. Potential factors that lead to falls were found to be decreased attention, fatigue, impaired proprioception, and limited vision, and some risk activities included bathing, housekeeping, and cooking (Nilsagård et al., 2009a). Frequent occurrences of falling were identified by increased postural sway without visual feedback, decreased coordination, and poor performance on the NHPT (Hoang et al., 2014). Discerning factors between those with frequent and occasional falls were disability status and proprioception, but the proprioceptive measurement was only performed in the lower limb (Nilsagård, Lundholm, Denison, & Gunnarsson, 2009b). It was found that the risk for falling could be decreased. Visio-proprioceptive training increased balance and decreased the risk of falls, which implied that patients with MS relied on vision for balance and had decreased proprioception (Prosperini et al., 2010).

MS stems from the demyelination of white matter in the CNS and is thought to be the reason for some of its symptoms. Some of these injured areas have been identified with reference to affecting the upper limbs. Diffusion tensor imaging (DTI) was used to find asymmetrical structural abnormalities that affected the conduction time from the motor areas to the muscle, which were correlated with anatomical changes in the spinal cord and normal appearing white matter (Meyenburg et al., 2013). More specifically the transcallosal hand motor fibers in the corticospinal tracts of MS patients showed an association with upper limb functionality assessed by the NHPT where radial diffusivity of these fibers was especially predictive (Kern et al., 2011). Movement deficits have been correlated most often to the damaged brain structures. Some major differences were found between the MS patients and healthy controls with regard to white and gray matter damage. Gray matter atrophy and white matter damage were correlated with clinical assessments of disability status and functional impairment as measured by the NHPT (Sbardella et al., 2013). Postural instability was also associated with atrophy of both white and gray matter. This postural instability was thought to be due to a disconnection between the spinal cord, cerebellum, and cerebral cortex (Prosperini et al., 2013). Furthermore, the atrophy of the cerebellum and spinal cord was found to be most related to balance deficits measured by the center of pressure while standing with or without visual feedback (Prosperini et al., 2014). The cerebellum is associated with balance, but also plays a role in upper limb function. DTI measurements have identified decreased white matter in the cerebellum of MS patients compared to healthy controls and found it was significantly related to a decreased upper limb function (Anderson et al., 2011). Functional MRI (fMRI) was utilized during hand movements and revealed that there was a reduced deactivation or inhibition in the ipsilateral pre and post-central gyri in MS patients, specifically those with relapsing-remitting, compared to healthy controls (Manson et al., 2008; Pantano et al., 2011). In addition, fMRI during fine upper limb movements showed more activation of the contralateral primary and supplementary sensorimotor areas, specifically that of the inferior frontal gyrus (Rocca et al., 2008). However, these correlations were moderated by other factors such as fatigue. Before being fatigued, MS patients showed a greater activation of the contralateral primary motor area, insula, and cingulate gyrus compared to healthy controls, which showed an adaptive change to the demyelination (White et al., 2009). Contrastingly, fMRI found that movement complexity and rate affect what areas of the brain were utilized independent of the level of fatigue (Rocca et al., 2009).

In addition to these areas, the CC stood out as a key component to upper limb function and bimanual coordination. It was known to have both inhibitory and excitatory influences on the motor areas of the brain (Gooijers & Swinnen, 2014). The CC was found to be an important area of the brain to assist in the characterization of disability. MS patients showed increased diffusivity of the CC at the earliest stage of the disease, before any atrophy of the CC was observed by MRI (Ranjeva et al., 2003). In addition, MRI measured atrophy of the CC after an attack and found that it occurred within a year of the inflammatory episode and was correlated to the change in disability status (Audoin et al., 2007). A significant loss in the number of axons crossing the CC in MS patients was correlated with axon density and lesion load (Evangelou et al., 2000b). A postmortem investigation of the CC of MS patients showed that the number of axons, in both density and area, in the white matter of the CC were decreased compared to healthy controls (Evangelou, Esiri, Smith, Palace, & Matthews, 2000a). The CC also showed some connections to other brain areas. MRI and DTI showed a correlation between the amount of diffusivity and the ipsilateral motor cortex, and the latency and duration of the transcallosal inhibition were altered in MS patients (Lenzi et al., 2007). Abnormalities in the CC were associated with upper limb dysfunction. As measured by the NHPT, upper limb function correlated with diffusivity but not with lesion load or white matter volume of the CC (Ozturk et al., 2010). On the other hand, the white matter in the CC was preserved after active rehabilitation of the upper limb compared to passive (Bonzano et al., 2014). Other fine motor movements such as an alternate finger-tapping test showed a relationship to the CC as measured by MRI. The interhemispheric transfer and integration were impaired in MS patients in proportion to their callosal atrophy and white matter lesions (Pelletier et al., 1993). These upper limb movements were not limited to correlations with CC activation, but also with structural damage. This damage was also related to the bimanual coordination of these movements. A significant difference in performance and the accuracy of timing of bimanual coordination was found in MS patients compared to healthy controls and was contributed to micro tissue damage of the CC as measured by DTI (Bonzano et al., 2008). Overall CC volume also related to the threshold at which the MS patients believed their bimanual movements were simultaneous. It was found to be negatively correlated to the threshold in MS patients and significantly different from healthy controls (L. N. Brown et al., 2010). The literature provided a large amount of evidence showing that the CC is important to upper limb function.

Proprioception has also been found as an important characteristic in MS. It has been studied in various areas of the body. Proprioception is defined as the sense of knowing where the limbs are in space at any given point by peripheral and central signals. Proprioception is position sense and kinesthesia is the position sense during a movement (Fortier & Basset, 2012). Proprioception has predominantly been studied in the lower limbs and torso, as it was important to balance and gait. Proprioceptive sensory loss, as measured by leg position, was found to relate to impaired balance, gait, and muscle strength in MS patients compared to healthy controls (Thoumie, 2002). Proprioception was also measured in fine motor movements of the lower limb. Static position sense of the big toe after passive movement was found to be more influential to sensory evoked potentials compared to a tactile stimulus (Fukutake et al., 1998). As proprioception was so important to sensory information of the lower limb, even in fine motor movements, it was important to sensory integration of gait. Sensory integration is affected by fatigue and balance measures. Fatigue and balance were associated, and there were differences seen in those measures between those that have cerebellar and brainstem involvement, and those who do not (Hebert & Corboy, 2013). Patients with MS that had slower walking speeds also had delayed postural responses compared to healthy controls, which was also associated with increased motion of the trunk during walking (Huisinga et al., 2014). The torso is important to balance, which was another area of dysfunction identified for MS patients. Greater postural instability was found in MS patients compared to healthy controls, no matter what severity level their disability. Balance was impaired in all MS patients (Fjeldstad et al., 2011). Patients with MS showed larger scaled postural responses with longer delays compared to healthy individuals. Slowed spinal somatosensory conduction, specifically afferent proprioceptive conduction was found to be the cause rather than cerebellar dysfunction (Cameron et al., 2008). However, no differences were found during quiet standing in various positions between MS patients and healthy controls (Frzovic et al., 2000). Proprioception functioned as the perceptions of position and movement after certain tasks. After tasks of the trunk or lower limb, MS patients were found to have worse balance in quiet standing and following activity compared to healthy controls (Cattaneo et al., 2014). Typically, proprioceptive impairment was measured by center of pressure while standing with eyes open or closed. It was found that MS patients use other strategies to make up for the impairment (Rougier et al., 2007). Research has shown that there were proprioceptive deficits in MS patients regarding balance, gait, and the torso or lower limbs.

Less research has been done on proprioceptive ability of the upper limb, because it has not been linked to risks such as falls. However, it was found that functional reach was impaired in MS patients compared to controls, which meant that proprioceptive issues may be evident in the upper limb before the lower limbs or balance (Frzovic et al., 2000). This was characterized by separating movements of the joints in the upper limb. When the digits of the hand were used, movements combining two joints were utilized as well as movements around a single joint. There was no difference when using the position sense of digits using single joints, but differences were found in dual joint position sense of the right hand digits but not the left (Beckmann et al., 2013), implying that multiple joints are useful to proprioception. When proprioception was inhibited and visual feedback was taken away during pointing tasks, the MS patients had more variation in movement path and larger movement angles in the wrist compared to healthy controls (Quintern et al., 1999). MS patients had difficulty with sensing proprioceptive movements as well as discerning hand positions. Their accuracy and response times were worse when determining how to position their hands in various orientations (Tabrizi et al., 2013). However, research shows that proprioceptive rehabilitation could be effective in MS patients. Bimanual function was maintained after active rehabilitation and was worse after passive rehabilitation, but there were no differences seen in unimanual performance (Gooijers & Swinnen, 2014).

As rehabilitative efforts were found to be successful and deficits were found in the upper limb, it would appear to be an effective area for characterizing fine motor movements in MS. Arms are more accustomed to finer movements. Specifically, the elbow was found to be more accurate in determining position than the knee due to the higher number of muscle spindles and lower innervation ratios (Paschalis et al., 2010). The NHPT is the most utilized clinical tool for assessing upper limb function in MS. It was predictive of physical and social participation limitations (Kierkegaard et al., 2012). The time to complete the NHPT alone did not characterize impairment. When accelerometers were used during the NHPT, it was found that MS patients had trouble with the manipulation, transportation, and release of objects and reaching. There was also a decreased velocity and smoothness that differed between the levels of impairment (Carpinella et al., 2014). Another study found similar results. Movements were found to be slower, less straight, and more variable along the trajectory due to a tremor compared to healthy controls (Lambercy et al., 2013). The amount of time it took to complete the NHPT was correlated with nervous system activation. MS patients with abnormal somatosensory evoked potentials took longer to complete the NHPT. In particular, the median nerve somatosensory evoked potentials correlated with the upper limb performance measures (Nociti et al., 2008).

Most research investigating the fine motor movements of the upper limb focused on grip and load performance as well as the coordination of these two things. Hand grip strength was used frequently with the NHPT because the NHPT alone was not sufficient to describe upper limb performance (Lamers et al., 2014). MS patients had a tendency to overgrip compared to healthy controls. This was found during both static and dynamic tasks performed under unimanual and bimanual conditions with or without feedback (Krishnan et al., 2008; Krishnan & Jaric, 2008). These findings were important because they affect daily activities such as opening or closing a jar. With a task like this, MS patients showed an increased grip force and a decrease in kinetic timing compared to healthy controls (Gorniak et al., 2014). In contrast, MS patients had trouble producing the necessary load forces required by a task. This impaired ability to produce the load forces necessary to complete a task was not affected by the conditions of the task whether it was unimanual or bimanual, with or without visual feedback (Krishnan et al., 2008; Krishnan & Jaric, 2008). This result was not consistent across studies. When static tasks were performed with visual feedback or feedforward mechanisms, MS patients had worse load force production compared to healthy controls under visual feedback but not when they relied on feedforward mechanisms (Marwaha et al., 2006). MS patients showed deficits in producing both grip and load forces.

Most daily activities combine these two forces. Further research studied the coordination effects of grip and load forces. Abnormal grip-load force coupling was seen in unimanual conditions, but coordination was worse in the bimanual condition and finer manipulations were more difficult (Gorniak et al., 2014). The MS patients showed an inability to couple the grip and load forces characterized by an unusual grip/load ratio, which meant that the MS patients were lacking the coordination (Krishnan & Jaric, 2008). The combination of overgripping and a lack of load force caused a higher grip to load ratio. The sensorimotor impairments and overgripping were found to precede the decoupling of grip and load force coordination (Krishnan et al., 2008; Marwaha et al., 2006). MS patients lacked the ability of coordination, both of forces within a limb as well as coordinating those movements bimanually.

A variety of unimanual tasks have been used to determine the characteristics and deficits of upper limb function in patients with MS. When TMS was used to produce movement, the silent period of movement in the ipsilateral upper limb was correlated with disability status in MS patients, which was due to the abnormalities of the CC found by MRI and DTI (Llufriu et al., 2012). Other tasks drew out deficits that were related to the CC. An alternate finger tapping test showed that MS patients were significantly slower than healthy controls, and was thought to be related to the CC (Scherer et al., 1997). More gross movements of the upper limb also showed a relationship to tissue damage. A reaching movement from the center of the body outwards with and without visual feedback was recorded on a digitizing tablet and compared to MRI, which revealed that the motor performance was related to lesion load (Solaro et al., 2007). This type of movement also revealed other cognitive limitations. A motor tracking task performed with the dominant arm showed that MS patients were slower than healthy controls and also performed worse on those tasks that required more depth perception, which implies that there is impaired motor learning, and that sensory and cognitive limitations need to be taken into account for upper limb movements (Leocani et al., 2007). A few studies looked at unimanual performance with reference to daily activities. Hand writing and drawing were found to be impaired. MS patients used the open-loop method of writing, which did not require proprioceptive feedback. They were incapable of using closed-loop handwriting like the healthy controls (Schenk et al., 2000). With the use of spiral drawing, the MS patients drew slower and with less pressure, more variability, and at a smaller scale than controls. They used adaptive strategies to reduce movement variability (Longstaff & Heath, 2006). Unimanual performance in MS patients had been studied more extensively than under bimanual conditions. Fine motor tasks such as moving finger to thumb was impaired in MS patients compared to controls, especially with bimanual coordination (Bonzano et al., 2013). During completion of a gross movement task, the MS patients were slower on the bimanual coordination test, as well as in the unimanual condition, compared to healthy controls. The difference in response time between the unimanual and bimanual conditions was larger for patients than controls. Specifically, it was found to be contributed to those with abnormal evoked potentials of the CC transmission (Larson et al., 2002). There were significant impairments in both unimanual and bimanual task performance in MS patients compared to healthy controls, but they seemed to improve from unimanual to bimanual.

Adaptive mechanisms were utilized to account for these impairments. MS patients were able to improve performance on a resistance force task between and within sessions (Basteris et al., 2011). The same was true for reaching movements with and without applied forces. When making reaching movements with either no force or a changing force field, MS patients initially showed more variability in their movements. Adjustments were later made based on sensory feedback, but the rate of adaptation to the changing force field was the same between patients and controls (Casadio et al., 2008). Adaptations and improvement were possible for MS patients just as with the healthy population.

These adaptations to performance seemed to be moderated by other factors. Upper limb function as measured by the NHPT in MS patients was predicted by cognitive function, specifically their processing speed (Benedict et al., 2011). A similar task of pointing arm movements as measured by an optoelectronic device showed another aspect of cognitive input. This task showed that MS patients had longer actual movement duration than when utilizing mental imagery compared to healthy controls, and that mental prediction was not preserved in MS patients because they needed an increased cognitive effort for nondominant movements (Tacchino et al., 2013). In a more general sense, upper limb strength, function and sensation were worse in MS patients than controls. In this case, sensation, proprioception, and strength were factors in upper limb functional ability (Guclu-Gunduz et al., 2012).

In addition to these measurements previously taken from the MS population, there were findings from research on similar neurological conditions that lent insight into what expectations were for this study. Patients with Parkinson's disease (PD) showed similar movement characteristics to those of the MS patients. PD patients had slower movements with alternating acceleration and deceleration, slower reaction times, and were less accurate than healthy controls when they reached for a target without utilizing visual feedback (Flash, Inzelberg, Schechtman, & Korczyn, 1992). Specifically, these patients were slower when making isotonic movements and had lower peak velocities. When performing bimanual movements, the movement time increased and the peak velocities decreased. This showed that PD patients dissociated the two limbs (Lazarus & Stelmach, 1992). This bimanual dysfunction and disassociation was similar to that found in MS patients due to the damage in the CC. Similar dysfunction was observed in those with cerebral palsy (CP), and they also utilized similar adaptive techniques compared to the MS population. Upper limb movements in hemiplegic CP were longer due to slower movement speed and were less straight compared to healthy controls. Movement of the torso was used to compensate for the upper limb (Jaspers, Desloovere, Bruyninckx, & Molenaers, 2009). These findings were consistent across all ages. Children with hemiplegic CP had slower movements than healthy controls and used trunk movement to compensate for the upper limb. 3D kinematics showed deficits in timing, range of motion, and adaptive movement strategies. Bilateral movement did not change the outcome measures (Mackey, Walt, & Stott, 2006). Those with hemiplegic CP showed unimanual movement deficits, but the bimanual did not seem to be beneficial. Bilateral movements were found to be temporally and spatially coupled due to the unaffected limb making alterations. Sequential bilateral movements improved movement times in both limbs (Langan, Doyle, Hurvitz, & Brown, 2010). Movement of the upper limbs in this patient population revealed other correlations that were important to be aware of. Assessment of handwriting, cognitive function, visual perception, and kinesthesia of children with hemiplegic CP and their healthy peers revealed correlations between handwriting skills with upper limb movement speed, proprioception, bimanual coordination, and visual perception of the unaffected limb (Bumin & Kavak, 2010).

In order to address the issue of whether MS patients suffered from disinhibition and lack of interhemisherpic communication through the CC, it was informative to look at how movements of callosotomy patients compared. Bimanual coordination was specifically important here because the posterior part of the CC was found to be involved. Split-brain patients did not show a decrease in temporal coupling of bilateral movements. Instead, the spinal cord was found to be important to temporal coupling (Tuller & Kelso, 1989). However, the temporal coupling was not maintained over the whole movement time. Callosotomy patients maintained temporal and spatial coupling, but the normal subjects only maintained temporal coupling at the movement onset. This showed that spatial interference relied on the CC while temporal coupling did not (Franz, Eliassen, Ivry, & Gazzaniga, 1996). Whether or not this temporal coupling was maintained also depended on the nature of the movement. Temporal coupling was maintained for discrete movements, but was lacking in callosotomy patients during continuous movements. This showed that synchronization of continuous movements depends on the CC (Kennerley, Diedrichsen, Hazeltine, Semjen, & Ivry, 2002). Continuous movements are seen in most of our daily activities such as handwriting. Drawing with mirror movements became less symmetrical and drawing with isodirectional movements improved (Eliassen, Baynes, & Gazzaniga, 1999). Most of the research with this population dealt with temporal coupling of bimanual movements, which could be evident in MS patients, but it failed to provide any information of how CC damage might affect the quality and accuracy of movements especially those under kinesthetic control.

Finally, specific case studies that observed MS patients also showed alien or useless hand syndrome and identified issues with kinesthesia. Others with sensory neuropathy and deafferentiation showed similar issues with controlled movements. The term useless hand syndrome was associated with damage to the dorsal column of the high cervical spinal cord, while alien hand syndrome was mostly associated with lesions or disconnection of the CC. Those with useless hand syndrome were found to have decreased movement ability without vision, increased muscle weakness, and loss of muscle endurance and kinesthesia (Hamada et al., 2005; Hashimoto et al., 1997). Where useless hand syndrome manifested in a loss of control over movements, alien hand syndrome resulted in involuntary movement of one hand activated by voluntary action of the other. In this case, there was no sense of what the involuntary hand was doing and was influenced by the damaged CC (Kurne et al., 2008; Lunardelli et al., 2014). Specifically, this occurred when the CC was thinner than compared to normal healthy controls and there were lesions present (Moroni et al., 2004).

Unlike these syndromes, neuropathy resulted in spatial and temporal dysfunction of movements. MS patients with sensory neuropathy showed curved trajectories and temporally decoupled movements without vision, which was improved with vision but they still lacked the ability to synchronize multi-joint movements (Sainburg & Poizner, 1993). This showed that kinesthesia was important to inter-joint coordination during movements. More specifically, the temporal decoupling caused the curved trajectories, and that feedforward mechanisms were impaired which caused the lack of kinesthesia (Sainburg, Ghilardi, & Poizner, 1995). Similar findings were seen in deafferented MS patients. Bilateral and unilateral deafferentiation showed a deformation from the given trajectory and a decrease in temporal stability during continuous bimanual isodirectional drawing. Spatial coupling and movement variability were worse in both anisodirectional and isodirectional movements with or without vision compared to unimanual movements. (Spencer, Ivry, Cattaert, & Semjen, 2005). For this study, in order to determine the movement characteristics of MS patients, movement onset and offset were determined based on temporal location. This typically involved the transition from centrally and peripherally controlled mechanisms of movement. An algorithm was defined for use in the measurements of our study (Teasdale, Bard, Fleury, Young, & Proteau, 1993).

The past research provided insight into how movements should be executed. When this was not the case in MS patients, specific areas of the CNS were identified as causing the dysfunction. Abnormal movement characteristics of MS patients were observed, and proprioception was studied in this patient population with respect to the lower body and balance. Research was lacking on a clear view of how kinesthesia, especially in the fine motor function of the upper limb, was affected. It was shown that MS patients utilize adaptation mechanisms, but it had yet to be seen whether this is true for kinesthesia. Bimanual coordination for fine motor movements was identified with respect to grip and load forces and was also looked at for more gross motor function in the upper limb, but it was not studied including kinesthesia and fine motor movements.

CHAPTER 3
Methods

3.1 Participants

Participants included eleven multiple sclerosis patients with mild to moderate clinical diagnosed severity and eleven age- and gender-matched healthy controls. The patients were recruited through Michigan State University's Neurology and Ophthalmology Clinic. The control participants were recruited from the East Lansing and Sault Ste. Marie communities in the state of Michigan.

3.2 Materials

Two joysticks were placed next to each other and positioned underneath a horizontal 19" LCD widescreen computer monitor. This placement insured that the hand movements were not visible to the participant during the procedure. Each joystick corresponded to a cursor on the screen, which was shown directly above the actual joystick's position. The computer software utilized for the procedure presentation and data collection was Presentation® by Neurobehavioral Systems. The position time series in the *(x,y)* position time series was collected at a 60 Hz sampling rate.

3.3 Procedure

Informed consent was obtained from all participants. They were evaluated by a nine-hole peg test to determine the level of clinical functionality, and completed a handedness survey to determine the dominant upper limb. The main movement task using the joystick apparatus involved moving the joysticks and respective cursors from the home position to a given target as straight and as quickly as possible. Once the cursor was in the target, the participant had to cease movement for at least 1500ms. At this point, the trial was over, the target disappeared, and the participant returned the joysticks to the home position for the next trial. On completion of the trial, visual feedback of a red X or green checkmark were shown in the center of the screen. This was done to restrict movement time. In order to identify kinesthesia as the only variable, time had to be held constant between MS patients and controls. A time limit of 600-1500ms for movement was given. If above or below this time range, a red X was given to indicate that the movement needed to be performed faster or slower. A green checkmark indicated that the movement was performed well. This ensured that the accuracy could be directly compared. The home positions were 1cm in diameter and centered on the screen 17cm apart. The targets were also 1cm in diameter and 7.5cm away from the home positions. The procedure included both unimanual and bimanual conditions with the unimanual being conducted with each limb. The bimanual conditions required isodirectional movements, or movements in the same direction to the same respective target, between the two limbs.

All unimanual trials had a kinesthetic and a visual condition. In the visual condition, the cursor was visible to the participant for the duration of the movement. In the kinesthetic condition, the cursor was not visible, nor was the target responsive to the joystick position. In the kinesthetic condition, the participant was instructed to cease movement when they estimated that they had reached the given target. The kinesthetic conditions had targets at 40 and 140 degrees with respect to each home position, while the visual condition utilized targets at 55 and 125 degrees. The use of targets at different angles minimized practice effects. The unimanual visual condition was followed by the unimanual kinesthetic condition with the dominant and nondominant hand conditions counterbalanced. In each of these conditions, there were twenty trials administered with ten trials/target.

Following the unimanual conditions, there was a mixed bimanual condition that combined both visual and kinesthetic characteristics. One hand had a visible cursor while the other did not and had to rely on kinesthesia. The targets for this condition were set at 40 and 140 degrees away from the respective home position. Both dominant and nondominant hands were exposed to the visual and kinesthetic conditions, and the order was counterbalanced. In each mixed bimanual condition, there were thirty trials with fifteen trials/target.

Finally, there was a visual bimanual condition where both hands had a cursor tracing their movement between the home position and the target. The targets and number of trials were the same as those in the mixed bimanual condition.

There was a short practice period of only 8 trials for each of the unimanual conditions and the bimanual conditions. This ensured that the participant understood the procedure and was able to perform consistent movements. The unimanual visual condition was meant to serve as a calibration phase, during which participants became more comfortable with the task requirements. During the practice condition only did the kinesthetic trials show a dot where the cursor was at the end of the movement so the participant had some visual feedback as to where they were in relation to the target. The primary comparison was between the kinesthetically controlled hand during the mixed bimanual condition and the unimanual kinesthetic condition. The secondary comparison of interest was that of the visually controlled hand during the bimanual condition and that of the visually controlled hand during the unimanual condition. The total duration of the experiment was approximately forty-five minutes.

3.4 Data Analysis

The limb utilizing kinesthesia and its response to coordination with the contralateral visually guided limb was of interest, thus only the kinesthetic trials for the mixed bimanual condition were averaged for each target in order to determine the kinesthetic performance of each arm during unimanual and bimanual tasks. Trials in every other condition were averaged for each target and across targets after finding no effect. Each trial was dual pass filtered through an eighth order Butterworth filter with a cutoff frequency of 10Hz. The beginning and end of a movement were determined by an algorithm from Teasdale et al. (Teasdale, Bard, Fleury, Young, & Proteau, 1993). Movement time (MT) was determined by the time between this starting and stopping of movement.

For the limb lacking visual feedback, the root mean squared error (RMSE) in centimeters – defined as the average perpendicular distance between the actual movement and a straight line between the start and end points – was calculated at each 60Hz sample taken. This represented the linearity of the movement, which was solely the feed-forward control of the movement trajectory. The absolute end point error (EPE) in centimeters – defined as the distance between the movement end point and the center of the target – was measured as well as the constant end point error in centimeters of the *x,y* dimensions, which determined over or under-shoot of the movement. These error coordinates were changed into movement trajectory space by making the end point error in the *x*-dimension parallel (EP_{par}) and those in the *y*-dimension perpendicular (EP_{ort}) to the direction of movement.

MT, RMSE, EPE, EP_{par}, and EP_{ort} were used in repeated measures ANOVAs where hand, task condition (unimanual or bimanual), and group were treated as within subjects factors. The Huyn-Feldt adjusted *p*-values and Bonferroni adjusted *p*-values for post-hoc comparisons were reported from the ANOVAs.

CHAPTER 4
Results

In order to assess the basic performance characteristics of the two groups, the unimanual and bimanual conditions were performed with visual feedback in addition to the kinesthetically controlled unimanual and mixed bimanual conditions. The unimanual conditions showed significant differences between the two groups (see Table 1). Both unimanual and bimanual results were analyzed together within either the kinesthetic or the visual condition using a 2(groups) x 2(hands) x 2(conditions – unimanual/bimanual) repeated measures ANOVA.

Table 1
Means and Standard Deviations for Unimanual and Bimanual Movements Under Kinesthetic and Visual Feedback for Patients and Controls

	MS patients		**Control group**	
	Unimanual	**Bimanual**	**Unimanual**	**Bimanual**
Visual				
MT				
Left Hand	1.075 (0.19)	1.491 (0.304)	0.906 (0.181)	1.424 (0.209)
Right Hand	1.067 (0.15)	1.376 (0.194)	0.909 (0.143)	1.317 (0.182)
RMSE				
Left Hand	0.388 (0.155)	0.45 (0.125)	0.248 (0.107)	0.324 (0.184)
Right Hand	0.427 (0.218)	0.459 (0.188)	0.28 (0.052)	0.365 (0.082)
Kinesthetic				
MT				
Left Hand	1.091 (0.211)	1.114 (0.224)	0.74 (0.197)	0.878 (0.25)
Right Hand	1.073 (0.189)	1.196 (0.193)	0.771 (0.229)	0.817 (0.208)
RMSE				
Left Hand	0.276 (0.097)	0.257 (0.077)	0.207 (0.078)	0.224 (0.114)
Right Hand	0.423 (0.192)	0.275 (0.088)	0.182 (0.032)	0.188 (0.046)
EPE				
Left Hand	2.129 (0.84)	2.641 (0.591)	1.214 (0.51)	1.603 (0.547)
Right Hand	2.268 (0.948)	2.678 (0.668)	1.272 (0.556)	1.504 (0.37)
EP_{ort}				
Left Hand	0.352 (0.815)	0.033 (1.074)	0.587 (0.422)	0.144 (0.897)
Right Hand	0.402 (0.597)	-0.319 (1.197)	0.376 (0.491)	-0.362 (0.587)
EP_{par}				
Left Hand	1.092 (1.662)	0.925 (1.699)	-0.048 (0.89)	0.695 (0.701)
Right Hand	1.099 (1.784)	1.059 (1.837)	-0.149 (0.963)	0.327 (0.855)
NHPT				
Left Hand	19.882 (1.874)		18.973 (1.959)	
Right Hand	19.876 (3.844)		18.03 (2.771)	

4.1 Visual condition

Unlike in previous studies, the nine-hole peg test (NHPT) did not show any significant differences between the MS patients and controls, or hands used, nor was there a Hand x Group interaction (see Table 1 and Figure 1). Handedness scores were similar, with the MS patients showing slightly lower scores on the Edinburgh handedness survey compared to the controls (MS = 67, Controls=73).

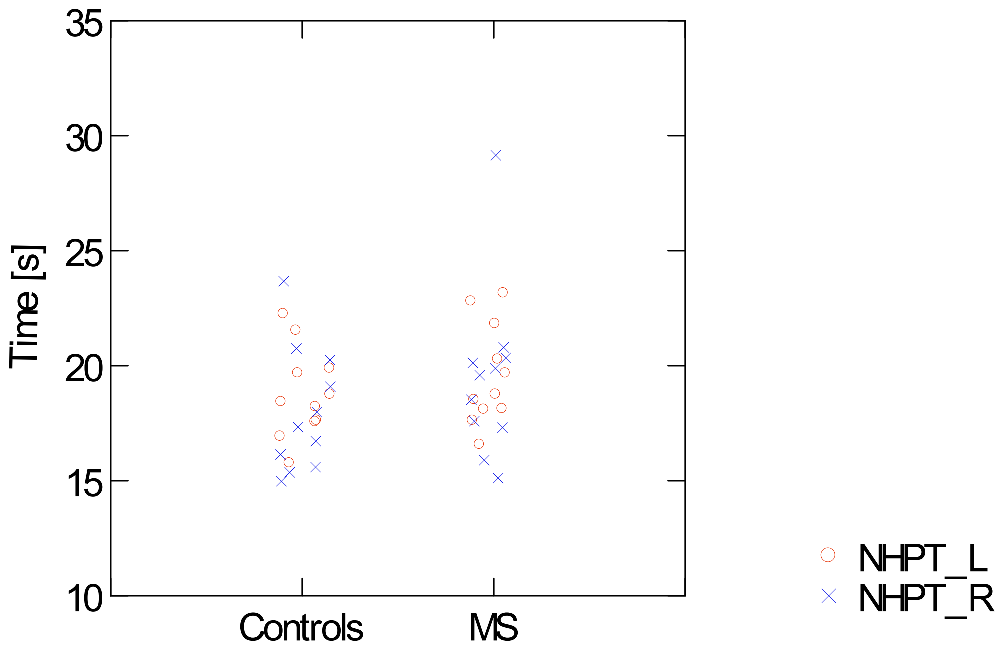

Figure 1: Average results of the nine hole peg test for patients (MS) and controls for each hand, (NHPT_L=left hand, NHPT_R=right hand).

In contrast, differences were seen in the experimental task. There was a trend that MT was different between the two groups, $F(1,9)=4.727$, $p=0.058$, with the patients taking longer to complete the task than the controls. However, there was a significant difference between the two conditions, $F(1,9)=139.523$, $p< 0.001$, which was further characterized by a Hand x Condition interaction, $F(1,9)=4.809$, $p=0.056$. Post-hoc paired t-tests revealed that for both the left, t(10)=-6.263, p=0.001, and right hands, t(10)=-7.133, p<0.001, MT was significantly longer in the bimanual condition (see Figure 2); this was true for both groups.

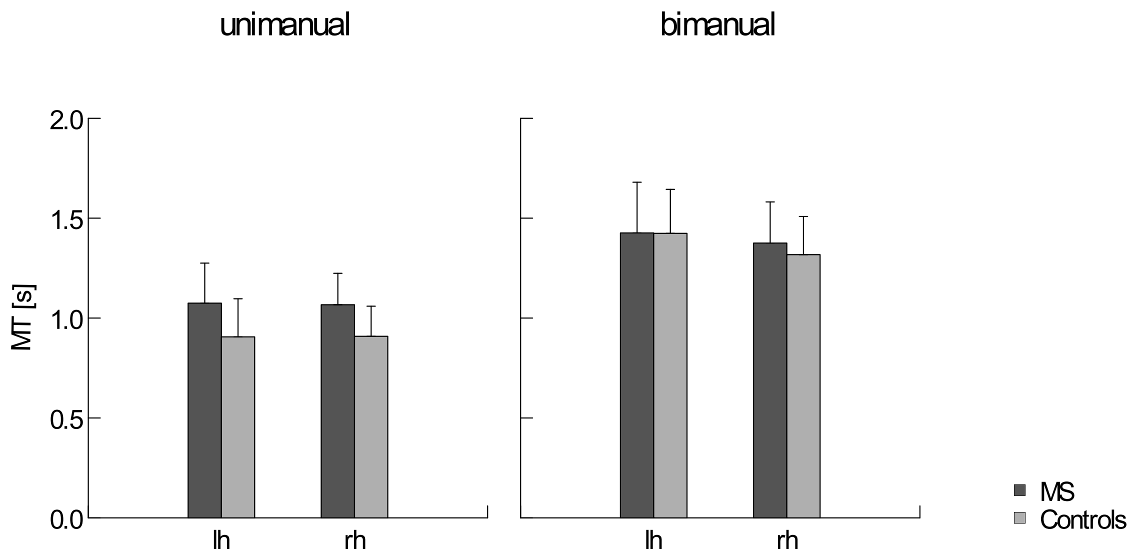

Figure 2: Movement times for patients (MS) and controls for each hand, (lh=left hand, rh=right hand), in both unimanual and bimanual conditions with visual feedback; error bars are in SD.

Similar results were seen for movement linearity, as there was a significant difference between the two groups with respect to RMSE, F(1,9)=10.276, p<0.05. There was also a significant difference between the two conditions, F(1,9)=12.712, p<0.01, without any interactions involving group. The MS patients always had higher RMSE compared to the controls, and both groups increased RMSE from unimanual to bimanual for both hands (see Figure 3); for means and standard deviations see Table 1.

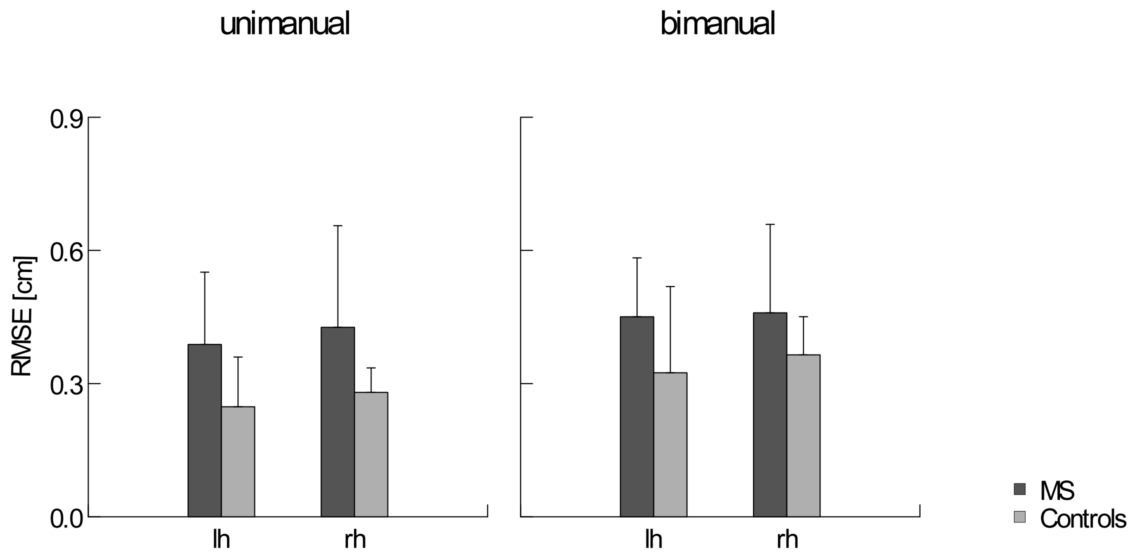

Figure 3: Movement linearity for patients (MS) and controls for each hand, (lh=left hand, rh=right hand), in both unimanual and bimanual conditions with visual feedback; error bars are in SD.

4.2 Kinesthetic condition

Similar performance was seen in the kinesthetic condition as the MS patients maintained their high movement times, which resulted in a significant difference between the two groups, $F(1,9)=22.06$, $p=0.001$. There was also a significant difference between the two conditions, $F(1,9)=5.535$, $p<0.05$; this was true for both hands and both groups (see Figure 4).

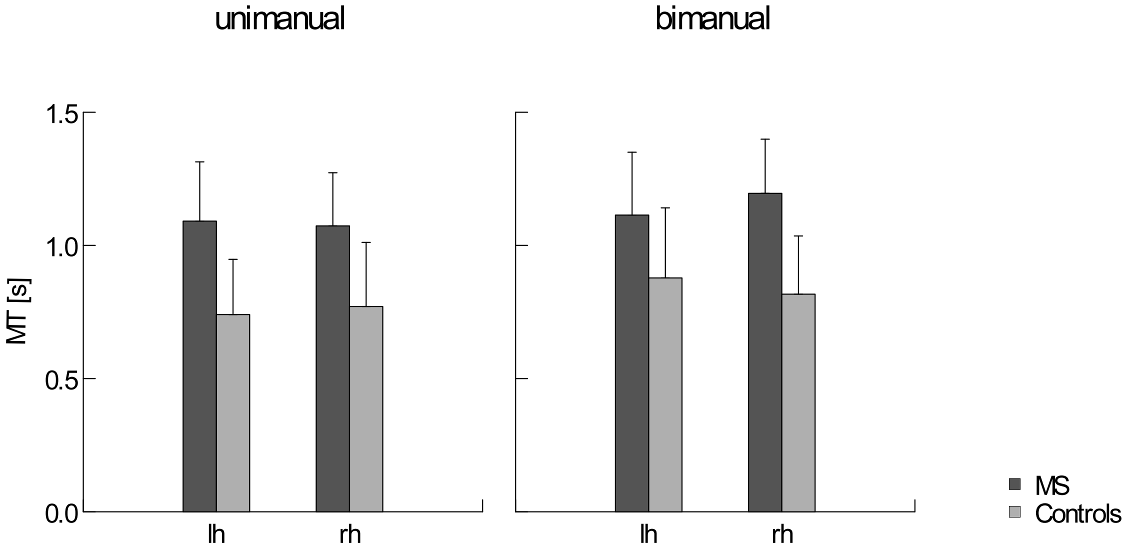

Figure 4: Movement times for patients (MS) and controls for each hand, (lh=left hand, rh=right hand), in both unimanual and bimanual conditions under kinesthetic control; error bars are in SD.

This tendency continued with respect to movement linearity. There was a significant difference between the two groups, $F(1,9)=19.333$, $p=0.001$, and a trend towards a difference between the two conditions, $F(1,9)=3.793$, $p=0.08$. These results are characterized by Group x Hand, $F(1,9)=8.443$, $p<0.05$, and Group x Condition, $F(1,9)=6.859$, $p<0.05$, interactions. Post-hoc paired t-tests revealed that the Group x Hand interaction was due to a significant difference between the right hand of the two groups with the MS patients having higher amounts of error, $t(10)=5.045$, $p<0.01$, and a trendwise difference between the two hands within the MS patients, $t(10)=-2.991$, $p=0.081$, as movement linearity of the right hand in the MS group decreases from unimanual to bimanual conditions (see Figure 5). The Group x Condition interaction stemmed from a significant difference between the two groups during unimanual performance, $t(10)=4.176$, $p<0.05$, and not during bimanual.

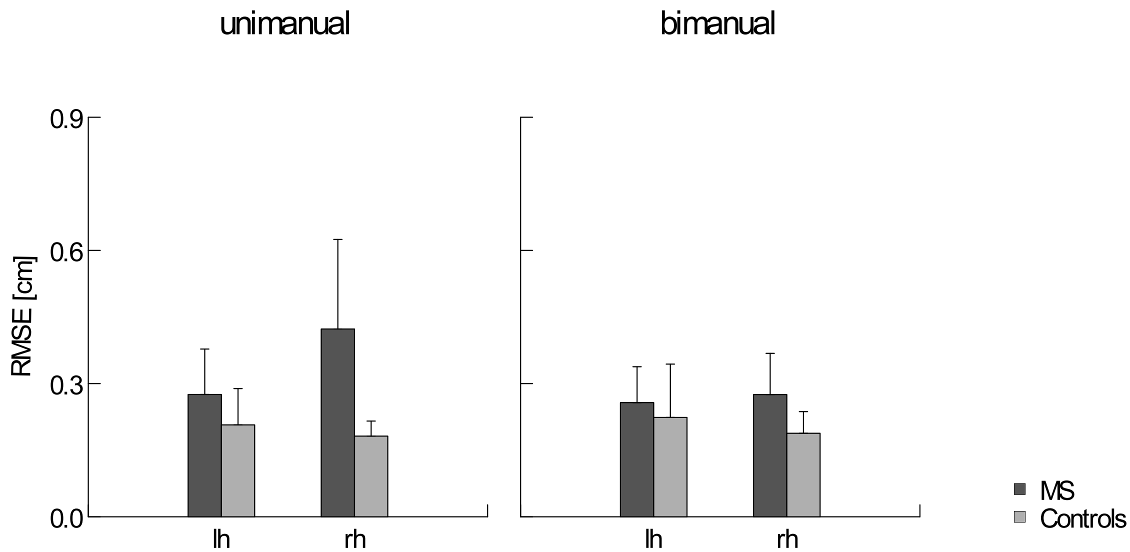

Figure 5: Movement linearity for patients (MS) and controls for each hand, (lh=left hand, rh=right hand), in both unimanual and bimanual conditions under kinesthetic control; error bars are in SD.

The MS patients also had significantly higher EPE compared to the controls, $F(1,9)=44.982$, $p<0.001$, in both hands and conditions (see Figure 6). There was also a marginally significant difference between the two conditions, $F(1,9)=4.611$, $p=0.057$, resulting from an EPE increase for both hands and groups. This is not simply a speed and accuracy tradeoff as MT and EPE are both increased in the MS patients.

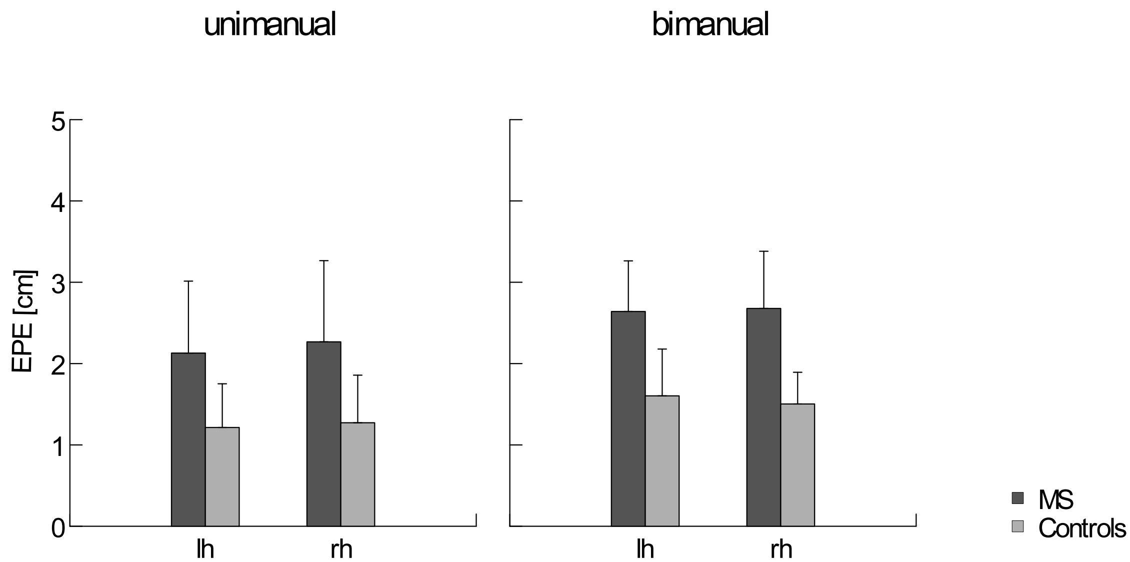

Figure 6: Absolute end point error for patients (MS) and controls for each hand, (lh=left hand, rh=right hand), in both unimanual and bimanual conditions under kinesthetic control; error bars are in SD.

EPE can be further differentiated as EP_{ort}, which defines it as falling too shallow or steep with reference to the target, or as EP_{par}, which defines it as overshoot or undershoot of the target. EP_{ort} showed a significant difference between the unimanual and bimanual conditions, $F(1,9)=37.561$, $p<0.001$, as both groups decrease their error from unimanual to bimanual (see Figure 7).

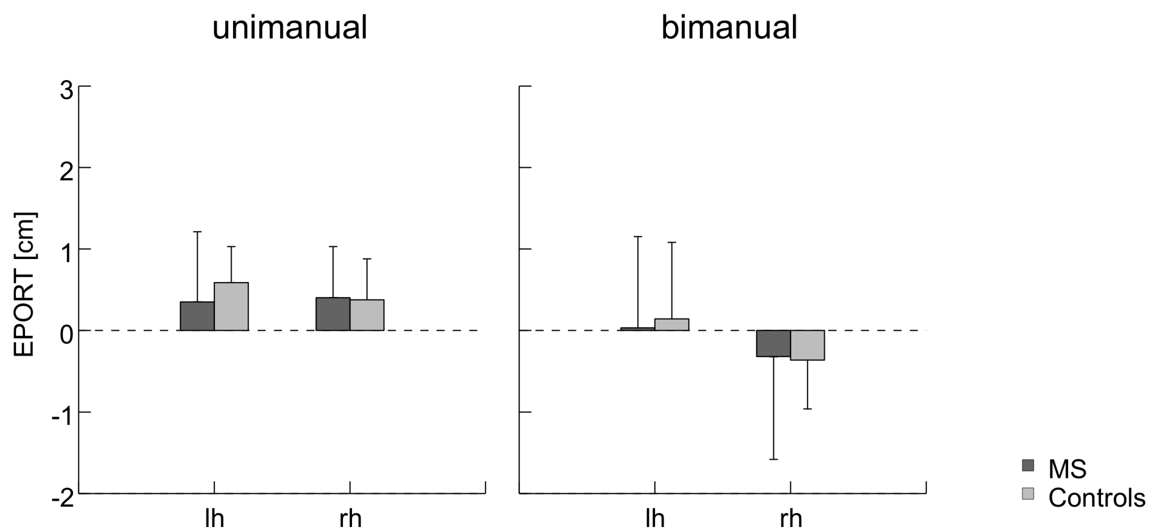

Figure 7: Orthogonal end point error for patients (MS) and controls for each hand, (lh=left hand, rh=right hand), in both unimanual and bimanual conditions under kinesthetic control; error bars are in SD.

This was not seen in EP_{par} as the MS group consistently overshot the target (see Figure 8), which resulted in a significant difference between the two groups, $F(1,9)=9.083$, $p<0.05$.

For means and standard deviations see Table 1.

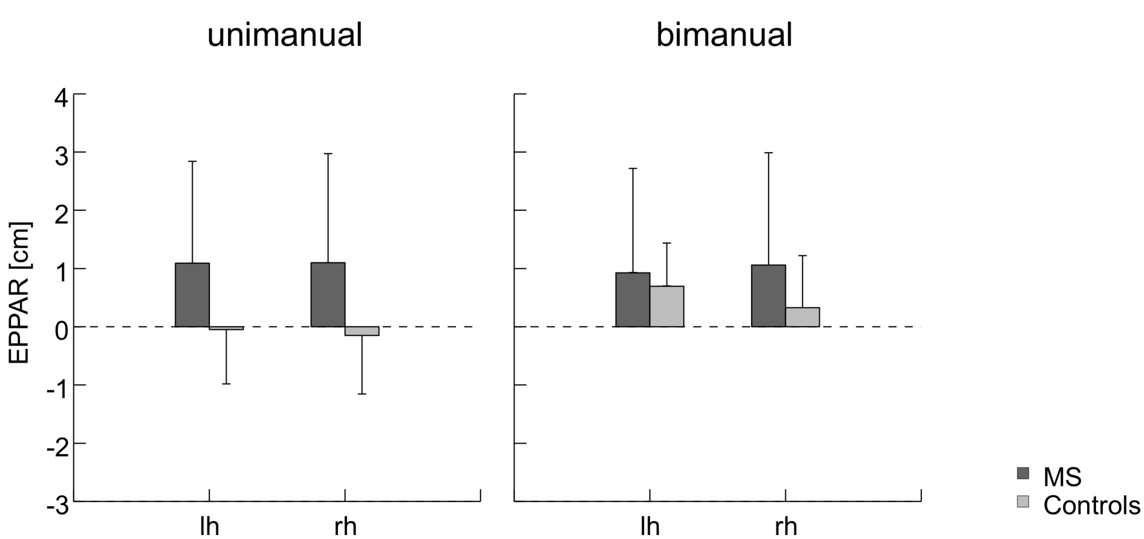

Figure 8: Parallel end point error for patients (MS) and controls for each hand, (lh=left hand, rh=right hand), in both unimanual and bimanual conditions under kinesthetic control; error bars are in SD.

CHAPTER 5
Discussion

In order to determine how kinesthesia and visual integration are utilized in both unimanual and bimanual movements, this study tested the unimanual performance with and without vision, bimanual coordinated performance with visual feedback, and bimanual performance of one kinesthetic limb matched with the visible contralateral limb. The movement characteristics of the MS patients were different compared to the controls under both kinesthetic and visual unimanual conditions.

5.1 Unimanual condition

In the unimanual kinesthetic condition, the MS patients maintained higher movement times compared to controls, but the controls were able to move faster in the kinesthetic compared to the visual condition. Similarly, the controls were able to improve their movement linearity compared to the visual condition because they did not have to make any feedback corrections. Again, the MS patients showed impairment as they also moved less linearly compared to the controls, but this was only seen in the left hand while the right hand stayed the same. This difference between hands was significant, which meant that the left, or nondominant, hand executed a more linear trajectory and was more responsive under the use of kinesthesia. This was somewhat expected as the nondominant limb has been shown to utilize kinesthesia more effectively and be more accurate under active kinesthetic movements (Goble et al., 2006). More importantly, it has been shown in the control population that the nondominant limb performs more linear movements compared to their dominant under unimanual conditions (Han et al., 2013). Kinesthetic ability was expected to be better in the nondominant limb because it is used less often under visual feedback and more accustomed to not needing visual integration during movements. The hypothesis that the nondominant hand would perform better under kinesthetic control was supported with reference to movement linearity.

The MS patients also showed accuracy impairments, as they had worse end point accuracy compared to the controls. This was evident in the significantly higher absolute end point error for patients compared to controls. In order to characterize in what way their end point accuracy was in error, orthogonal and parallel error was analyzed. There was no difference between the orthogonal end point errors of the two groups, but the positive values indicate that movement endpoints for both groups were too 'steep' with reference to the target. This suggests that both the patients and controls continued the movement trajectory to the previously shown visual targets rather than adjusting their movements toward the kinesthetic targets. This was expected for the dominant hand because it uses predictive mechanisms from previously learned movements, as found in the healthy control population (Mutha et al., 2013). The parallel end point error, however, explained where the significant difference in absolute end point error between the two groups stemmed from. The MS patients had higher parallel end point errors compared to the controls with the patients having positive values and the controls having slightly negative values. This indicates that the MS patients overshot the target, while the controls undershot it. The controls' left hand was slightly more accurate compared to the right as was expected, since other research has shown that the nondominant limb utilizes proprioceptive feedback more effectively compared to the dominant limb to arrive more accurately at a target (Goble & Brown, 2010). This is true even when the movement path is visible but the target is from memory (Goble & Brown, 2008). Again, this supports the hypothesis that the nondominant hand would perform better under kinesthetic control. Overall, the MS patients still performed slower movements with less linear trajectories and less end point accuracy compared to the controls under kinesthetic conditions, and they did not improve with the use of kinesthesia to the same extent the controls did as compared to their visual condition performance. The nondominant hand seemed to perform better with kinesthesia compared to the dominant, and the hypothesis that the patients would show impaired movements compared to the controls under kinesthetic control is supported. However, it cannot be concluded that the patients' movements under kinesthetic control were worse than with visual feedback because movement time did not change and the movement trajectory became more linear.

Similar results were seen in the unimanual visual condition as the MS patients showed compromised performance compared to the control group. The MS patients performed movements significantly slower than the controls without any difference between the hands used. They also had significantly higher RMSE compared to the controls. This suggests that under visual feedback, the left and right hands of the MS patients perform similarly but were slower and had a less linear trajectory, or less control over their movements, than controls. These findings were expected, as they are similar to previous research that utilized other tasks such as a virtual nine hole peg test (Lambercy et al., 2013), a virtual object tracking task (Leocani et al., 2007), spiral drawing on a graphics tablet (Longstaff & Heath, 2006), and a finger tapping task (Scherer et al., 1997). End point error was not analyzed under visual conditions because the participants were required to hit the target in order to end the trial. In this case, the hypothesis was also supported in that the normal movements with visual feedback are impaired in MS patients compared to their controls in both movement linearity and overall time.

The MS patients showed deficient performance in both unimanual conditions compared to the controls and became only slightly better with the use of kinesthesia, which implies that they may have an impaired ability to integrate visual feedback into their movements as well as an impaired sense of kinesthesia. Inhibiting visual feedback alone caused more variable and less accurate movements in MS patients, but when proprioception is also inhibited, these hindered movements disappear (Quintern et al., 1999). This suggests that MS patients rely heavily on visual feedback for accurate movements but they have an impaired ability to integrate this visual feedback into their movements, and kinesthetic ability seems to be impaired and hinder movements without visual feedback. Since both visual integration and kinesthetic ability are impaired, it raises the question of whether visual feedback can override kinesthesia and become beneficial.

5.2 Bimanual condition

The mixed bimanual kinesthetic data showed an increase in movement time for both groups and hands. This meant that both groups took longer to perform the bimanual task compared to the unimanual, but the difference between the two groups still existed. This suggests that both the patients and controls are affected in a similar fashion by the required costs of attention during the more complex tasks of kinesthetic bimanual coordination. Both groups needed to slow their movements in order to improve accuracy during a bimanual task. This also showed that the original differences between the groups' movement times still exist. The MS patients did not significantly increase their movement times compared to their unimanual baseline measurements, and the controls showed more of an increase in their left hand. This suggests that the MS patients already move slow enough that they do not need to or cannot slow down further in order to increase accuracy, similar to a ceiling effect for movement time. The nondominant hand for the controls is more susceptible to the costs of a more complex kinesthetic task.

The patients showed an improvement for movement linearity in the right, or dominant hand, while movement linearity decreased in both hands in the controls. However, this was not enough to produce a difference between the unimanual and bimanual conditions. Overall, this suggests that the patients might be able to improve movement linearity for the dominant hand with coordination 'assistance' from the contralateral limb, especially as there was no difference between the groups in this bimanual condition like there was in the unimanual condition. In contrast, the controls did not show any kinesthetic benefit from bimanual coordination with the contralateral limb being visible. This suggests a floor effect for the controls in that their movements are as linear as they are able to be. This is somewhat contradictory to previous research, as it has been shown that the healthy controls had a more linear trajectory in the dominant limb compared to the nondominant (Gooijers et al., 2013). Kinesthetic performance has also been found to improve under the bimanual coordination compared to unimanual conditions (Han et al., 2013). Although this was not seen in the control group in the present study, this trend was seen in the patient group. This implies that the MS patients' kinesthetic abilities might be able to be improved, and their dominant limbs were more responsive to bimanual coordination and visual integration than their non-dominant, which could be a key factor in rehabilitation techniques. However, at this age, the controls already performed to the best of their kinesthetic ability so bimanual coordination hindered their performance more than providing any benefit. Instead, they seemed to be more susceptible to the costs of bimanual coordinated movements than the MS patients. The MS patients still performed less linear movements compared to controls in both hands, but there was not significant difference between the left hands of the two groups, only in the right hand. These findings partially support the hypothesis that movement linearity would be improved in the kinesthetic hand when used with a contralateral visible limb as this result was seen in the dominant limb in the patient group. This was not true for both hands or across all participants as expected.

With respect to movement accuracy, the absolute end point error for both groups and hands increased, and there was a difference in accuracy performance of each group. Again, this implies that the requirements of the bimanual task affected the patients and controls similarly because the group differences existed in both conditions. Neither group changed their performance significantly from the unimanual condition, as seen by the lack of a significant difference between the two conditions. This suggests that the MS patients already performed accurately to the best of their kinesthetic ability in the unimanual condition, and their performance could not be improved with the coordination 'assistance' of the visible contralateral limb. However, the controls became less accurate due to the costs of bimanual movement. This is because the controls performed more accurately in the unimanual conditions compared to the patients so they were able to get worse due to bimanual coordination effects.

It needed to be determined how this end point accuracy was changed. Both groups showed a decrease in the orthogonal end point error and more so for the right than the left hand. These changes reflect a shallower end point with respect to the target compared to their performance in the unimanual condition, which was too steep. This resulted in a significant difference between the two conditions. The right, or dominant hand, was more receptive to the visual feedback of the contralateral limb, especially for the controls. This implied that they have the ability to integrate the visual feedback of one hand into the kinesthetic movements of the other more so than the patients. This was related to previous findings that show that the dominant limb is more reliant on visual feedback for end point accuracy (Srinivasan & Martin, 2010). It is possible that the visual feedback required for end point accuracy could come from the contralateral limb movement and have the same mirrored effect on the dominant limb.

The changes to parallel end point error were not as prominent as those to orthogonal end point error. Both groups increased the amount they overshot the target, especially the controls. Even so, the MS patients continued to overshoot the target more than the controls. The MS patients slightly increased the amount of overshoot in their right hand, but neither hand's changes were different from the performance in the unimanual condition. However, the controls had end points that farther overshot the targets compared to their unimanual placements. The MS patients did not change their performance under bimanual coordination. This suggests a ceiling effect for the patients with their kinesthetic performance already impaired to the point where they could not perform worse. At the same time, they did not benefit from bimanual conditions with a visible contralateral limb. The MS patients maintained their higher level of error compared to the controls. The controls became susceptible to the costs of a more complex bimanual task, but they still performed more accurately than the patients. This did not support the hypothesis that the

MS patients would improve their accuracy of kinesthetic movements with simultaneous use of a visible contralateral limb. It does not falsify it either as the patients showed no change in their kinesthetic accuracy from a unimanual to bimanual task.

The controls performed worse in the kinesthetic bimanual condition compared to their kinesthetic unimanual condition, likely because they were more susceptible to attention and motor control costs since they performed so well in the unimanual condition. The MS patients did not seem to be affected by this change in task complexity in the same way because their performance is already so impaired to the point that they cannot move much slower or degrade their quality of movement. In most cases, the baseline differences still stand in the kinesthetic bimanual condition. This suggests that the MS patients have performance impairments with the use of kinesthesia compared to controls that are not impacted by unimanual or bimanual tasks because they cannot get much worse. Overall, they did not get worse, nor did they improve with the use of a visible contralateral hand to assist in the task as was expected. This suggests that their seemingly impaired ability to integrate visual feedback into their movements is not able to be translated into the contralateral limb and override the impaired kinesthesia. The controls did not show improvement either, which suggests that increased age may play a role in overall attenuation of kinesthetic ability.

In the bimanual visual condition, both groups moved slower compared to their baselines. In this case, there was a difference in the magnitude of change for each group, which implies that visually guided bimanual tasks affect the MS patients and controls differently. The controls increased their movement time more than the MS patients in the bimanual visual condition compared to their unimanual performances. They increased their movement times to the point where they performed movements in the same amount of time as the patients, which causes the group differences to subside. Although there was no difference between the hands within either unimanual or bimanual condition, there was a difference within a hand from unimanual to bimanual. Both groups had increases in both hands for movement time compared to their unimanual performance, as has been previously shown for MS patients (Larson et al., 2002). This suggests that the MS patients suffer due to attention, integration, and bimanual coordination motor control costs under visual feedback like the controls, but the controls' performance is more susceptible. This is possibly due to the MS patients already having such an increased movement time under unimanual task conditions.

Results for movement linearity under bimanual conditions were similar to the unimanual condition: both groups decreased movement linearity to maintain the difference between the groups. This also resulted in a difference between this condition and the unimanual. The MS group showed a larger decrease for the left hand compared to the right, while the opposite was true for the controls. This difference is opposite of what was expected to occur. The MS patients in the kinesthetic bimanual condition showed the expected result that the dominant hand would have a more linear trajectory. However, their upper limb impairment seems to be severe enough that when visual feedback from both hands needs to be integrated into movements and attention is given to the dominant hand that needs the visual assistance more for end point accuracy, which was noted by the patients to be affected by the disease more than the left in this sample, the nondominant hand suffers during movement. This agrees with past research that has shown that the dominant hand requires vision for end point accuracy more than the nondominant

(Srinivasan & Martin, 2010). The nondominant limb suffers in this case for the patients because they have an impaired sense of kinesthesia, implying their nondominant limb relies more on visual feedback than in the control group. The MS patients showed a decrease in movement linearity in the left hand compared to unimanual performance, while the controls decreased the linearity in both hands. The MS patients' performance became less linear with visually guided bimanual movement compared with use on a unimanual task, but only for the nondominant hand, which further suggests that attention was preferably given to the dominant hand. The controls were able to divide that attention between the hands, which caused them both to decrease linearity to a greater extent than the patients. This might also be due to the discrepancy that existed between the two groups in the unimanual condition. The MS patients already showed impaired movements at baseline so they may not be able to get much worse. However, the MS patients were able to change their performance under visual unimanual and bimanual conditions, unlike when kinesthesia is being used. This implies that the MS patients rely heavily on visual feedback for upper limb movements and adaptations, and that they are still susceptible to attention and integrative motor costs that come from bimanual coordination. They did not show as much of an impairment compared to the controls because they already showed more impaired performance under visual unimanual conditions. MS patients seem to have difficulties with integrating visual feedback into their movements and to a greater extent with bimanual coordination. This lack of visual integration is seen in their impaired movement mechanics during a goal directed reaching movement (Lambercy et al., 2013).

These differences between groups and hands were not seen in other clinical tasks. It should be noted that there were no differences shown between the two groups when the

NHPT was used as a measurement. This suggests that the NHPT may not be the best clinical test for upper limb movements, especially those of a fine motor nature. In fact, motor impairments of the upper limb might be more noticeable in fine movements earlier in disease progression, as the patients in this study were those of a mild to moderate condition. The MS patients in this study claimed to be right hand dominant, but the Edinburgh Handedness Inventory showed left handed tendencies. This suggests that MS patients adapt to impairments in their dominant limb by learning to increase the use of their nondominant limb. There was a left hand dominant control participant that was not excluded, as their handedness did not affect their performance compared to the other control participants.

This study suggests that fine motor impairments in the upper limb could be an early symptom of MS, as these participants were of mild disease severity and showed slowed, variable, and inaccurate movements that were not detected by the NHPT. In addition, kinesthesia was found to be impaired in the upper limb of MS patients. More specifically, they lack feedforward mechanisms utilized in kinesthesia (Sainburg et al., 1995). Kinesthetic ability in this patient population was found to be impaired to such an extent that it could not succumb to attentional costs of bimanual movements, nor was it improved with the use of simultaneous contralateral visual movement. This lack of improvement with visual feedback from the contralateral limb suggests an impairment of the CC that could include microtissue damage (Bonzano et al., 2008), overall decreased volume (L. N. Brown et al., 2010), diffusivity or lesion load (Ozturk et al., 2010), or abnormal evoked potentials (Larson et al., 2002), that have all been implicated as factors in impaired bimanual coordination. It also implies that they lack the efficient visual integration the controls still have, as demonstrated in the visual baseline differences.

5.3 Conclusions

Utilization of kinesthetic feedback, as well as visual integration, is impaired in MS patients. During unimanual movements, the patients' performance was characterized by slower, less linear, and less accurate movements when compared to controls. In conditions where one hand had to rely only on kinesthesia, while the simultaneously moving contralateral limb was visible, performance of the kinesthetically guided hand did not benefit from visual feedback in the contralateral limb. With respect to their unimanual abilities, the patients did not benefit from bimanual coordination, nor did they suffer from the more complex task. Further studies should determine how these kinesthetic findings correlate to CNS tissue damage especially the CC, as that is the main clinical measurement for diagnosis. The CC is important for communication between the two hemispheres of the brain as it utilizes both inhibitory and excitatory inputs to the motor areas, and therefore the two limbs (Gooijers & Swinnen, 2014).

For the MS patients in the kinesthetic bimanual condition, the kinesthetically guided limb did not benefit from the visual or other sensory feedback from the contralateral limb, nor did it match in movement linearity or end point accuracy. The lack of similarity in the kinesthetic hand's performance could indicate a lack of communication between the two cortical hemispheres. This lack of communication seems to include both visual integration as well as kinesthetic information because the MS patients did not show any improvement in either bimanual condition. Although the MS patients rely heavily on visual feedback to complete upper limb movements, it is not enough for visual feedback of the contralateral limb to assist in the use of kinesthesia in the other limb for completing a bimanual task.

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