BIMANUAL INTERFERENCE AND NEUROMOTOR CONTROL IN HEALTHY INDIVIDUALS AND THOSE WITH CERVICAL DYSTONIA

By

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PUBLIC ABSTRACT

BIMANUAL INTERFERENCE AND NEUROMOTOR CONTROL IN HEALTHY INDIVIDUALS AND THOSE WITH CERVICAL DYSTONIA

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The purpose of this dissertation was to investigate interference during bimanual movements in healthy individuals, and those with impaired movement due to cervical dystonia, a movement disorder. During complex bimanual movements, interference can occur, where one hand influences the action of the other hand. Interference likely results from conflicting brain signals for movement being shared between brain areas. However, how different types of motor processes interact with each other during bimanual reaching movements is not well understood. This dissertation reports two studies that address processes underlying interference in healthy individuals, and one in individuals with cervical dystonia. In the first study, groups experienced different kinds of perturbations in their right hand during bimanual reaches. The left hand was examined for interference. The results indicated that the visuomotor perturbations generate greater interference than other kinds of perturbations and were not affected by other kinds of perturbations. This suggests that primarily visuomotor processes result in interference between the hands.

The results of Experiment 1 could be explained by different perturbations being coordinated in reference frames that were differentially shared between brain areas controlling movement. Reference frames are a theoretical construct which explain how the motor system coordinates movements relative to the environment and/or itself. Research suggests that unimanual responses to forces are coordinated in unilateral reference frames specific to the adapting arm, while visuomotor perturbations are coordinated in bilateral reference frame

relative to the environment. To date, little is known about the role of reference frames in interference during bimanual movements. As such, interference may only occur when movements of each hand share a reference frame. In Experiment 2, two groups made bimanual reaching movements while their right hand experienced a force perturbation. In one group, separate cursors represented each hand. In the other group, both hands shared control of a single cursor. Shared control was hypothesized to compel the system to coordinate both hands with a shared representation. The results indicated that the shared-cursor group demonstrated more interference than the dual-cursors group, suggesting that a shared reference frame may induce greater interference.

Finally, motor coordination is often disrupted in individuals with movement disorders, such as cervical dystonia (CD). Additionally, patients with CD can show "mirror movements", in which voluntary actions of one effector cause involuntary actions in another effector, suggesting the presence of abnormal sensorimotor integration and neural inhibition. However, how the coordination of bimanual actions and interference are different in cervical dystonia has been unexplored. In Experiment 3, patients with CD and healthy controls performed a bimanual interference task before and after treatment with *botulinum toxin*. Brain activity was simultaneously recorded. Results indicated that overall, movements were coordinated similarly between patients and controls. However, greater brain activity was found in patients, particularly in the post-treatment session. This suggests that bimanual coordination necessitates greater neural resources for successful coordination in CD patients. Together, these studies advance the understanding of how bimanual coordination and interference occurs in healthy individuals, and those with cervical dystonia.

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The purpose of this dissertation was to investigate interference during bimanual movements in healthy individuals, and those with impaired movement. During complex bimanual movements, interference can occur, where one hand influences the action of the contralateral hand. Interference likely results from conflicting sensorimotor information shared between brain regions controlling hand movements via neural crosstalk. However, how visual and dynamic feedback processes interact with each other during bimanual reaching movements is not well understood. This dissertation reports two studies that address mechanisms underlying interference in healthy individuals, and one in individuals with dystonia. In the first study, groups experienced either a visuomotor perturbation, dynamic perturbation, combined visuomotor and dynamic perturbation, or no perturbation in their right hand during bimanual reaches. The left hand was examined for interference. The results indicated that the visuomotor and combined perturbations showed greater interference than the dynamic perturbation, but that the combined and visuomotor perturbations were equivalent with one another. This suggests that dynamic and visuomotor sensorimotor processes do not interact between hemisphere-hand systems, and that primarily visuomotor processes result in interference between the hands.

The results of Experiment 1 could be explained by visuomotor and dynamic perturbations being coordinated in reference frames that were differentially shared between hemisphere-hand systems. Reference frames are a theoretical construct which explain how the motor system coordinates movements relative to the environment and/or itself. Research suggests that

unimanual responses to dynamic perturbations are coordinated in unilateral intrinsic joint-centered reference frames, while visuomotor perturbations are coordinated in bilateral extrinsic reference frames. Little is known about the role of reference frames in interference during bimanual movements. As such, interference may only occur when movements of each hand share a reference frame. In Experiment 2, two groups made bimanual reaching movements while their right hand experienced a dynamic perturbation. In one group, separate cursors represented each hand. In the other group, both hands shared control of a single cursor. Shared control was hypothesized to compel the system to coordinate both hands with a shared representation. The results indicated that the shared-cursor group demonstrated more interference than the dual-cursors group, suggesting that a shared reference frame may induce greater interference.

Finally, motor coordination is often disrupted in individuals with movement disorders, such as cervical dystonia (CD). Additionally, patients with CD can show "mirror movements", in which voluntary actions of one effector cause involuntary actions in another effector, suggesting the presence of abnormal sensorimotor integration and neural inhibition. However, how the coordination of bimanual actions and interference are different in cervical dystonia has been unexplored. In Experiment 3, patients with CD and healthy controls performed a bimanual interference task before and after treatment with *botulinum toxin*. Brain activity was simultaneously recorded with EEG. Results indicated that overall, movements were coordinated similarly between patients and controls. However, greater event-related desynchronization was found in patients, particularly in the post-treatment session. This suggests that bimanual coordination necessitates greater neural resources for successful coordination in CD patients. Together, these studies advance the understanding of how bimanual coordination and interference occurs in healthy individuals, and those with cervical dystonia.

Dedication

To my parents
For their endless support,
and for always encouraging me to be “a question boy”

To my wife
My partner in all things,
Who I learn from every day
And without whom this dissertation would not exist

And to my daughter
Who I cannot wait to meet in a few short months.
May this work help provide her endless opportunities,
And inspire her to think, learn, and grow to be her best self

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shanked off the tee box, the support and friendship of these great people made it easy to get through this program.

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KEY TO ABBREVIATIONS

ADE	Apex Directional Error
afex	Analysis of Factorial Experiments (R package)
AKA	Also Known As
ANOVA	Analysis of Variance
CD	Cervical Dystonia
CMA	Cingulate Motor Area
CNS	Central Nervous System
Combo Pert.	Combined Perturbation
DBS	Deep Brain Stimulation
DLPFC	Dorsolateral Prefrontal Cortex
DOF	Degrees of Freedom
DYN Pert.	Dynamic Perturbation
EEG	Electroencephalography
EMG	Electromyography
ERD	Event-related Desynchronization
ERS	Event-related Synchronization
EXP	Exposure
ez	Easy Analysis and Visualization of Factorial Experiments (R package)
FEDE	Final Endpoint Directional Error
FEE	Final Endpoint Error
FHD	Focal Hand Dystonia

fMRI	Functional Magnetic Resonance Imaging
ggplot2	Grammar of Graphics Plots (R Package)
GLM	General Linear Model
IDE	Initial Directional Error
IEE	Initial Endpoint Error
IHI	Inter-hemispheric Inhibition
INT	Interference
KBL	Kinesthetic Baseline
LC	Left Central
L-DOPA	Levodopa (l-3,4-dihydroxyphenylalanine)
LF	Left Frontal
LP	Left Parietal
M	Mean
M1	Primary Motor Cortex
MC	Midline Central
MEG	Magnetoencephalography
MEM	Mixed Effects Model
MF	Midline Frontal
MP	Midline Parietal
MSU	Michigan State University
MT	Movement Time
NOCH	Neural Optimal Control Hierarchy theory
OFCT	Optimal Feedback Control Theory

PFC	Prefrontal Cortex
PMC	Premotor Cortex
Post-EXP	Post-Exposure
RC	Right Central
RF	Right Frontal
RMSE	Root mean square error
ROI	Region of Interest
RP	Right Parietal
RT	Reaction Time
S1	Primary Somatosensory Cortex
SD	Standard Deviation
SE	Standard Error
SMA	Supplementary Motor Area
TMS	Transcranial Magnetic Stimulation
Tukey HSD	Tukey's Honest Significant Difference
TWSTRS-2	Toronto Western Spasmodic Torticollis Rating Scale, Second Edition
UCM	Uncontrolled Manifold Hypothesis
VBL	Visual Baseline
VM Pert.	Visuomotor perturbation

CHAPTER 1 – THE NEURAL BASES OF BIMANUAL COORDINATION AND INTERFERENCE: A REVIEW

From the ungainly early steps and clumsy reaches of a toddler, to the precision of a golfer and the skilled syncopation of a drummer, we interact with the world around us through motor actions. Motor actions are fundamental to our daily existence, as they allow for communication through speech, locomotion from one place to another, the manipulation of tools and implements, and a vast host of other integral functions. We are able to consistently produce movements profoundly complex in their biomechanical, spatial, and temporal properties without significant conscious effort. Yet, when the movement of our bodies is impaired through disease or injury, the inability to execute basic movements can dramatically alter the most fundamental and essential components of our daily lives. Thus, understanding the underlying processes governing neuromotor control—the means by which the central nervous system controls purposeful, voluntary movements—is an important field of study.

The control of bimanual movements is a key component in the larger scope of neuromotor control. Bimanual actions comprise a majority of daily voluntary hand movements, and can reveal information regarding the lateralized contributions of different hemispheres to action, since each hand must be able to operate both together and separately from its counterpart (Swinnen and Wenderoth, 2004). Sometimes, difficult coordination constraints can cause interference to occur. Interference is a phenomenon in which the action of one effector can influence the action of another effector. It is aptly demonstrated by the familiar childhood challenge of attempting to pat the head and rub the belly at the same time. Interference is a

normal occurrence in the healthy motor system, thought to result from neural crosstalk between the hemispheres (Swinnen & Gooijers, 2015; Swinnen, 2002).

While interference during bimanual actions is well documented, the type (or types) of motor information causing interference and the degree to which different types of motor information cause interference is still poorly understood. Furthermore, the presence of interference during bimanual movements can be used to probe how sensorimotor systems may be improperly transmitting information between the hemispheres in individuals with movement disorders. Thus, the objective of this dissertation is to examine the processes by which interference occurs between the hands during bimanual movements in both healthy individuals and those with motor impairments. In this chapter, I will review current theories regarding the neural control of bimanual movements, discuss the current understanding of how interference occurs during bimanual movements, examine how bimanual control is affected in individuals with motor impairment, and discuss the significance and specific aims of this dissertation.

1.1 What causes interference during bimanual movements?

Interference is a well-known phenomenon of complex sensorimotor control and has received considerable research attention in recent decades. The human sensorimotor system is highly complex and adaptable, and capable of a wide range of movements. Interference represents a breakdown in the typically well-coordinated movements of the body, and thus provides a key window into specific processes by which the sensorimotor system organizes and controls movement. Research into these processes has revealed that interference occurs when the nervous system attempts to execute movements under specific temporal, spatial, or perceptual constraints (Swinnen, 2002; Swinnen and Gooijers, 2015; Swinnen and Wenderoth,

2004). In other words, depending on the coordinative structure and motor parameters during an action, interference will arise. It has been suggested that "neural crosstalk", carrying conflicting information within the sensorimotor system, underlies interference during the performance of asymmetrical or out-of-phase movements within these constraints. However, the specific nature of this information (i.e., visual, proprioceptive, kinetic, etc.), the mechanisms by which it is communicated between brain regions, the underlying neural processes and brain areas involved, and how bimanual interference can be explained by broader theories of voluntary movement remain a key area of research in sensorimotor control.

1.1.1 Temporal constraints in bimanual actions

Bimanual movements exhibit tight temporal coupling, entrained to the same temporal parameters. In instances where this coupling becomes more difficult, subjects demonstrate instabilities in their patterns of coordination. The seminal research in this area came from Kelso and colleagues who, over a career's worth of work, described and characterized the dynamics of phasic movements and their neural underpinnings (Haken et al., 1985; Kelso, 2010, 1984, 1995; Schoner and Kelso, 1988). At a basic level, Kelso and his collaborators formulated the notion that when performing cyclical, repetitive movements, humans display the most temporally stable patterns of coordination when they move in-phase, activating homologous muscles within participating effectors. These movements are performed with relative ease at high frequencies. Meanwhile, anti-phase movements, activating opposing muscle groups, are more difficult to perform at high frequencies. Indeed, when cycling frequency and/or movement amplitude increases to a point such that the tasks demands are too significant, the motor system spontaneously adopts an in-phase coordination pattern, reverting to the most stable method of

coordinating movement (Kelso, 1984). This spontaneous switching of coordination patterns was mathematically described using principles taken from dynamical systems theory (Haken et al., 1985). This work showed that the hands were nonlinearly coupled, and that interference between the hands was modulated by task difficulty. Further, it showed that flexibility and stability of actions followed a defined coordinative structure that was self-organized by the demands of the action. Later, research by Kelso and his colleagues brought light to similar patterns of recombinant neural activity at the levels of the network and neuron (Jantzen and Kelso, 2007; Jantzen et al., 2008; Schoner and Kelso, 1988). Dynamical systems frameworks have been used to describe patterns of firing of motor cortex neurons (Pandarinath et al., 2018), and remains a compelling theory of how the nervous system controls movement in redundant systems. This work has had a profound effect on the field of neuromotor control, being extended from intermanual coordination to pattern generation, gait, and postural coordination (Dijkstra et al., 1994; Hausdorff et al., 1995; Taga et al., 1991). Taken together, this body of work shows that the sensorimotor system exhibits tight temporal coupling that is modulated by task constraints.

Following the discovery of temporal coupling during bimanual movements, other researchers worked to further characterize temporal instabilities during bimanual movements. Multifrequency movements (i.e., 3:8 or 5:8 polyrhythmic tapping frequencies) experience similar spontaneous recombination of motor actions to lower-order ratios (Byblow and Goodman, 1994; Peper et al., 1995a, 1995b; Summers et al., 1993a, 1993b; Treffner and Turvey, 1993). Instability of multi-frequency coordination is also affected by hand dominance and simultaneous activation of homologous or non-homologous muscles, suggesting that underlying control processes themselves might be asymmetrical or change their coupling based on task constraints (Kennedy et al., 2015, 2016a, 2017; Shih et al., 2019). Furthermore, sensory and perceptual

modalities also influence instabilities during continuous motions, suggesting higher order processes may influence interference between the hands (Bingham, 1995; Bingham et al., 2018; Kovacs et al., 2010; Temprado et al., 2003).

A concerted effort has also been made to understand the neural processes associated with temporal instabilities and interference during bimanual coordination. Many have focused on interhemispheric synchronization during continuous bimanual movements, often evaluated with transcranial magnetic stimulation (TMS), functional magnetic resonance imaging (fMRI), electroencephalography (EEG), or magnetoencephalography (MEG). In these studies, changes in neural activation or functional connectivity within and between hemispheres has been investigated in relation to temporal instability and complex coordination patterns. Difficult coordination patters are associated with stronger interhemispheric connectivity and facilitation, particularly in the beta (~13-30 Hz) frequencies and in the non-dominant hemisphere (Fujiyama et al., 2016; Rueda-Delgado et al., 2017; Serrien and Brown, 2002). This heavily implies that motor information relevant to task complexity is transmitted between hemispheres via the corpus callosum, the band of white matter connecting the two halves of the brain. This is supported by evidence that patients who exhibit degradation of the corpus callosum show degraded temporal coordination during continuous movements, and that in healthy participants, better temporal coordination is associated with greater callosal tract integrity (Johansen-Berg et al., 2007; Kennerley et al., 2002; Serrien et al., 2001; Wahl et al., 2016). Excitability of the corticospinal tract is also elevated during more complex polyrhythms (Nomura et al., 2016). Areas of the brain associated with motor planning and sensorimotor integration are preferentially activated during performance of more complex phasic movements, including parietal cortex, supplementary motor area (SMA), premotor cortex (PMC), cingulate motor area (CMA), and

medial and vermal cerebellum (Debaere et al., 2004; Jäncke et al., 2000; Lin et al., 2017; Rémy et al., 2008; Tracy et al., 2001; Zhuang et al., 2005).

Taken together, these studies support a critical role of temporal constraints in the ability for humans to accurately control bimanual movements. Changing the parameters of these temporal components causes significant changes in both brain activity and behavior. As such, temporal control parameters represent a significant factor that modulates the ability of the hands to work in unison.

1.1.2 Spatial constraints in bimanual actions

Spatial symmetry of movements also plays a critical role in bimanual coordination. It is much easier to move the hands along symmetrical trajectories than along asymmetrical trajectories (Swinnen and Wenderoth, 2004; Swinnen et al., 2001). Typically, studies investigating spatial interference compare movements (typically reaches) made by participants moving with congruent or incongruent directions, with different amplitudes, or by drawing different shapes. In one of the earliest studies, Franz and colleagues (1991) asked participants to simultaneously draw a line with one hand and a circle with the other. They observed that each shape took on spatial characteristics of the other. Since these tasks were done with equivalent patterns of timing, the authors realized that this constituted a constraint separate from the temporal coordination, which had received the bulk of research interest to that point. In other tasks, participants have been asked to simultaneously draw other asymmetrical shapes with each hand, such as a line versus a star or a block C vs. a block U (Franz et al., 1991, 1996; Swinnen et al., 2002; Wenderoth et al., 2003).

Interestingly, patients with a callosotomy exhibit little spatial interference, indicating that interference critically depends on communication between the hemispheres (Franz et al., 1996), and particularly through the posterior callosal tracts (Eliassen et al., 1999). As with actions performed under temporal constraints, this again highlights the importance of the corpus callosum in coordinating bimanual movements (Diedrichsen et al., 2003a; Gooijers and Swinnen, 2014; Kennerley et al., 2002; Serrien et al., 2001). Interestingly, individuals with callosal agenesis are able to function similarly to controls in both spatial and temporal domains, which suggests that other (likely subcortical) brain areas can adapt to supplement or adopt callosal functions (Diedrichsen et al., 2003a).

Examination of interference has provided insight into how discrete movements are coordinated, and the neural processes underlying the planning and execution of actions. Spatial interference during asymmetrical reaches can be mitigated with training, as long as that training occurs bimanually; unimanual training does not positively influence coordination patterns (Wenderoth et al., 2003). Importantly however, even extensive practice is unable to completely resolve interference between the hands (Albert and Ivry, 2009). This suggests that discrete bimanual actions are coordinated in a unified framework, as opposed to being to singular processes that are linked together. Making movements of different amplitudes can also result in interference, in which each hand's reach distance will be drawn to that of the opposing hand (Kovacs and Shea, 2010; Pan and Van Gemmert, 2019; Swinnen et al., 2001). Additionally, spatial interference appears to be driven by top-down, efferent motor planning processes, as opposed to the influence of bottom-up, afferent proprioceptive information (Swinnen et al., 2003). This is in agreement with studies in repetitive circling, suggesting that temporal motor characteristics are not affected by lack of afferent input (Spencer et al., 2005). Obhi and

Goodale (2005) investigated whether interference arose primarily from motoric sources (i.e., a preference to activate homologous muscles) or from spatial sources (i.e., a preference to move in the same direction). They asked participants to make finger flexion movements that differed in motoric congruency, spatial congruency, or both. They found that incongruence in both parameters led to increases in reaction time (RT), but that RT received the greatest penalty for spatially incongruent movements. Spatial parameters of movements also show greater deficit than temporal parameters following middle and posterior cerebral artery stroke (Rose and Winstein, 2013), suggesting important contributions of cortical areas to spatial control, and supporting the importance of subcortical and cerebellar areas in temporal control processes (Bares et al., 2007; Dreher and Grafman, 2002; Pressing et al., 2003)

It is important to note that research examining spatial constraints in movement progressed in two avenues. In one line of study, different movements were examined in terms of disrupted motor kinematics and trajectories, usually as the result of asymmetrical shapes or movement trajectories (Franz et al., 2001; Swinnen et al., 2001, 2003; Wenderoth et al., 2003, 2004). The other has examined how movements of different spatial constraints affect certain temporal parameters (usually reaction times; Diedrichsen et al., 2003b; Hazeltine et al., 2003; Spijkers et al., 2000). In general, these studies have shown that movements with different amplitudes or directions elicit increases in reaction times, which is interpreted as increased processing demands on the sensorimotor system. Symbolically cuing targets results in an increase in reaction time between congruent and incongruent movements, while pre-cuing or directly cuing targets abolishes increased reaction times between movement types (Albert et al., 2007; Diedrichsen et al., 2001, 2006; Hazeltine et al., 2003; Spijkers et al., 1997; Weigelt et al., 2007). These studies show that spatial interference may be the result of assigning or selecting movement parameters

during self-generated or internally guided movements. This supports the idea that the specific nature of sensorimotor information or sensory modality used by the neuromotor system to plan movements can influence the resulting actions.

Interference can also occur during movements in response to visual cues. Visuomotor processes in one hand influence the action of the opposing hand. Visual feedback of the right hand supports the trajectory control of the left hand moving without feedback, while visual feedback of the left hand supports endpoint control of the kinesthetically controlled right hand (Kagerer, 2015a). This supports transcallosal coupling between movements and suggests that visual guidance can further modulate these effects.

Visuomotor perturbation of one hand also elicits deviation in the opposing kinesthetically controlled hand (Kagerer, 2015b). These perturbations are hypothesized to necessitate the formation of novel sensorimotor representations in the CNS to resolve introduced sensorimotor error between motor command and observed feedback due to the perturbation. In these paradigms, participants are able to correct large amounts of error as they adapt to the novel sensorimotor environment. In a visuomotor perturbation task, a cursor representing the one hand is rotated by an angle $\theta°$, such that if the participant reaches straight to a target, the cursor moves $\theta°$ clockwise. Thus, to move the cursor to the target, the participant must reach $-\theta°$. Meanwhile, participants simultaneously reach to targets in the opposing hand without visual feedback, leaving that hand susceptible to interference due to updating of the sensorimotor representation in its adapting counterpart.

In right-hand dominant individuals, the effects of the perturbation are greater from the right to the left hand, indicating that interhemispheric communication of updated visuomotor maps may be stronger from the left to the right hemisphere. Interestingly, this lateralization is

not as evident for left-handers (Kagerer, 2016a), supporting differences in functional lateralization of motor control processes in left- and right-handed individuals (Przybyla et al., 2012; Serrien et al., 2012; Wang and Sainburg, 2004). However, lateralized patterns of interference in right-handers was not found when the visuomotor perturbation was introduced gradually, playing to endpoint-control strengths of the left hand (Kagerer, 2016b). Interference due to visuomotor perturbation of one hand is also associated with changes in the engagement and functional connectivity of neural populations between- and within-hemispheres (Desrochers et al., under review). Further, this interference is specifically due to updating of visuomotor maps, indicated by the time course of interference, and because interference is greater when participants adapt to rotated visual feedback as opposed to making asymmetrical reaching movements with deviation of the same magnitude (Brunfeldt et al., in prep).

As with temporal constraints, efforts have been made to understand the underlying neural mechanisms governing spatial constraints on movement. Broadly, a similar premotor-parietal network is implicated in the control of bimanual movements (Swinnen and Gooijers, 2015). In particular, the influence of the parietal cortex has emerged as a primary candidate for mediating spatial interference and coordination (Diedrichsen et al., 2006; Eliassen et al., 1999; Le et al., 2017; Wenderoth et al., 2004, 2006), possibly due to its importance in spatial localization and motor planning in response to visual stimuli (Goodale and Milner, 1992). Supporting the influence of this network on spatial interference, in a motor neglect patient, movements of incongruent directions failed to evoke increased activation in posterior parietal cortex (PPC) and pre-SMA, and consequently did not show coupling between hand movements (Garbarini et al., 2015). Symbolic cueing of asymmetrical movements additionally involves left hemisphere frontal and parietal areas in the left hemisphere, supporting the notion of possible left hemisphere

functional lateralization of spatial interference (Diedrichsen et al., 2006), and possibly underlying lateralized interference in right-handers (Kagerer, 2015b). Functional connectivity in the oscillatory activity of neural populations is also widely reported both within- and between-hemispheres, and is associated with changes in spatial interference (Desrochers et al., under review; Rueda-Delgado et al., 2014; Serrien, 2009; Serrien and Spapé, 2009).

Taken together, there is robust evidence for the importance of spatial constraints on bimanual coordination. Asymmetrical spatial task demands not only influence the kinematic control of movements, but also temporal components of motion. Spatial constraints are also particularly modulated by vision and depend on the engagement of a frontoparietal network in addition to transcallosal communication. Thus, spatial parameters impose a significant constraint on the motor system.

1.1.3 Perceptual/conceptual constraints in bimanual actions

While temporal and spatial constraints influence our ability to perform bimanual actions, the perceptual characteristics of a task also impose constraints on movement that may either exacerbate or resolve interference between effectors. In these cases, abstract, unifying stimuli or concepts, separate from direct neuromotor or spatiotemporal control parameters, may assert a stabilizing influence on bimanual control. Indeed, this constraint may actually have the greatest effect on the stability of coordination between the hands by combining (or not) separate actions into a meaningful 'gestalt' (Ivry et al., 2004; Shea et al., 2016; Swinnen and Wenderoth, 2004).

For example, as stated earlier, difficult temporal coordination patterns are more easily performed when participants focus on higher order perceptual components of the task, or anchor their coordination pattern to a sub-component of the task (Ivry et al., 2004; Semjen and Ivry,

2001; Swinnen and Gooijers, 2015; Swinnen and Wenderoth, 2004). Playing of tones or manipulating the perceptually anchored hand during multi-frequency coordination tasks can influence temporal accuracy, though do not affect the fundamental organization of the action (Summers et al., 1993b). Individuals who perceive stimuli as moving in-phase, even though the movements controlling them are multi-frequency, show more stable movement patterns (Mechsner et al., 2001). The presence of visual information can also aid performance. For example, the presentation of Lissajous displays, designed to visuospatially depict the temporal relationship between the hands, facilitates the performance of difficult polyrhythms (Kovacs and Shea, 2011; Kovacs et al., 2009, 2010; Shea et al., 2016). This suggests that much of the difficulty in coordinating multifrequency movements is due to visuospatial or attentional parameters disrupting coordinated movements. Interestingly, removal of feedback after training shows a greater deterioration in coordination after training with Lissajous feedback as opposed to tone feedback, suggesting a dependency on specific feedback for successful coordination is formed during performance under certain conditions (Chiou and Chang, 2016; Vaz et al., 2017).

In spatial bimanual tasks, manipulating the type of targets to which individuals reach can also change behavior. For example, increased reaction times are typically observed for bimanual movements with different amplitudes or directions when they are symbolically cued. However, when movements are cued with direct target locations, reaction time effects are mitigated, likely due to lowered cognitive load in associating a movement to a symbol (Diedrichsen et al., 2001, 2006; Hazeltine et al., 2003; Hesse et al., 2018; Stanciu et al., 2017). Furthermore, if targets are presented as a unified object, as opposed to discrete, separate objects, increased reaction times are likewise eliminated (Franz and McCormick, 2010). The same study also demonstrated that the verbal conceptualization of the task also modulated reaction times to targets of different

amplitudes. Still other studies showed that spatial trajectory control of repetitive half-circle movements were more stable when the task was presented with a conceptually unified structure (i.e., a full circle), as opposed to when they were presented with a conceptually unfamiliar structure (i.e., separated half-circles; Franz et al., 2001), suggesting a positive influence of object- or goal-conceptualization on unifying bimanual movements. Visual information also can be used to spatially coordinate movements, and can override anatomical orientation or co-activation of homologous muscles (Brandes et al., 2016, 2017). Furthermore, the presence of goal-directed action can even partly rescue bimanual movements that are impaired due to hemiparesis (Kantak et al., 2016a).

Humans also tend to gravitate towards coordinating their movements within the same reference frame. In motor control, a reference frame (AKA a coordinate system) represents the theoretical coordinate system within which movements are planned and executed. Understanding reference frames used by the sensorimotor system to coordinate movement has been one of the primary goals of the field of motor control. However, how reference frames are formulated by the nervous system varies depending on the movement and its context. For discrete, spatial reaching movements, research suggests that humans represent the world in a radial egocentric reference frame (i.e., with reference to the self), such that the environment can be represented in a polar coordinate system, with the body at the origin (Swinnen, 2002; Swinnen et al., 2002). Bimanual movements made in the same polar orientation, within this reference frame (i.e., away from the body's midline) exhibit less interference than movements made with different orientations within this reference frame. Other movements, such as finger and wrist flexion, are also preferentially coordinated in an egocentric reference frame, with homologous muscle activations being more easily coordinated than non-homologous muscles.

Conversely, movements of non-homologous limbs (i.e., right arm and right leg) tend to be more easily coordinated in allocentric space, in which they are moved in the same direction relative to each other (Swinnen, 2002).

Early research in unimanual studies suggested that humans also tend to plan and execute visuomotor actions in an egocentric-extrinsic, Cartesian-based reference frame, whereas dynamic actions, requiring forces, were planned and executed in an egocentric-intrinsic (i.e., joint centered) reference frame (Shadmehr and Mussa-Ivaldi, 1994). This notion was held for almost two decades, until recent evidence suggested that different actions may be represented along a spectrum of egocentric-intrinsic reference frames that is modulated by task constraints. Coordination of movements may thus rely on a simultaneous mixture of both types of coordinate systems (Berniker et al., 2013; Brayanov et al., 2012; Franklin et al., 2016). The flexibility to use a mixture of reference frames follows from the notion of gain fields encoding both intrinsic and extrinsic coordinates that are modulated by the context of a task. This is in accordance with predictions made by Optimal Feedback Control Theory (OFCT; addressed below).

How changing coordinate systems may influence bimanual control is not well understood. To this point, most research investigating changing coordinate systems has focused on a single limb. Interestingly, the coordinate system in which a movement is being planned may influence whether interference is present (or not) during bimanual movements. Indeed, this may, at least in part, underlie the observed findings that the conceptualization or perception of a task heavily influences the presence or absence of interference. If movements are being coordinated in the same reference frame, interference of asymmetrical or anti-phase movements may be present, while movements that are coordinated in different, intrinsic reference frames

may be more robust to the effects of asymmetrical movements. This dissertation represents an initial investigation into this question.

Taken together, it is evident that the nervous system must manage an array of spatial, temporal, and perceptual constraints when coordinating bimanual movements. These constraints can vary widely depending on the context, stimuli, utilized effectors, and many other movement parameters. Movements that make the coordination of these constraints more difficult will likewise impair the coordination of the hands. Understanding how these constraints modulate the coordination of the hands is an ongoing challenge in the study of bimanual motor control.

1.1.4 Neural crosstalk and motor overflow as a mechanism underlying interference

Several studies suggest that interference is the result of neural crosstalk, mediated by the corpus callosum (Diedrichsen et al., 2003a; Houweling et al., 2010a; Kennedy et al., 2016b; Kennerley et al., 2002). This is most aptly shown through differences in interference in bimanual drawing between callosotomy patients and healthy controls (Franz et al., 1996). Studies in non-human primates have shown that the corpus callosum allows for hand-specific information to be projected between the hemispheres, particularly from the supplementary motor area (SMA) and pre-SMA (Liu et al., 2001). Such findings emphasize the notion that motor plans are transmitted between hemispheres. Furthermore, evidence in humans demonstrates that greater spectral power and functional coupling between brain areas as measured by EEG is associated with increased interference between the hands and related to bimanual coordination (Desrochers et al., under review; Andres et al., 1999; Gerloff and Andres, 2002; Houweling et al., 2010b; Rueda-Delgado et al., 2017; Serrien and Brown, 2002). Thus, it can be deduced that neural activity in one hemisphere may influence activity in the opposing hemisphere.

Neural crosstalk is also invoked as a mechanism to describe the phenomenon of motor overflow. During motor overflow, action of one hand causes involuntary muscle activity, and sometimes movement, in the opposing hand (Addamo et al., 2011). Motor overflow is associated with increased excitability of corticospinal tracts contralateral to voluntary muscle activation, and reduced interhemispheric inhibition (IHI; Cunningham et al., 2017; Fling and Seidler, 2012; Muellbacher et al., 2000; Tinazzi and Zanette, 1998). Interestingly, IHI is increased in unimanual movements, and decreased in bimanual movements, suggesting a functional and supporting role of motor overflow and neural crosstalk in coordinating bimanual movements and isolating movement to one arm when unilateral actions are desired (Cunningham et al., 2017; Fling and Seidler, 2012; Perez and Cohen, 2008).

During complicated bimanual actions, the observed interference may also be the result of conflicting internal models created by the CNS (Kagerer, 2015b, 2016b). An internal model is a theoretical neural construct that contains the motor command of a predicted outcome for a given movement (Kawato, 1999; Wolpert et al., 1995a, 1998). By making a comparison between the expected and actual movement result, online corrections can be made by the sensorimotor system to reduce error and increase accuracy. While internal models are constructed independently for each effector, rich communication must occur between hemispheres to coordinate effectors with one another. To coordinate opposing sides of the body, lateralized motor plans generated in frontal and parietal cortical motor areas of one effector (i.e., primary motor cortex, premotor cortex, supplementary motor area, posterior parietal cortex) may influence motor plans in the opposing hemisphere. During interference tasks utilizing adaptation in one hand, an updated internal model and sensorimotor map may be transmitted between hemispheres via neural crosstalk (Desrochers et al., under review).

Interestingly, the exact nature of the information crossing between hemispheres is still not fully understood. Interference and motor overflow are thought to occur under many different circumstances and in many different tasks, which may or may not share motor parameters. Depending on the task and context, various modes of information are assumed to be shared between hemispheres, including, but not limited to temporal information, visuomotor information, muscle forces, or internal models. Additionally, to the brain, not all modes may be equal, and certain types of sensorimotor information may dominate over another in terms of interhemispheric communication. Alternatively, their importance could vary depending on task-relevance or context. Thus, understanding the mode and degree of information being shared between hemispheres in a given scenario is an ongoing challenge in those studying bimanual coordination (and one that will be addressed in this dissertation).

1.1.5 Optimal feedback control may explain interference behavior

Among the greatest problems that face motor control research is the manner by which the motor system coordinates movement considering incredible redundancy. This issue, first raised by Nikolai Bernstein (Bernstein, 1967), posited that for a given movement, the nervous system must control an inordinate number of degrees of freedom (DOF), given all the joints, muscles, motor units, and environmental constraints that influence a certain action. As such, any given movement could be completed in a vast number of different ways. Further, during any given movement, this also means that there are many redundant degrees of freedom that must be controlled. If the nervous system separately controlled each degree of freedom for a movement in any given context, the computational demands on the system quickly spiral out of the realm of possibility. Thus, the nervous system must adopt a solution to shed degrees of freedom from its

explicit control. As such, over the last half-century, many eminent minds investigating neuromotor control have worked to understand how the nervous system might solve this problem, producing the notions of, among others, dynamical systems in motor control (Davids et al., 2003; Haken et al., 1985; Kelso, 1995; Schoner and Kelso, 1988; Scott Kelso and Tuller, 1984; Thelen et al., 1987), uncontrolled manifold hypothesis (UCM; Latash, 2012; Scholz and Schöner, 1999, 2014), and motor synergies (Krishnamoorthy et al., 2003; Latash, 2010; Scholz et al., 2000).

A second important issue in neuromotor control is the manner in which feedback is used by the motor system to coordinate movement. It is well understood that afferent feedback from many different sources (i.e., eyes, skin, muscles) is essential for perception and action; hence, many motor control scientists refer to the neural systems controlling movement as the *sensorimotor* system. However, transmission of feedback from the periphery to the CNS takes time (on the order of 10s of milliseconds) to travel to the central nervous system for use in action. For fast movements, this information arrives too slowly to be used to correct for error (Dewhurst, 1967). Thus, how the nervous system organizes and integrates feedback for voluntary movements, particularly fast movements, has received much attention.

Optimal Feedback Control Theory (OFCT; Scott, 2004; Todorov and Jordan, 2002) represents a possible solution to these two problems. OFCT describes how these two components are incorporated into the motor system via a process of optimization (Diedrichsen et al., 2010; Scott, 2004). Here, the theory assumes that the motor system will attempt to optimize performance with respect to biologically relevant goals which are prescribed through the context and parameters of the movement. Some of these parameters include jerk (Viviani and Flash, 1995), muscle activation (Burdet et al., 2001), joint torque (Kuo, 1995), temporal parameters

(Hudson et al., 2008), sensorimotor noise (Todorov, 2005), and even mental effort (Shadmehr et al., 2016). The result is a movement that requires minimum effort in the motor system, as well as reduced variability in task-relevant movement parameters. Additionally, OFCT describes how the nervous system may integrate feedback about the current effector state into future states. In a context where there is high unpredictability or variability in the motor system (i.e., intrinsic sensorimotor noise or extrinsic environmental factors), OFCT predicts that the nervous system will preferentially weight incoming feedback over learned movement parameters, accelerating the learning of novel internal models (Dimitriou et al., 2013; Franklin et al., 2012, 2017). Conversely, during stable movement contexts, OFCT predicts that the motor system will preferentially weight established internal models. This allows for experimenters to predict how task-specific feedback might influence motor performance. Based upon incoming feedback, the OFCT framework provides a process by which the nervous system can use feedback to estimate low level interactions between effectors or higher level interactions between task-relevant control parameters (Diedrichsen et al., 2010). These estimates can then be used to optimize subsequent movement with respect to task relevant goals, simplifying control parameters and constraining detrimental variability. In effect, OFCT provides a theoretical means through which feedforward motor representations are developed from sensory information and estimates of motor consequences (i.e., the efference copy).

OFCT has great relevance in bimanual control. In particular, it predicts ways in which one effector will interact or compensate for actions of the other effector, particularly when movement goals are shared between effectors. For example, Diedrichsen (2007) showed that when participants controlled a single cursor with both hands, dynamic perturbation of one hand led to a systematic compensation in the opposing hand approximately 190ms after perturbation

onset. In contrast, when each hand controlled its own cursor, similar compensation resulting from perturbation was not evident. Furthermore, he also demonstrated that adaptation to the perturbation also differed between conditions. In the shared-cursor condition, both hands made early compensations based upon the previous trial, whereas in the unshared-cursors condition, only the perturbed hand made early compensatory movements. This study showed that when both hands shared task parameters, the action of the two hands was modified to achieve an optimal solution and was aligned with predictions made by OFCT. Furthermore, the motor system will modify its movement based upon task dependent constraints.

Supporting the notion of optimizing movement in accordance with task demands, additional work showed that even early reactive reflexes in the contralateral limb are modulated based on task conditions (Mutha and Sainburg, 2009). Similar results were found in a study in which participants had to compensate for forces applied to each limb in a task akin to balancing a food tray, where the response of one limb was modulated by the perturbation of the contralateral limb (Dimitriou et al., 2011). Different goals in a conceptually identical task will also differentially affect bimanual coordination (Diedrichsen and Gush, 2009). Taken together, these studies show that when two hands are jointly controlling task parameters, both hands will compensate for perturbations of a single hand in an optimized fashion, minimizing some task-relevant movement parameter with both hands. These studies lend support to the relevance of OFCT in bimanual actions and suggests that, depending on context, interference between the hands may arise due to shared task goals within the motor system. Importantly, this is in agreement with a major constraint in interference – that the perception or conceptualization of a task has a profound effect on the interference observed between effectors.

1.2 Neural control of bimanual movements

The neural circuitry controlling bimanual movements must be able to coordinate the actions of both hands across a variety of spatial, temporal, and task-specific contexts. As such, a great number of neural systems contribute to the control of bimanual movements. While earlier studies attempted to isolate structures that were explicitly involved in bimanual movements, we now understand that bimanual coordination is controlled via an interplay of brain regions that contribute at varying levels depending on task complexity, stimuli, context, and a host of other factors (Swinnen and Gooijers, 2015).

On the whole, activation studies have shown that brain regions engaged in bimanual tasks are not dramatically different from unimanual tasks (Swinnen and Gooijers, 2015), though the dominant hemisphere does seem to play a distinct role in initiating bimanual movements (Walsh et al., 2008). However, some key distinctions are clear. First, the supplementary motor area seems to be highly related to increasing task complexity, including simultaneous bimanual coordination (Garbarini et al., 2015; Jäncke et al., 2000; Toyokura et al., 1999; Tracy et al., 2001). When tasks continue to increase in difficulty, other areas can also be recruited, including premotor, parietal, and temporal cortices, and subcortical structures (Berger et al., 2018; Debaere et al., 2004). For example, bimanual diadochokinetic movements activate cerebellar areas (Nair et al., 2003; Tracy et al., 2001), while training in a continuous bimanual movement task elicited activation in the basal ganglia and hippocampus (Rémy et al., 2008). Additionally, a study using a directional interference task showed increased activation in posterior parietal and premotor areas, and show greater interhemispheric connectivity, likely reflecting integration of visual and sensorimotor information within and between hemispheres (Walsh et al., 2008; Wenderoth et al., 2004). This relationship is in line with the what-how theory of visual perception (Goodale and

Milner, 1992). This further suggests that interference during bimanual movements may be mediated by information transfer between highly interconnected frontal and parietal cortices involved in movement planning.

Such information transfer is dependent on robust tract integrity between brain areas active during bimanual movements. To this end, most research has focused on the corpus callosum, connecting the hemispheres and likely mediating interhemispheric crosstalk (Gooijers and Swinnen, 2014). The size and integrity of the transcallosal fibers are more robust in individuals who specialize in bimanual coordination (Schlaug et al., 1995; Schmithorst and Wilke, 2002; Scholz et al., 2009). In a bimanual finger tapping task, subregions of the corpus callosum were found to be associated with better performance (Johansen-Berg et al., 2007). Moreover, these regions were highly connected to the SMA and caudal CMA. Meanwhile, supporting parietal involvement in complex visuospatial motor tasks, training in the acquisition of complex bimanual skills (i.e., juggling) resulted in increased white matter integrity in the interparietal sulcus, as well as overlying parietal gray matter (Scholz et al., 2009).

Finally, bimanual movements are associated with differences in functional connectivity between multiple brain regions. Performance of different polyrhythms and opening and closing of the hands are associated with a rich connectivity between the SMA and the premotor (PMC) and primary motor (M1) cortices, particularly from the left hemisphere to the right hemisphere (Grefkes et al., 2008; Zhuang et al., 2005). Both intra- and interhemispheric functional connectivity in M1, the SMA, the dorsolateral prefrontal cortex (DLPFC) and the primary sensory cortex (S1) are also modulated by bimanual skill acquisition, with greater connectivity occurring early in learning of a novel skill (Sun et al., 2007). These connectivity analyses also clarify whether different regions serve excitatory or inhibitory roles within the sensorimotor

network. In this regard, intra- and interhemispheric communication contains both excitatory and inhibitory properties. During bimanual movements, communication is mostly excitatory both within and across hemispheres, possibly contributing to interference when tasks become complex (Grefkes et al., 2008; Zhuang et al., 2005). Interestingly, most of these studies have examined continuous movements exhibiting varying levels of temporal control, but not discrete movements that target spatial control of the hands.

In summary, bimanual movements are coordinated via a dynamic, distributed network of brain regions that include M1, PMC, SMA, S1, parietal cortex, basal ganglia, and the cerebellum. Bimanual movements typically are associated with increased activation of these areas, particularly in the SMA, as well as greater connectivity within and between these structures. This network is also modulated by task complexity, context, and sensory input. Investigating bimanual movements continues to be a valuable means of probing this intricate network.

1.3 Bimanual movements in individuals with impaired motor control

Bimanual movements can provide great insight into the performance of neural systems controlling movement. As such, they have been investigated at length in individuals with motor impairments. A great amount of attention has been paid to individuals with stroke, as bimanual movements may provide a promising avenue for rehabilitation (Cauraugh and Summers, 2005; Cauraugh et al., 2010; Kantak et al., 2017; Rose and Winstein, 2004). While it is well known that many stroke patients experience hemiparesis, or lack the ability to control the "affected" limb, the contralateral "unaffected" limb can also experience movement impairment, exhibiting greater movement time and greater spatial and temporal error (Cunningham et al., 2002;

Dickstein et al., 1993; Gosser and Rice, 2015; Lewis and Byblow, 2004). In discrete bimanual movement tasks, an increase in movement time of the non-paretic limb is primarily driven by an extended deceleration phase compared to unimanual movements (Rose and Winstein, 2005). In other words, during bimanual movements, the unaffected hand slows while the paretic hand increases its velocity to maintain coupling of movement. Indeed, this signals that some aspects of shared control over the hands are still functional, reflecting continued coordination within the sensorimotor network despite damage due to stroke. Further, the non-paretic limb has difficulty in matching a passively moved paretic limb, exhibiting increased jerk and disrupted relative position control (Torre et al., 2013), though the particular patterns in which patients display differences in positioning between the hands can be highly variable (Dukelow et al., 2010). Stroke patients have difficulty controlling the joint coordination of force production with both hands simultaneously (Lodha et al., 2012), possibly signifying disrupted motor synergies or inability to produce optimized bimanual movements (Kang and Cauraugh, 2017). However, bimanual force production can improve with training (Kang and Cauraugh, 2014). Finally, and importantly, while stroke patients exhibit greater overall movement variability in the paretic arm and show difficulty in controlling movements of both hands (Kantak et al., 2016a, 2016b), they are still able to modulate the variability of the paretic arm to accomplish a task with a shared goal (Ranganathan et al., 2018). This suggests that the context- and goal-dependent perceptual constraints continue to drive bimanual coordination in stroke patients. Taken together, these studies suggest that bimanual coordination can be influenced by unihemispheric deficits but can also potentially be used to enhance recovery of function in the affected hemisphere. This motivates further research into understanding the active networks that continue to coordinate

movements between the hands after stroke, and provides impetus to utilize bimanual movements for rehabilitation and recovery of function (Cauraugh et al., 2010; Kantak et al., 2017).

Bimanual control in individuals with movement disorders has received somewhat less attention than in stroke, and most research has focused on bimanual control in Parkinson's disease. In Parkinson's patients, anti-phase continuous movements are impaired, while less impairment is observed during in-phase movements (Almeida et al., 2002; van den Berg et al., 2000; Byblow et al., 2002; Johnson et al., 1998; Ponsen et al., 2006; Song et al., 2010). These coordination deficits remain even when patients are provided L-DOPA medication (Brown and Almeida, 2011). Interestingly, activation of some sensorimotor control centers, particularly the SMA and the basal ganglia, is attenuated when Parkinson's patients are performing anti-phase movements, whereas other regions, such as M1, parietal cortex, and cerebellum are more strongly engaged (Wu et al., 2010; Yu et al., 2007). Importantly, Parkinson's disease symptomology is not homogeneous; Parkinson's patients who show freezing of gait also lack the ability to keep repetitive anti-phase bimanual movements temporally steady without an external cue, whereas non-freezing of gait patients did not show the same dysfunction (Vercruysse et al., 2012). This may reflect basal ganglia contributions to bimanual control, which may degrade as the disease advances. In discrete motions, Parkinson's patients show decreased movement time and have difficulty producing separate forces with the upper limbs (Lazarus and Stelmach, 1992). However, patients still exhibit increased reaction time and temporal linkage during movements of asymmetrical amplitudes (Stelmach and Worringham, 1988). Fortunately, evidence exists that L-DOPA medication induces greater PFC to PMC coupling, and is associated with modest gains in bimanual coordination (Nettersheim et al., 2018), though more research is still needed to confirm this finding and understand its mechanism of action.

Impaired bimanual control has been found in a range of other neurological disorders as well. Deficits similar to those observed in Parkinson's disease have also been found in patients with cerebellar degeneration and Huntington's disease (Brown et al., 1993). Unimanual and bimanual coordination is impaired in developmental coordination disorder (Volman and Geuze, 1998), Alzheimer's disease (Martin et al., 2017), schizophrenia (Gorynia et al., 2003), Tourette's syndrome (Avanzino et al., 2016), and even across normal aging (Maes et al., 2017). Thus, the control of bimanual movements can be affected by sensorimotor deficits across a variety of disorders and conditions.

Finally, a dysfunctional bimanual control network may underlie a common clinical observation known as mirror movements, found in disorders such as Parkinson's disease and dystonia. In mirror movements, action of one part of the body causes involuntary activations in another muscle group or effector, usually homologous muscle groups on the contralateral effector (Cox et al., 2012; Sitburana and Jankovic, 2008; Sitburana et al., 2009). Mirror movements are common during early childhood, and likely reflect low transcallosal inhibition due to immature myelination of corpus callosum leading to enhanced neural crosstalk (Espay et al., 2005; Galléa et al., 2011). However, when mirror movements persist into adulthood, they may reflect abnormal sensorimotor processing. In disease, these movements are thought to be the result of dysfunctional intra- and intercortical inhibition. In Parkinson's disease, greater mirror movements are associated with more lateralization of Parkinson's symptoms (Espay et al., 2005). Transcranial Magnetic Stimulation (TMS) has been used to probe mirrored muscle activity in Parkinson's disease, demonstrating abnormal activation of the contralateral hemisphere (Cincotta et al., 2006; Li et al., 2007).

Likewise, TMS showed that interhemispheric inhibition was substantially decreased in focal hand dystonia (FHD) patients with mirror movements compared to controls and patients who did not display mirror movements (Sattler et al., 2013). Intriguingly, weaker interhemispheric inhibition was correlated with disease severity and the presence of mirror movements. Similar effects were found during tasks of force production in the hands (Beck et al., 2009). Others have shown abnormal motor unit synchronization and motor overflow of a central command using intramuscular EMG in patients with FHD (Farmer et al., 1998). Taken together, the atypical intra- and interhemispheric inhibition in these disorders may allow for increased neural crosstalk and abnormal sharing of movement information between the hemispheres, and thus leave patients more susceptible to mirror movements. These abnormal network interactions may underlie some deficits seen in bimanual movements in these disorders.

Understanding bimanual control in those with motor impairment is important for understanding how bimanual movements are disrupted in specific ways. Further, the study of bimanual actions in patients also provides a tool to probe whether specific neural processes are intact. This in turn allows neuroscientists to gain information about the underlying disease etiology, while also advancing our understanding of the sensorimotor system at large.

1.4 Significance and Specific Aims

Performing coordinated bimanual actions is an integral part of daily life, and understanding the processes controlling bimanual actions can yield important insight into the capabilities of the system in both healthy and impaired states. Accurate control of bimanual movements relies on a complex interconnected network of sensorimotor brain areas. To investigate the contributions of this network to bimanual actions, tasks that produce interference

between the hands are often used. These tasks manipulate the timing or symmetry of movement patterns or include task components that are shared or optimized between effectors to modulate neural crosstalk. However, the nature of sensorimotor information that is shared between the hemispheres, and how different modes of information may interact, is not well understood. Furthermore, how brain networks respond to interference paradigms in individuals with movement disorders that are susceptible to mirror movements is unexplored. Studying interference in healthy individuals and those with motor impairment will expand the understanding of the neural control of bimanual coordination, promote better identification and diagnosis of movement impairment, and provide further insight into disease phenomenology and potential treatment strategies.

The goal of this dissertation will be to examine how different kinds of sensorimotor information contribute to interference in bimanual control, and how bimanual interference manifests in cervical dystonia – a disorder of the sensorimotor network which shows compromised motor inhibition and integration processes that can cause impairments in bimanual coordination (e.g., mirror movements). To this end, I have devised a series of aims to study interference and the communication of motor information within sensorimotor network in healthy and impaired individuals.

Aim 1: To determine the influence of visuomotor and dynamic perturbations in bimanual interference. I will measure the degree of interference from visuomotor or dynamic perturbations, and additionally measure whether simultaneous exposure to visuomotor and dynamic perturbations result in greater interference than either type alone. This will provide key

insight into how visual or dynamic sensorimotor information contribute to interference in bimanual movements.

Aim 2: To determine the contribution of reference frames on bimanual interference. I will examine whether dynamic perturbations, typically coordinated in a unilateral shoulder-centric reference frame, can be experimentally manipulated to be coordinated in a more global bilateral reference frame, thereby increasing observed interference. This will reveal how hierarchical reference frames contribute to bimanual coordination.

Aim 3: To determine the degree of interference and measure underlying brain dynamics, in individuals with cervical dystonia. Participants will perform a bimanual interference task while their brain activity is recorded with electroencephalography (EEG), prior to and following botulinum toxin treatment to mitigate dystonic postures. This will allow me to discern how the sensorimotor network governing bimanual movements is affected in cervical dystonia, and how treatment may affect the neural control underlying bimanual coordination.

The proposed studies will establish a better picture of sensorimotor control in healthy and impaired individuals. Aims 1 and 2 will provide insight into the mechanisms behind interference in bimanual coordination. Meanwhile, Aim 3 will develop a greater understanding of sensorimotor impairment in patients with cervical dystonia, a pathology that is known to affect processes of cortical inhibition and sensorimotor integration in non-symptomatic effectors. Together, these studies will provide valuable information that will advance our knowledge of the

sensorimotor network underlying bimanual control and has the potential to contribute to novel approaches used in the identification, diagnosis, and rehabilitation of movement disorders.

CHAPTER 2 – AIM 1: THE EFFECTS OF SIMULTANEOUS VISUOMOTOR AND DYNAMIC PERTURBATIONS ON INTERFERENCE BETWEEN THE HANDS

2.1 Introduction

For humans, bimanual actions comprise a significant part of everyday life. While the adult neuromotor system is usually capable of performing simple bimanual tasks without problems, more complicated movements, particularly those with spatial incongruences, can produce interference between the hands (Franz et al., 1991). Interference is a process by which the action of one hand can influence the action of the opposing hand. Interference during bimanual coordination has been well studied (Kagerer, 2016b; Obhi and Goodale, 2005; Semjen et al., 1995), and is thought to result from neural crosstalk between brain areas controlling bimanual movements. However, the specific domain of movement information (i.e., direction, force etc.) being shared between the hemispheres, and how these movement domains might interact in the context of interference, remains an open question.

It is possible to probe the function of different motor domains within the CNS by asking participants to adapt to domain-specific perturbations during movements. To probe visuomotor processes, the visual feedback received by a participant can be manipulated to introduce a discrepancy between the intended and observed movement consequences. To probe dynamic motor processes, the forces experienced during a movement can be manipulated to likewise provide unexpected dynamic feedback. Such perturbations require participants to modify internal models to minimize movement error introduced by the perturbation (Kawato, 1999; Wolpert et al., 1995a). When these perturbations are applied to one hand during bimanual reaches, interference in the opposing hand can be inferred to be due to sharing of motor

information and internal representations between hemisphere-hand systems in that specific movement domain (Kagerer, 2015a).

It has been shown previously that visuomotor perturbation of the right hand causes interference in the left hand (Kagerer, 2016; Kagerer, 2015; Desrochers et al., under review). However, recent evidence demonstrated that a dynamic perturbation does not produce substantial interference (Desrochers et al., 2017). While surprising, given that both perturbations theoretically require the formation of new internal models, this finding is supported by studies showing that learning of a dynamic perturbation in one hand neither interferes with nor facilitates learning of a separate dynamic perturbation in the opposing hand (Tcheang et al., 2007). Furthermore, different neural processes may be involved in the adaptation to visuomotor vs. dynamic perturbations, since one can be learned without simultaneously interfering with the other (Krakauer et al., 1999). Swinnen et al. (2001) also demonstrated that adding force constraints to a bimanual spatial interference task did not result in additional interference. Finally, Diedrichsen (2007) showed that when participants control individual cursors with each hand and reach to separate targets, a force perturbation in the right hand did not influence the trajectory of the left hand.

It appears, however, that dynamics are still pertinent to motor learning and interference paradigms. Recently, Brunfeldt and colleagues (in prep) have shown that during a bimanual interference task with a constant visuomotor perturbation, the presence of a force opposing the direction of the movement results in increased left-hand interference. Furthermore, the amount of interference increased with greater resistance in a dose-response fashion, such that more resistance force yielded greater interference. Additionally, unimanual studies have shown an interaction between visuomotor and dynamic perturbations within the sensorimotor system.

Franklin and colleagues (2012) demonstrated that while adapting to a dynamic perturbation, participants' motor responses to a visuomotor perturbation is upregulated compared to when they are not adapting to a dynamic perturbation. These findings suggest that the presence of task relevant dynamics may increase sensorimotor gain and upregulate responses to visuomotor perturbations. However, it is unknown whether the upregulated sensorimotor network in one hemisphere-hand system will increase interference in the opposing hand.

In Experiment 1, I examined how visuomotor, dynamic, and a combined visuomotor and dynamic perturbations in the right hand affected interference in the left, unperturbed hand. I hypothesized that if visuomotor and dynamic motor information are differentially shared between hemispheres, interference due to perturbations of similar magnitude will be observed at disparate levels. Additionally, if the motor system responds to dynamic and visuomotor perturbations synergistically, as suggested by Franklin and colleagues (2012), interference in the left hand due to a simultaneous dynamic and visuomotor perturbation of the right hand would be greater than interference during dynamic or visuomotor perturbation alone.

2.2 Methods

2.2.1 Participants

Sixty young adults between 18 and 30 years old were recruited to participate in the study. Participants were free of any history of cognitive or neurological impairment, had not sustained a concussion in the past year, and had normal or corrected-to-normal vision. All participants provided informed consent, and all procedures were approved by the Michigan State University Institutional Review Board.

2.2.2 Study design

Participants were randomly assigned to one of four groups (15 participants per group; Figure 1): no perturbation, visuomotor perturbation, dynamic perturbation, or combined perturbation (simultaneous dynamic + visuomotor; Table 2-1). Participants were cued to move two Kinarm robotic manipulanda (BKIN Technologies Inc., Kingston, Ontario, Canada) simultaneously from two home positions to two targets located 10 cm directly forward or backward from the home positions (90° or 270°). They were instructed to "reach straight, fast,

		Visuomotor Perturbation	
		RH Not Perturbed	RH Perturbed
Dynamic Perturbation	RH Not Perturbed	Control n = 15	Visuomotor Pert. n = 15
	RH Perturbed	Dynamic Pert. n = 15	Combined Pert. n = 15

Table 2-1: Design for Experiment 1. Participants received no perturbation (control), a 40º visual rotation (visuomotor perturbation), a 20 Nsm-1 velocity dependent force (dynamic perturbation), or both perturbations (combined perturbation) in their right hand

and accurately" from the home position to the target. Targets were randomly presented but were always in the same direction. After holding steady in the target position, participants were cued to return to the home positions. Hand position was represented by a cursor on a screen that occluded vision of the hands. Participants performed unperturbed reaches during two blocks of 30 trials. In the first "visual baseline" (VBL) block, hand feedback was displayed for both hands. Then, in the "kinesthetic baseline" (KBL) block, visual feedback was removed for the left hand, requiring participants to rely on kinesthetic control. Participants were instructed to continue reaching to the target with their invisible hand, stopping where they believed their hand was in the target. Then, in the "exposure" (EXP) block of 250 trials, participants were exposed

to the perturbation (Figure 2-1). For the visuomotor perturbation group, the cursor representing the right hand was rotated 45° clockwise about the home position, such that participants needed to adapt their right-hand movement trajectory -45° to hit the target. For the dynamic perturbation group, the participants encountered a force acting 90° perpendicular to the movement direction with a magnitude of 20 N per m/s of the reach velocity. The combined perturbation group received both perturbations simultaneously, such that the visual feedback was rotated 40° and a 20 N per m/s force perpendicular to the movement direction was applied. The control group experienced no perturbation in the right hand. Finally, in the "post-exposure" (Post-EXP) block of 50 trials, the perturbations for the three experimental groups were removed. During the EXP and Post-EXP blocks, left hand visual feedback remained off, leaving the left hand susceptible to interference.

To ensure that all participants achieved the same reaching velocity (since the dynamic perturbation is velocity dependent), participants were given feedback regarding the time elapsed from the initiation of the reach to the moment both hands were in the targets and had a between-

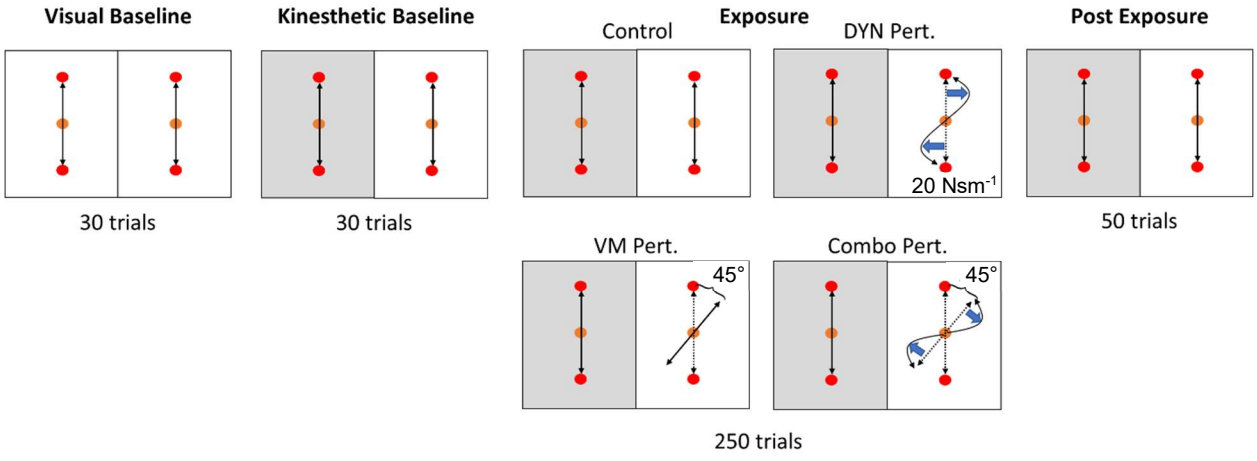

Figure 2-1: Experiment 1 task protocol. Boxes show the task design for the visual baseline, kinesthetic baseline, exposure, and post-exposure blocks. In the exposure blocks, the different groups received null (control), visuomotor, dynamic, or combined visuomotor and dynamic perturbations. Orange circles represent the home position, and red circles represent the targets. Shaded boxes indicate lack of visual feedback for the corresponding hand.

hand mean velocity under 3 cm/s. If the time elapsed during the reach was under 300 ms, a red rectangle was displayed in the center of the screen, indicating that the reach was too fast. If the time elapsed was over 450 ms, a blue rectangle was displayed, indicating that the reach was too slow. If the time elapsed was within the 300-450 ms window, a green rectangle was displayed, indicating that the participant successfully reached with the proper velocity

2.2.3 Kinematic and kinetic outcome measures

Movement onset and offset were semi-automatically identified using custom written Matlab scripts (Mathworks, Inc., Natick, MA), and onset/offset algorithms (Teasdale et al., 1993) that were subsequently checked for accuracy by trained experimenters. To evaluate motor performance in the right hand and interference in the left hand, kinematic error was assessed via four primary outcome measures at each trial. First, root mean square error (RMSE) was computed as a measure of movement straightness across the entirety of the reach. RMSE was calculated with reference to a straight line between the targets and normalized to movement length. RMSE represented the movement error across the entirety of the movement.

Next, initial directional error (IDE) was computed at the moment of peak tangential velocity as the angle between a vector from the home position to the position of the cursor and a vector from the home position to the target. IDE represented a measure of feed-forward or predictive error of the motor plan, since the moment of peak velocity occurs at a time before sensory information could be processed by the CNS.

Next, initial endpoint error (IEE) was computed at end of the initial ballistic movement, or the moment where the primary reach ends (i.e., before any subsequent corrective movements) as the angular deviation from the vector between the home target and the hand and the vector

between the home position and the target. The end of the initial ballistic movement was defined as the first moment after peak tangential velocity where the hand's velocity experienced a local minimum (i.e., the start of a secondary propulsive movement) or where the hand's velocity crossed zero (i.e., a reversal of direction). IEE was a moment during which afferent sensory information was beginning to be integrated into the sensorimotor system, and online error correction was beginning to occur (Seidler, 2006).

Finally, final endpoint error (FEE) was computed as the lateral displacement between the hand position and the target at the moment when all movement had ceased in the left hand. FEE occurred at a time in which the sensorimotor system had integrated all relevant feedback and corrected any perceived movement error.

Additionally, a virtual force channel was applied to the left hand in 20% of trials that constrained movement to a straight-line path to the target. Force sensors embedded in the Kinarm manipulanda endpoints measured the lateral force applied against the wall. During these trials, the force asserted against the channel wall was measured as an indicator of interference in the left hand. Each reaching movement was interpolated to 1000 data points, and these movement traces were averaged within early-EXP (first 30 trials of exposure) and late-EXP (last 30 trials of exposure). The force applied to the handles was assessed at three timepoints during the reach: the average point of peak velocity (where IDE was calculated), the average point of the end of the initial ballistic movement (where IEE was calculated), and at the end of the movement (where FEE was calculated).

2.2.4 Data processing and statistical analyses

Outcome measures for each dependent variable were baseline corrected to the KBL block by subtracting the mean for the KBL block from each trial before averaging. Kinematic and kinetic measures were evaluated in blocks that comprised the first and last 30 trials in the EXP period. A 2 (Block: Early, Late) x 4 (Group: Control, Dynamic Perturbation, Visuomotor Perturbation, Combined Perturbation) mixed-design ANOVA was used to assess adaptation in the right hand and interference in the left hand for each dependent measure. If present, violations of sphericity were adjusted with a Huynh-Feldt correction. Subsequent post-hoc analyses were performed by collapsing across non-significant independent variables, or by examining simple effects within blocks using one-way ANOVAs when significant main effects or interactions were present. Tukey HSD was used to determine differences between groups within each block. Statistical analyses were performed using custom written scripts in RStudio 1.2 software (RStudio Inc., Boston, MA) using the 'afex', 'ez', and base R packages.

2.3 Results

2.3.1 Kinematic measures

It was first necessary to confirm that the magnitude of the visuomotor and dynamic perturbations was roughly equivalent. An independent samples t-test was used to evaluate the kinematic error in the right hand in the first 10 trials of EXP in the visuomotor and dynamic perturbation groups, before participants were able to significantly adapt to the perturbation. No significant difference between these two groups was found for RMSE ($t(28) = -0.65$, $p = 0.52$) or

IEE ($t(28) = 0.22$, $p = 0.83$), though IDE was significant ($t(28) = 7.98$, $p < 0.001$)*. This showed that while the perturbations were not equivalent in magnitude at peak velocity, the net effect of the perturbation throughout the full movement trajectory was similar (as shown through IEE and RMSE). This difference was not surprising, since the maximum effect of the dynamic perturbation does not occur until the moment of peak velocity, whereas the visuomotor group experiences the full effect of the perturbation from the start of the movement. Thus, differences between the movements in the early, feed-forward components of the reach in the earliest moments of the EXP block would be expected. However, these findings show that overall, these perturbations were similar in magnitude.

Next, participants' adaptation to the respective perturbations was evaluated. For RMSE across the exposure block, there were significant main effects of group ($F(3, 56) = 85.16$, $p < 0.0001$), and block ($F(1, 56) = 463.50$, $p < 0.0001$) with RMSE decreasing across exposure in the perturbation groups as participants adapted to the perturbations. A significant interaction was also present ($F(3, 56) = 65.35$, $p < 0.0001$). Similar patterns of results were also found for IDE and IEDE (all $p < 0.0001$)†. As such, subsequent analyses of right-hand adaptation focused on RMSE as a measure of error across the full reach. Within each block of RMSE, one-way ANOVAs revealed significant main effects of group at early-EXP ($F(3, 56) = 84.44$, $p <0.0001$) and late-EXP ($F(3, 56) = 54.36$, $p < 0.01$). Tukey HSD tests within each block, with family-wise adjustment for four estimates, showed that all three perturbation groups had significantly greater RMSE than controls at early EXP (all $p < 0.01$). The combined perturbation group showed

* An independent samples t-test was not performed on FEE between the visuomotor and dynamic perturbation groups in the right hand, since participants were required to finish with their hand in the target. Thus, no differences would be expected in the right hand between these groups.

† ANOVAs were not performed on FEE between the visuomotor and dynamic perturbation groups in the right hand, since participants were required to finish with their hand in the target. Thus, no differences would be expected in the right hand between these groups.

significantly different RMSE than the dynamic and visuomotor perturbation groups ($p < 0.0001$), while the dynamic and visuomotor perturbation groups did not differ from one another. At late EXP, all groups again showed significantly greater RMSE than the control group ($p < 0.01$). Additionally, all perturbation groups were significantly different from one another ($p \leq 0.01$), with the greatest RMSE in the combined perturbation group, followed by the dynamic perturbation, visuomotor, and control groups.

How participants responded when the perturbation was removed was then investigated by performing a 2 (Late EXP vs. first 30 trials post-EXP) x 4 (Group) mixed-design ANOVA. If participants had adapted to the perturbation, a subsequent increase in error once the perturbation was removed (a phenomenon known as an "after-effect") was expected. As expected, a main effect of group showed that RMSE was significantly larger in the perturbation groups following removal of the perturbation ($F(3, 56) = 104.70$, $p < 0.0001$), and was greater in the post-EXP block ($F(1, 56) = 134.37$, $p < 0.0001$). A significant interaction was also present ($F(3, 56) = 22.89$, $p < 0.0001$). A similar pattern of findings was observed for both IDE and IEE (all $p <$

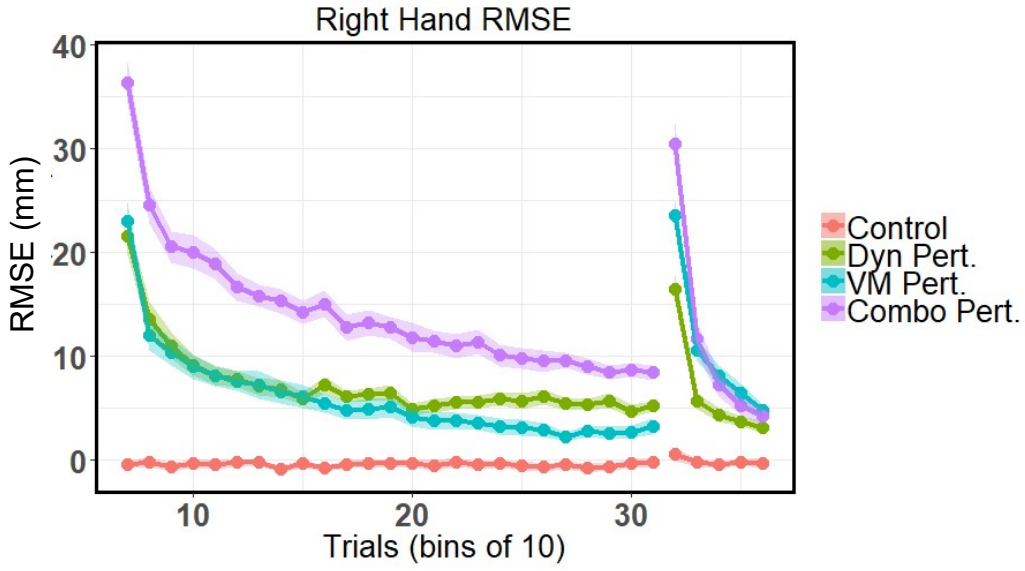

Figure 2-2: Right hand RMSE across the exposure and post-exposure blocks. Points represent means of 10 consecutive trials. Clouds denote standard error.

$0.01)^2$. Thus, remaining analyses again focused on RMSE. Analysis of simple effects at post-EXP revealed a significant main effect of group ($F(3, 56) = 68.38$, $p < 0.0001$), and subsequent Tukey HSD post-hoc tests showed that all groups were significantly different than each other ($p = 0.001$), with the exception of the difference in aftereffects between the combined and visuomotor perturbation groups ($p = 0.12$). The combined perturbation group showed the greatest aftereffects, followed by the visuomotor perturbation group and dynamic perturbation group. These demonstrate that all perturbation groups were able to successfully adapt to the perturbation and had significant aftereffects once the perturbation was removed (Figure 2-2).

Reaching behavior of the left, interfered-with hand was then investigated. For RMSE, the overall measure of left-hand reaching error, a mixed-effects ANOVA revealed significant main effects of group ($F(3, 56) = 18.33$, $p < 0.0001$) and block ($F(1, 56) = 25.09$, $p < 0.0001$), with RMSE decreasing across the exposure period, and a significant Group x Block interaction ($F(3, 56) = 3.62$, $p = 0.02$; Figure 2-3, A). Examination of the simple effects within each block showed significant group main effects in both early- and late-EXP (all $p < 0.0001$). In early-EXP, Tukey HSD showed that all perturbation groups were significantly different from the controls (all $p < 0.001$). However, after correcting for multiple comparisons, RMSE did not significantly differ between the perturbation groups, though the difference between the combined perturbation and dynamic perturbation groups approached significance ($p = 0.08$). In late-EXP, the combined and visuomotor perturbation groups showed significantly more RMSE than controls ($p < 0.01$), whereas the dynamic perturbation group did not show more interference than controls. Between perturbation groups, the difference between the combined and dynamic perturbation groups was significant ($p = 0.03$).

For IDE in the left hand, which measured feed-forward reaching error, the mixed-effects ANOVA revealed significant main effects of group ($F(3, 56) = 4.82$, $p < 0.01$) and block ($F(1, 56) = 22.71$, $p < 0.0001$). Interference increased over the course of exposure, mostly driven by the visuomotor and combined perturbation groups (Figure 2-3, B). The interaction term was also significant ($F(3, 56) = 6.90$, $p < 0.001$). Examination of simple effects showed that group differences were not significant in early-EXP ($F(3, 56) = 1.98$, $p = 0.13$), but achieved significance in late-EXP ($F(3, 56) = 7.14$, $p < 0.001$). In late-EXP, Tukey HSD showed that the visuomotor group had significantly greater interference than the controls ($p < 0.001$), and marginally greater interference than the dynamic perturbation group ($p = 0.08$). Additionally, the combined perturbation group had significantly more interference than controls ($p < 0.01$). All other contrasts were not significant after correcting for multiple comparisons.

Next, IEE in the left hand was evaluated, measuring interference at the end of the initial ballistic movement, before any secondary corrective movements occurred. The mixed-effects ANOVA revealed significant main effects of group ($F(3, 56) = 5.85$, $p < 0.01$) and block ($F(1, 56) = 19.16$, $p <0.0001$), with interference increasing over the course of the exposure block (Figure 2-3, C). The interaction term was also significant ($F(3, 56) = 5.07$, $p < 0.01$). Within each block, main effects of group were not significant in early-EXP ($F(3, 56) = 1.39$, $p = 0.25$), but achieved significance in late-EXP ($F(3, 56) = 9.35$, $p < 0.0001$). In late-EXP, the visuomotor perturbation ($p <0.001$) and combined perturbation ($p < 0.01$) groups developed significantly greater interference in their left hand than controls, while interference in the dynamic group was marginally different than controls ($p = 0.07$). Differences between the perturbation groups were not significant after correcting for multiple comparisons.

Finally, FEE was examined, measuring the lateral displacement of the left hand from the target once all movement had ceased, and incorporating feedback driven corrections at the movement endpoint. The mixed-effects ANOVA revealed main effects of group ($F(3, 56) = 5.08$, $p < 0.01$) and block ($F(1, 56) = 6.27$, $p = 0.02$), with FEE decreasing across exposure (Figure 2-3, D). The interaction term was not significant. In early-EXP, the main effect of group was significant ($F(3, 56) = 3.15$, $p = 0.03$), and remained significant at late-EXP ($F(3, 56) = 3.46$, $p = 0.02$). Tukey HSD revealed that that the combined perturbation group had greater deviation than the control group in early-EXP ($p = 0.06$) and in late-EXP ($p = 0.01$)[‡].

2.3.2 Kinetic measures

A virtual force channel constrained movement to a straight line between the targets pseudorandomly in 20% of trials. Across participants and trials, the average point of peak velocity was calculated as 23% of the whole movement, while the average point of the end of the initial ballistic movement was calculated as 69% of the movement. As such, lateral force applied against the channel wall by the left hand was evaluated between groups at early- and late-EXP at these points, as well as at the end of the movement.

At the average moment of peak velocity, early on in the reach, the mixed-design ANOVA revealed significant main effects of both group ($F(3, 56) = 4.55$, $p < 0.01$) and block ($F(1, 56) = 25.58$, $p < 0.0001$), with the lateral force increasing from early- to late-EXP. The interaction term was not significant. Examination of the simple effects in each phase showed a marginal difference between groups in early-EXP: $F(3, 56) = 2.38$, $p = 0.08$) and a significant group

[‡] See Appendix F for analysis of final endpoint directional error (FEDE), which measures the angle between a vector that runs from the home position to the target, and one that runs from the home position to the position of the hand at movement offset.

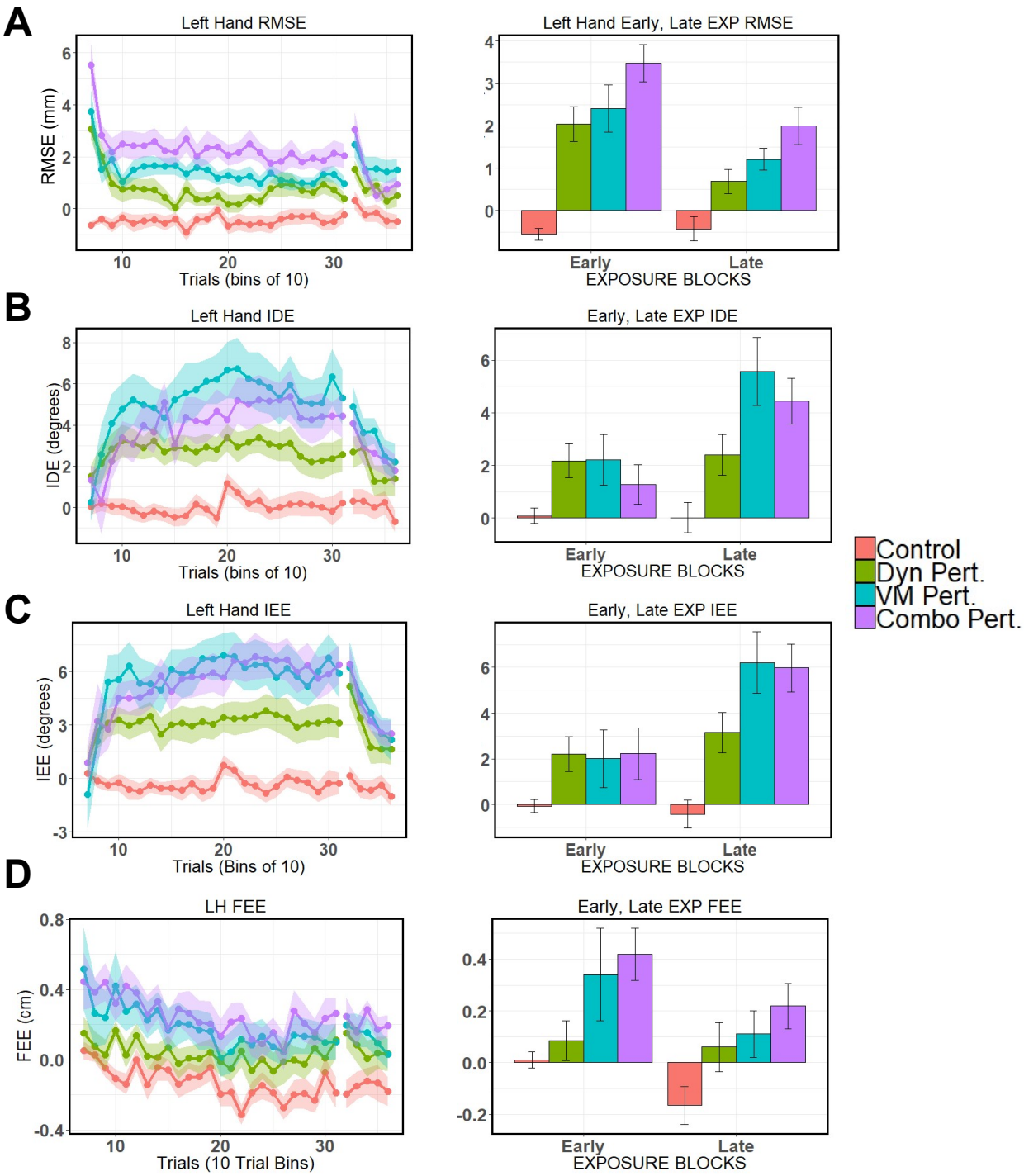

Figure 2-3: Left hand kinematic dependent variables. A: RMSE, B: IDE, C: IEE, & D: FEE. Means are baseline corrected to the KBL block. Left panels depict each respective measure in bins of 10 trials each across the exposure (trial bins 7-31) and post-exposure (trial bins 32-36) blocks. Clouds represent standard error (SE). Right panels depict mean ± SE for each respective measure at early-EXP (first 30 trials of EXP) and late-EXP (last 30 trials of EXP) for each group.

difference in late-EXP ($F(3, 56) = 4.22$, $p < 0.01$). In early- and late-EXP, post-hoc tests showed that the visuomotor perturbation group produced greater lateral force against the channel walls than controls (Early-EXP: $p = 0.06$; Late-EXP: $p < 0.01$). No other contrasts were not significant.

At the end of the initial ballistic movement, ANOVA revealed significant main effects of group ($F(3, 56) = 5.10$, $p < 0.01$) and block ($F(1, 56) = 8.19$, $p < 0.01$), driven by a decrease in lateral force generated by the visuomotor and combined perturbation groups across the exposure period. The interaction term was also significant ($F(3, 56) = 5.53$, $p < 0.01$). Examination of the simple effects showed a significant group main effect at early-EXP ($F(3, 56) = 7.17$, $p < 0.001$), with the combined perturbation ($p < 0.01$) and visuomotor perturbation ($p < 0.01$) generating greater lateral force than the control group. At late-EXP, the group effect was not significant, though visual inspection of the force produced by the left hand showed the dynamic, visuomotor, and combined perturbation groups each producing respectively more force against the channel (Figure 2-4).

Finally, at the end of the movement, ANOVA showed significant main effects of group ($F(3, 56) = 5.19$, $p < 0.01$) and block ($F(1, 56) = 11.95$, $p < 0.01$), and a significant interaction ($F(3, 56) = 4.46$, $p < 0.01$), again driven by decreasing lateral force generated by the combined and visuomotor perturbation groups across exposure. Examination of simple effects showed significant group differences in early-EXP ($F(3, 56) = 5.61$, $p < 0.01$) and late-EXP ($F(3, 56) = 3.45$, $p = 0.02$). The combined perturbation group generated significantly more force than controls in both early-EXP ($p < 0.01$) and late-EXP ($p = 0.01$), while the visuomotor group generated greater force than controls in early-EXP only ($p = 0.02$).

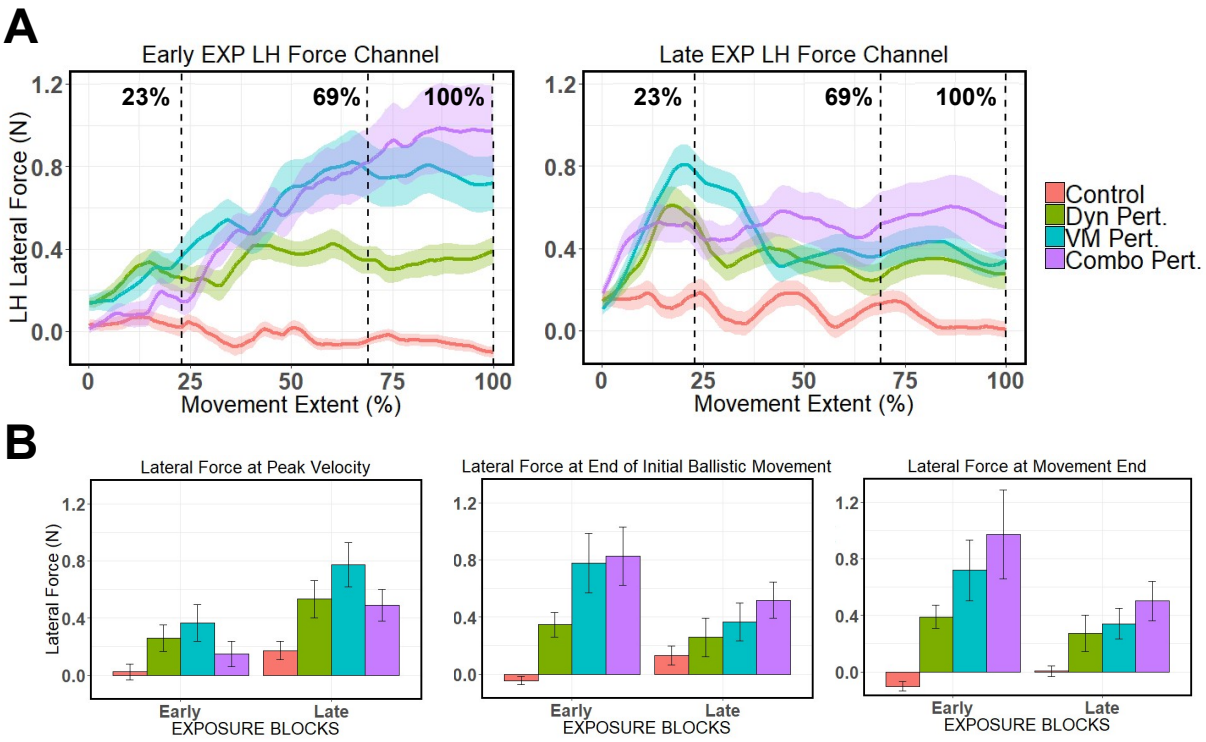

Figure 2-4: Left hand kinetic results during force channel trials. Top row (A) shows the force applied against the force channel throughout the movement in early-EXP (left panel), and late-EXP (right panel). Bottom row (B) depicts group mean±SE at the average point of peak velocity, end of the initial ballistic movement, and at the end of the movement (23%, 69%, and 100% of the way through the movement, respectively

2.4 Discussion

This first chapter examined interference in the left hand during perturbations of the right hand. Importantly, these perturbations targeted different domains of movement, probing either visuomotor or dynamic processes. First, based on prior experimental data (Desrochers et al., 2017) I predicted that interference would be greater in the visuomotor perturbation than the dynamic perturbation. Overall, this was observed our results; across several dependent measures, the group that received a visuomotor perturbation showed consistently greater interference than the group that received the dynamic perturbation. This was particularly

pronounced in measures that evaluated feed-forward and early feedback driven control (IDE and IEE, respectively), and later in the exposure phase, when participants had adapted to the perturbations. Of note, this effect was less pronounced in variables that incorporated feedback driven processes (FEE and RMSE).

Further, I hypothesized that interference would be greater when participants were exposed to both perturbations simultaneously. This hypothesis was not supported by the results. In measures of feed-forward driven processes, which assessed movement parameters prior to the integration of reaching feedback (IDE and, to a lesser extent, IEE), the group that received both perturbations tended to show roughly equivalent (and sometimes, even slightly less) interference compared to the group that received the visuomotor perturbation alone. This occurred despite the combined perturbation being larger in magnitude than either the visuomotor or dynamic perturbation. Interestingly, however, in measures that assessed feedback driven processes (FEE), it was the combined perturbation group that showed the greatest interference. This was also evident in the overall interference measure (RMSE), which likely captured interference during late corrective movements. This pattern of results was also evident from the kinetic measures – at the end of the exposure period, early on in a given movement (i.e., at peak velocity), it was the visuomotor group that showed the greatest interference, and late in the movement (i.e., at the end of the initial ballistic movement and end of the reach), it was the combined perturbation group that showed greater interference.

These findings are intriguing given the evidence that the sensorimotor system can selectively upregulate its sensitivity to certain types of feedback during learning. For example, participants respond more strongly to a rapid visuomotor perturbation when they are adapting to a dynamic perturbation, as opposed to when they are performing normal reaches (Franklin et al.,

2012). These responses can also be selectively tuned to different factors affecting the reach, showing that the nervous system can not only learn a specific perturbation, but also modulate secondary mechanisms to adapt to the environment at large (Dimitriou et al., 2011; Franklin et al., 2014, 2017). Gain-scaling of visuomotor responses also coincides with selective scaling of long-latency stretch reflexes (35-105 ms) during voluntary movements in the early phases of movement learning in unpredictable environments (Cluff and Scott, 2013; Pruszynski et al., 2011), suggesting that the nervous system can modulate both feed-forward and feedback control processes during learning. Selectively upregulating sensitivity of certain motor domains is thought to allow the sensorimotor system to rapidly correct for further perturbation during environmental uncertainty. Such uncertainty can arise from internal sources such as feedback delays or increased sensorimotor noise (van Beers, 2009; Churchland et al., 2006; Faisal et al., 2008), or from external sources such as limited feedback or an unpredictable environment (Cluff and Scott, 2013; Nashed et al., 2014). Importantly, the ability to scale responses in a context-dependent fashion is a key prediction of optimal feedback control theory (OFTC; (Diedrichsen et al., 2010; Franklin et al., 2017; Scott, 2004; Scott et al., 2015; Todorov, 2005; Todorov and Jordan, 2002)

Despite this compelling evidence of gain scaling in unimanual studies, this study suggests that sensorimotor upregulation may not be shared to the contralateral hemisphere-hand system in our task. If gain scaling parameters are shared via neural crosstalk, the presence of a dynamic perturbation with a visuomotor perturbation in the right hand should have amplified the effects of interference across effectors. Interestingly, research suggests feedback gain responses can be independently controlled by the sensorimotor system during bimanual movements. Brouwer and colleagues (2017) examined corrective responses when cursors were shifted in one hand or in

both hands during bimanual reaches and compared resulting motor responses to cursor shifts in unimanual reaches. They found a small but significant decrease in feedback gains during bimanual movements, but also found that the sensorimotor system could independently control responses in each hand. Furthermore, by asymmetrically manipulating the size of the targets to which participants reached, they found that gain responses could independently change within each effector in response to the corresponding target size. As such, each hand could modify its gain response with respect to its own goal. This response is in line with OFCT, which predicts that the sensorimotor system will constrain variability and motor responses if they affect the overall task goal (Diedrichsen, 2007).

In the current experiment, interference in the combined perturbation group may not be increased beyond that of the visuomotor perturbation alone because the left hand does not receive forces with similar characteristics of those in the right hand. In other words, since the left hand is not required to interact with a dynamic perturbation, that limb will not be susceptible to the effects of the perturbation in the right hand. This may be due to dynamic adaptation occurring in independent, intrinsic frames of reference specific to the adapting hand (Shadmehr and Mussa-Ivaldi, 1994). Thus, these results suggest that feedback gains within each hemisphere-hand system can be independently regulated in parallel with one another. Furthermore, these results suggest that upregulated feedback-gains in one hemisphere-hand system are not communicated between hemispheres via neural crosstalk. These findings may initially appear to be somewhat contradictory to recent findings in our lab that visuomotor interference scales with increased resistive forces experienced by participants during bimanual reaches (Brunfeldt et al., in prep). However, in that study, since both hands experienced the

same forces, feedback-gain upregulation likely occurred simultaneously in both hemisphere-hand systems, leading to increased interference due to the visuomotor perturbation with larger forces.

This study thus raises interesting questions as to why visuomotor perturbations produce greater interference than dynamic perturbations during bimanual movements. One could argue that a simple answer may lie in the fact that in the visuomotor perturbation task, the reaching movements of the hands are inherently asymmetrical, as the right hand must change its trajectory to hit the target. However, research from our lab suggests that the process of adapting to the visuomotor perturbation increases interference above and beyond asymmetrical reaches of the same magnitude with veridical hand feedback (Brunfeldt et al., in prep). Additionally, the time course of interference in our task, which increases gradually over the course of exposure, suggests that interference is tied to adaptive processes – if interference was strictly due to asymmetrical reaches alone, it would be present at its maximal magnitude as soon as the task required the participants to reach asymmetrically. Finally, a majority of participants anecdotally reported that they were unaware that their reaches were asymmetrical by the end of the exposure period in the visuomotor condition. Instead, they perceived their reaching movements as being symmetrical – yet, interference remained robust towards the end of exposure. Thus, the differences in interference between these two perturbation types is likely, at least in part, driven by adaptive neural processes tied to the visuomotor perturbation itself.

As such, the neural apparatus used to adapt to these perturbations may play an integral role in the observed differences in interference. Research suggests that adaptation to visuomotor and dynamic perturbations may recruit slightly different neural substrates, particularly in the cerebellum (Donchin et al., 2011; Rabe et al., 2009). Additionally, visuomotor control also requires a complex premotor-parietal network responsible for localizing targets in space and

planning movement trajectories, in addition to contribution of M1 (Culham, 2015; Desmurget et al., 1999; Kurata, 1994; Manuweera et al., 2018; Mutha et al., 2011; Tanaka et al., 2009; Werner et al., 2014). Critically, visuospatial information is also projected to both hemispheres, requiring posterior parietal cortices of both hemispheres to successfully plan spatial movements (Goodale and Milner, 1992). As such, is not surprising that severing portions of the corpus callosum that connect posterior parietal cortex preferentially abolishes spatial interference (Eliassen et al., 1999). It is possible that visuomotor processes hold a privileged status in being shared between hemispheres via the corpus callosum over dynamic processes. However, attempts to determine whether each type of adaptation elicits differential patterns of activity are equivocal, and dynamic adaptation may share several common brain areas with visuomotor perturbations, including some parietal and cerebellar loci (Diedrichsen et al., 2005; Ferrari-Toniolo et al., 2015; Graydon et al., 2005; Krakauer et al., 2004). Additionally, differences between neural responses to visuomotor and dynamic perturbations may also involve the manner by which engaged brain regions communicated throughout the acquisition of adaptive responses, which may differ between the two perturbation types (Tunik et al., 2007).

These perturbations are also functionally distinct. Visuomotor and dynamic perturbations do not interfere with one another (Krakauer et al., 1999; Tcheang et al., 2007), and may use different reference frames (Flanagan and Rao, 1995; Shadmehr and Mussa-Ivaldi, 1994). However, more recent evidence suggests that multiple reference frames may be utilized depending on the context of the movement (Berniker et al., 2013; Parmar et al., 2015). As such, it is possible that visuomotor perturbations affect reference frames that are shared between effectors, whereas dynamic perturbations utilize reference frames that are isolated in a single effector. If true, then manipulating reference frames to become more shared during dynamic

perturbations could increase interference. This hypothesis will be investigated in Chapter 3 of this dissertation.

This study is not without some limitations. First, the combined perturbation group consisted of perturbations that each forced participants to make counterclockwise corrective actions (either reach direction or force). It was anticipated that this would be the best method to elicit the largest amount of interference in left hand. However, previous research has suggested that some individuals may show mirrored patterns of interference, as opposed to interference in the same direction (Kagerer, 2015b). As such, these perturbations may have acted to inhibit the observed interference, each cancelling out left-hand effects from the other. We deem this unlikely, since all participants exhibited interference in the same direction as the perturbations. However, future studies could combine perturbations of different directions, and observe how left-hand interference is modulated as a result of these different directions. This could provide additional information into how visuomotor and dynamic perturbations interact within the sensorimotor system. Second, conditions in which asymmetrical reaches were performed without the presence of a visuomotor rotation were not included. This was because the main objective of the study was to see if concurrent dynamic adaptation upregulated the effects of the visuomotor perturbation. Further, research showing upregulation of visuomotor feedback gain also uses a shifted cursor to probe the visuomotor activity (Franklin et al., 2012). Given that the combined perturbation did not show increased interference, it is also unlikely that dynamic perturbation combined with non-adaptive asymmetrical reaching would have resulted in increased patterns of interference.

In summary, this chapter has shown that upregulation of sensorimotor feedback gains may not transfer between hemispheres. This was demonstrated by similar levels of left-hand

interference when participants received visuomotor perturbation in the right hand or simultaneous visuomotor and dynamic perturbations. Further, visuomotor and dynamic perturbations with similar magnitude show different levels of left-hand interference, with the visuomotor perturbation eliciting greater interference, particularly in feed forward measures during late exposure. This supports evidence that the sensorimotor system independently controls adaptation to dynamic perturbation separately for each hand. These findings are in line with the optimal feedback control theory for motor control.

CHAPTER 3 – AIM 2: MANIPULATION OF REFERENCE FRAMES IN A DYNAMIC PERTURBATION AND ITS EFFECT ON INTERFERENCE BETWEEN THE HANDS

3.1 Introduction

As demonstrated in Chapter 2, a visuomotor perturbation elicits greater interference than a dynamic perturbation. Given that interference is thought to occur due to a sharing of information between hemispheres, the question thus arises: what is occurring between the two perturbation types that modulates the way interference occurs in the sensorimotor system? Neural crosstalk and the sharing of internal models between hemispheres represents one possible explanation as to why greater interference is found during visuomotor as opposed to dynamic perturbations. However, it is possible that this pattern of results is instead due to the way in which each perturbation modulates reference frames. Reference frames, or the coordinate system by which we judge the spatial relationships between objects in our environment and ourselves, are an integral part of spatial perception. The search for the reference frames used by the sensorimotor system to learn and coordinate movement has been a predominant goal of research in the field motor control for several decades (Feldman and Levin, 1995; McIntyre et al., 1998; Souman et al., 2006; Stockinger et al., 2015; Vindras and Viviani, 1998).

Reference frames are important for coordinating motor actions, since we must integrate our perception of the spatial properties of our environment with our internal models to allow for successful movement (Culham, 2015; McIntyre et al., 1998; Wenderoth et al., 2006). Importantly, different stages of motor planning occur in different reference frames, and the CNS must compute transformations between reference frames at each stage in the motor planning process (Desmurget et al., 1998; Flanders et al., 1992). For example, visual perception must be

transferred from a retina-centered reference frame to a head-centered reference frame for object localization. Then, the head centered reference frame must be transformed into a joint-centered reference frames for functional coordination of muscles and joints (Andersen et al., 1985; Soechting and Flanders, 1992).

Early experimental work revealed several key differences in reference frame utilization between visuomotor and dynamic perturbations. Visuomotor perturbations seemed to be encoded using extrinsic, head-centered reference frames, while dynamic perturbations used intrinsic, joint-centered reference frames (Flanagan and Rao, 1995; Wolpert et al., 1995b). In a seminal study, Shadmehr and Mussa-Ivaldi (1994) asked participants to learn and adapt to a novel dynamic perturbation. They then asked participants to shift the position of their arm and examined null field after-effects of the adaptation. They found robust after-effects even when the position of the arm was shifted and interpreted this as evidence that the effects of the perturbation generalized across different effector states. Additionally, they investigated whether the orientation of the after-effects changed as the participants changed the position of their arm. They tested this by having participants learn the dynamic perturbation in one arm position, and then tested their performance during another dynamic perturbation in the second position. There, the orientation of the perturbation was modified so that it had the same relative extrinsic (i.e., Cartesian) orientation or the same relative intrinsic (i.e., join-centered) orientation. They found that participants were much better at reaching in the second orientation when the perturbation was of the same intrinsic orientation. These findings led to the notion that while visuomotor adaptation may occur at the egocentric-extrinsic level, dynamic adaptation occurs at the egocentric-intrinsic level.

Supporting the distinction between visuomotor and dynamic adaptation processes, dynamic and visuomotor perturbations were found not to disrupt one another across a period of offline procedural memory consolidation (this, importantly, is an entirely different process than between-hand interference discussed in Chapter 2; Krakauer et al., 1999). This suggested that visuomotor and dynamic perturbations actually occur in "different coordinate frames, and possibly, in different sensory modalities, using separate working-memory systems" (Krakauer et al., 1999). Furthermore, a bimanual interference task using cyclical star vs. line drawing suggests that interference effects observed in that study occurred in a radial egocentric reference frame (Swinnen et al., 2002).

Research also showed that a velocity-dependent dynamic perturbation was disrupted by a position-dependent dynamic perturbation (Bays et al., 2005). Further, dynamic perturbations did not transfer well when subjects were retested when the arm position was changed (Malfait et al., 2005). These findings were taken as evidence that dynamic perturbations were learned in intrinsic, joint-centered coordinate systems. However, other more recent evidence suggested that the distinction in reference frames utilized in each perturbation type is not as well defined as once thought. Instead, combinations of different reference frames may be utilized depending on different contexts. Tong et al. (2002) used visuomotor and dynamic perturbations that were both position dependent (as opposed to Krakauer (1999), who examined how a position-dependent visuomotor perturbation disrupted a velocity-dependent dynamic perturbation). They showed that when visuomotor and dynamic perturbations depended on the same parameter (i.e., position), one perturbation did in fact disrupt the other.

More recently, evidence has accumulated that the CNS executes movements through a mixture of intrinsic and extrinsic coordinate systems. Brayanov and colleagues (2012) used

multiple combinations of reaching directions and arm configurations during visuomotor learning to show that the motor system uses a gain-field composite of intrinsic and extrinsic representations. Later, others found a similar mixed coordinate system phenomenon during adaptation to a dynamic perturbation (Berniker et al., 2013), and failed to replicate the findings of Shadmehr & Mussa-Ivaldi (1994). Adaptation through multiple coordinate systems also generalized within and between effectors (Parmar et al., 2015). The orientation of the hand (or hand-held tool) in extrinsic coordinates, however, may hold a privileged place in facilitating motor learning in distinct coordinate workspaces (Yeo et al., 2015). Interestingly, the ability of the CNS to flexibly modulate gain between multiple coordinate system fits with predictions made by OFCT, which postulates that the CNS will selectively control parameters by optimizing feedback gains according to a particular cost function (Scott, 2004).

However, to date, no known studies have examined how reference frames might be shared from one hemisphere-hand system to the other. While some research has examined whether different dynamic perturbations in each hand can be learned during bimanual movements (Casadio et al., 2010), the question of how reference frames could be shared from an adapting hand to the opposing hand simultaneously reaching under normal parameters remains unexplored. Importantly, the manner in which reference frames are shared between hemisphere-hand systems could explain the findings from previous research in our lab (Desrochers et al., 2017; Chapter 2), in which interference was greater in the left hand when the right hand adapted to a visuomotor perturbation than to a dynamic perturbation. Interference may only occur when both hands are operating under similar coordinate structures. During visuomotor perturbations, the adapting reference frame is likely shared between hemispheres. Visual information regarding the nature of the perturbation will project to both primary visual cortices (V1) and

proceed through posterior parietal cortex for target localization and motor planning (Goodale and Milner, 1992). As such, the learning/adaptation in one hand may concurrently generalize to the opposing hand. Without visual feedback, as in our tasks, the non-adapting hand may thus begin to move in the new coordinate space, manifesting as interference between the hands. Conversely, during dynamic perturbations, feedback-gains through proprioceptive inputs in the adapting arm may drive the sensorimotor system to modify the coordinate systems for the joints controlling that arm alone, while the lack of any perturbation in the opposing limb would cause the motor system to ignore, or even inhibit, modification of the coordinate system of the opposing limb.

The goal of Experiment 2 was therefore to experimentally manipulate the sensorimotor system to share a dynamic perturbation across limbs during bimanual movements, thus increasing interference and reaching error in the opposing, non-adapting limb. This could occur if the sensorimotor system simultaneously shared the coordinate system of one limb with the other. If interference increased in the non-adapting limb, this would suggest that the coordinate structure of the adapting hemisphere-hand system was transferred to the opposing hemisphere-hand system, possibly through mechanisms of neural crosstalk.

3.2 Methods

3.2.1 Participants

Thirty young adults aged between 18 and 30 were recruited to participate in the study. Participants were free of any history of cognitive or neurological impairment, had not lost consciousness or sustained a concussion in the past year, and had normal or corrected to normal

vision. All participants provided informed consent, and all procedures were approved by the Michigan State University Institutional Review Board.

3.2.2 Study design

Participants were randomly assigned to one of two groups: a two-cursor dynamic perturbation group, or a shared-cursor dynamic perturbation group. The two-cursor group received the same experimental setup as the dynamic perturbation group in Chapter 2. In the shared-cursor group, participants controlled a single cursor located between the two hands. Movement of the cursor in the *y*-direction was controlled by both hands. Movement of the cursor in the *x*-direction was only controlled by the right hand (Figure 3-1). These control parameters were explicitly described and shown to the participant, so that they understood that both hands controlled movement in the *y*-direction, but only the right hand controlled the *x*-direction.

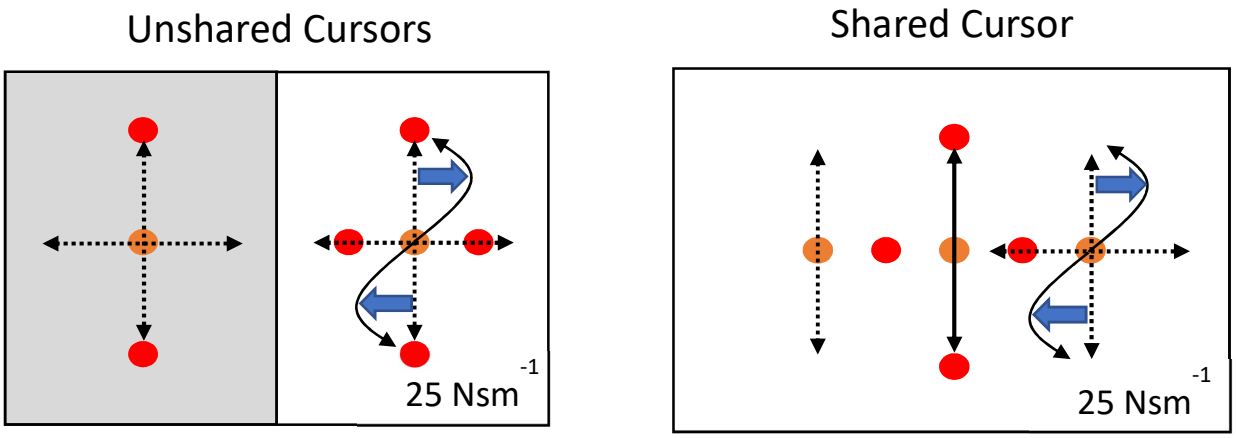

Figure 3-1: Task protocol for experiment 2. Boxes demonstrate the unshared and shared cursor conditions. Orange circles represent the home position, and red circles represent the targets. Shaded boxes in the unshared cursor condition indicate lack of visual feedback for the corresponding hand. In the shared cursor condition, only the central (shared) cursor was visible. Dotted lines represent the dimensions controlled by each hand for the cursor(s).

For the shared-cursor group, at the start of a given trial, three home positions were shown: one for the right hand, one for the left hand, and one for the shared cursor located directly between the left- and right- hand home positions. Throughout all blocks, cursors for the left and right hands were only displayed when they were in their home targets; otherwise, only the shared cursor remained visible. When cued, participants moved the cursor from the shared home position out to a single shared target. In the EXP block, a 25 N per m/s dynamic perturbation was applied to the right hand, while the left hand was observed for interference. Otherwise, all other task components were the same between the dual-cursor group and the shared-cursor group. Outcome measures for both hands were the same as in Chapter 2.

This paradigm is very similar to an excellent study by Diedrichsen (2007). In that study, Diedrichsen tested whether a dynamic perturbation in one hand caused the opposing hand to deviate according to predictions devised by optimal feedback control theory (OFCT). Diedrichsen hypothesized that if two hands contribute to a control scheme, any perturbation of one hand would result in an optimal correction by both hands. As predicted, he found that when one hand was perturbed with a dynamic perturbation, the contralateral hand deviated from a straight-ahead reaching pattern when the hands shared control of a cursor, but not when they controlled independent cursors. He also found that when cursor control was shared, both hands adapted to the perturbation together. Conversely, when the hands controlled independent cursors, only the perturbed hand adapted to the perturbation. The behavior of the hands occurred in accordance with OFCT, with both hands working together to minimize the distance of the shared cursor to a spatial target.

In the present study, a key distinction existed, in which only the *y*-direction was controlled between the hands, whereas the *x*-direction was controlled by the perturbed hand only.

Lateral movement of the left hand did not have any effect on the participants' ability to move the cursor to the target. If participants encoded movement in the *x*-direction as a task-irrelevant parameter, any movement in the *x*-direction by the non-perturbed hand would not have been result of an optimal compensatory action for the right-hand perturbation. Instead, if lateral movement occurred in the non-perturbed hand, this would have suggested that the response to the perturbation became shared in coordinate-system space, and that the action of the perturbed hand was interfering with the action of the non-perturbed hand. Thus, instead of optimally controlling for the position of the cursor, the sensorimotor system in the current task might have optimally controlled for the utilization of the coordinate system between hands. If lateral deviation of the left hand occurred, the present study would extend the findings of Diedrichsen (2007).

It remained possible that participants could have interpreted the action of the single cursor as being shared in both the *x*- and *y*-dimensions, even though only the *y*-dimension was shared. This would be a key confound and would lead to deviation of the non-perturbed hand due to mistaken compensation for shared *x*-dimension control of the cursor, in effect replicating Diedrichsen (2007). As such, participants were explicitly informed about the nature of the control parameters of the central cursor in this task. Additionally, to confirm that participants did not mistakenly think that they controlled lateral movement of the cursor with both hands, lateral probe trials were introduced in 10% of trials. In these probe trials, for the shared cursor group, a target appeared 4.25 cm directly to the left or right of the shared home position. Likewise, for the dual cursor group, a target appeared 4.25 cm to the left or right of the right-hand home position. Participants were asked to move into that target in the same manner as they reached out to the main targets. If participants correctly understood that only action of the right-

hand controlled lateral movement of the target, they would have moved only the right hand laterally to shift the cursor into the target, keeping the left hand stable.

3.2.3 Data processing and statistical analyses

As in Chapter 2, outcome measures for each dependent variable were baseline corrected to the KBL block by subtracting the mean for the KBL block from each trial before averaging. Kinematic and kinetic measures were evaluated in blocks that comprised the first and last 30 trials in the EXP period. A 2 (Block: Early, Late) x 2 (Group: Dual-cursor vs. Shared-cursor) mixed-design ANOVA was used to assess adaptation in the right hand and interference in the left hand for each dependent measure. If present, violations of sphericity were adjusted with a Huynh-Feldt correction. Subsequent post-hoc analyses were performed by collapsing across non-significant independent variables, or by examining simple effects within blocks using one-way ANOVAs when significant main effects or interactions were present. Independent-samples t-tests were used determine differences between groups within each block. Statistical analyses were performed using custom written scripts in RStudio 1.2 software (RStudio Inc., Boston, MA) using the 'afex', 'ez', and base R packages. Data visualization was also performed in R using the 'ggplot2' package.

3.3 Results

3.3.1 Kinematic measures

The probe trials were examined first, where each participant was asked to move the cursor to a laterally positioned target. Participants in the shared-cursor group should have understood that the left hand would not impart any influence on the lateral movement of the

cursor and moved only the right hand to shift the cursor into the lateral target. In the dual-cursor group, participants were cued to move only their right hand, while the left hand was asked to remain in the home position. As such, the difference in the movement length of the left hand between groups during probe trials in the exposure period was evaluated. An independent samples t-test showed that the difference in left-hand movement length approached significance ($t(28) = -1.77$, $p = 0.09$), with the shared-cursor group actually showing less left-hand movement (M = 0.98 cm, SE = 0.14) than the dual-cursor group (M = 1.33 cm, SE = 0.14; Figure 3-2).

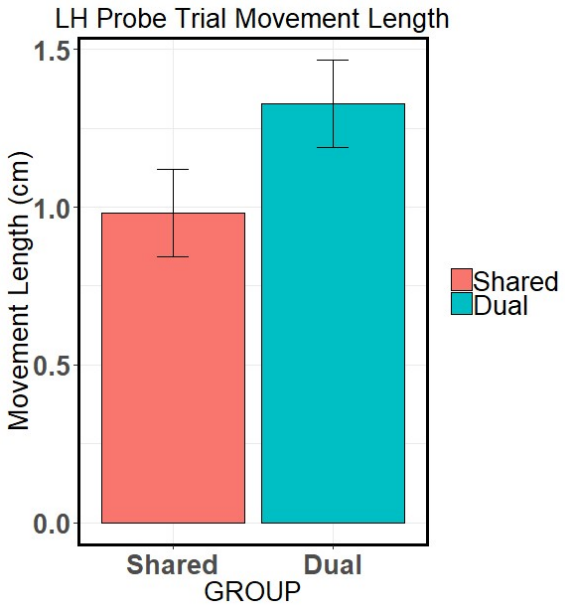

Figure 3-2: Left hand movement length during probe trials. Bars and whiskers represent mean ± SE.

With such little movement (approx. 1 cm in both groups), it was determined that the shared-cursor group successfully understood that the left hand did not influence the lateral movement of the cursor. Thus, any findings showing lateral movement of the left hand as a result of the perturbation could be determined to be the effect of interference between hands.

The right hand's adaptation to the perturbation was then examined (Figure 3-3). In RMSE, the ANOVA revealed a significant main effect of block ($F(1, 28) = 123.01$, $p < 0.0001$),

showing that participants were able to learn to move straighter over the course of the exposure period. The group main effect and Group x Block interaction were not significant, indicating that both groups adapted similarly to the perturbation. Similar effects were found for IDE and IEE ($p < 0.0001$). Examining the last 30 trials of EXP to the first 30 trials of Post-EXP, the main effect of block was again highly significant ($F(1, 28) = 98.71$, $p < 0.0001$), showing that both groups had large aftereffects. Neither the main effect of group nor the interaction were significant. IDE and IEE showed similar patterns of results.

Interference was then investigated in the left hand. For RMSE (Figure 3-4, A), the main effect of block in the left hand was significant ($F(1, 28) = 27.41$, $p < 0.0001$), but the main effect of group was not ($F(1, 28) = 0.08$, $p = 0.77$), nor was the Group x Block interaction ($F(1, 28) = 0.00$, $p = 0.99$). Collapsing across the group term, participants' RMSE decreased significantly ($t(29) = 5.33$, $p < 0.0001$), showing that as the right hand adapted to the perturbation, RMSE in the left hand decreased for both groups.

For IDE (Figure 3-4, B), the main effect of group was significant ($F(1, 28) = 5.06$, $p = 0.03$). The main effect of block was not significant ($F(1, 28) = 1.90$, $p = 0.18$), nor was the

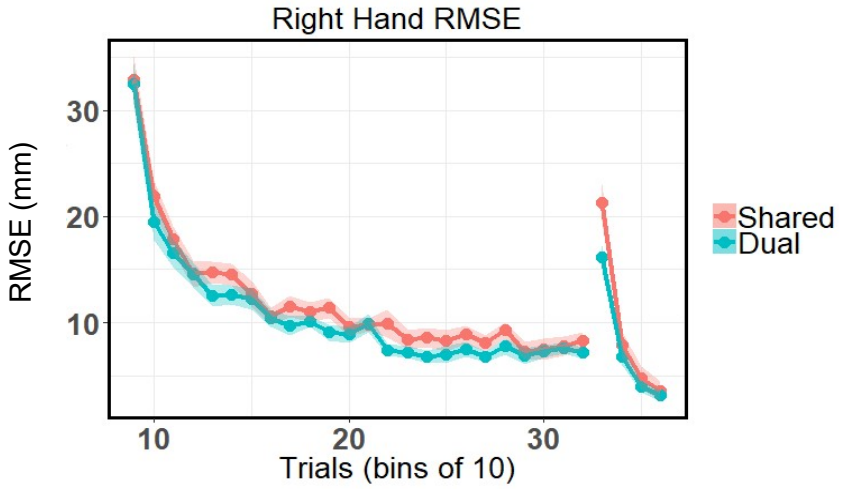

Figure 3-3: Right hand RMSE across the exposure and post-exposure blocks. Points represent means of 10 consecutive trials. Clouds denote standard error.

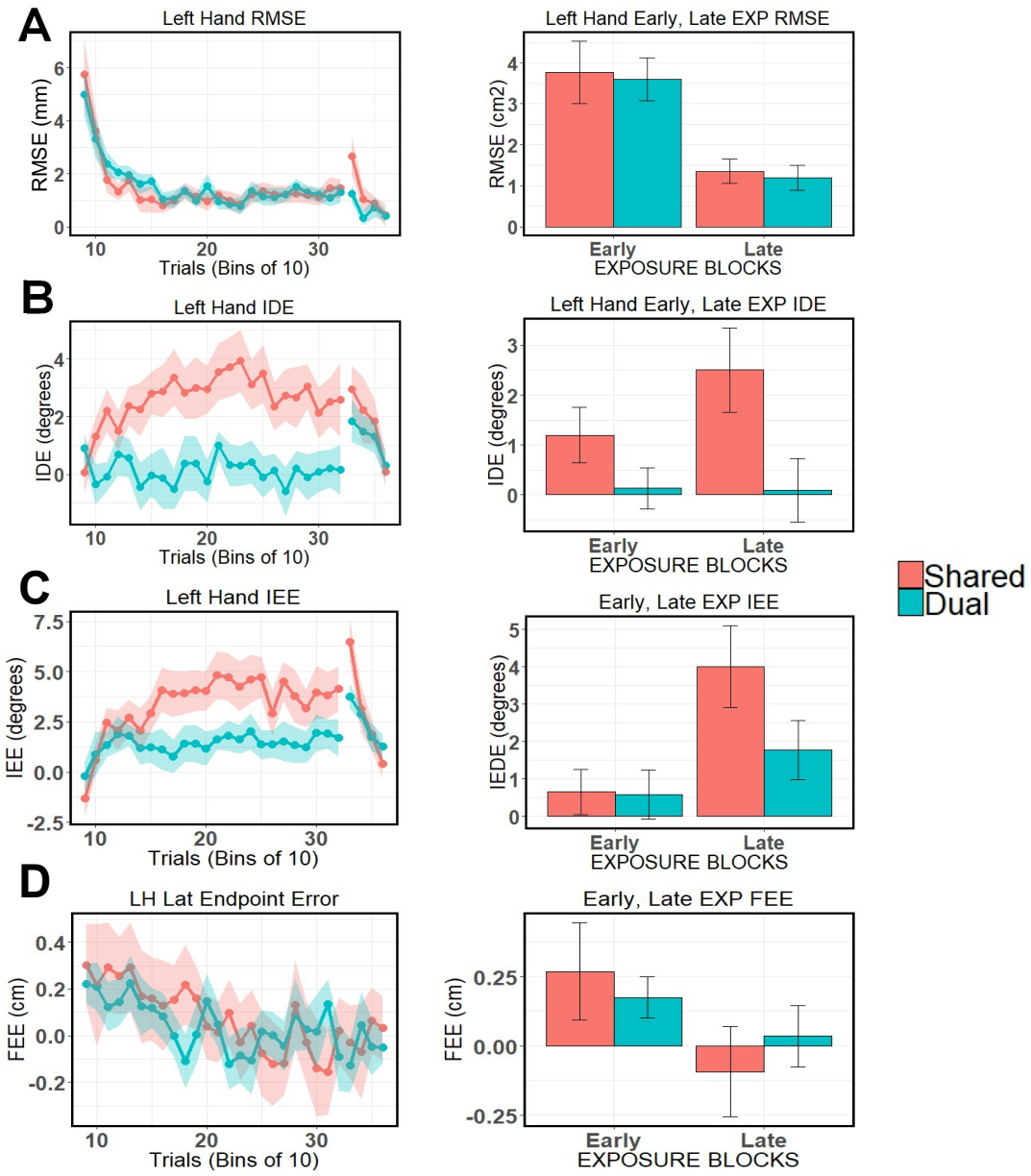

Figure 3-4: Left hand kinematic dependent variables. A: RMSE, B: IDE, C: IEE, & D: FEE. Left panels depict each respective measure in bins of 10 trials each across the EXP (trial bins 9-32) and post-EXP (trial bins 33-36) blocks. Clouds represent standard error (SE). Right panels depict mean ± SE for each respective measure at early-EXP (first 30 trials of EXP) and late-EXP (last 30 trials of EXP) for each group.

interaction ($F(1, 28) = 2.14$, $p = 0.16$). At early-EXP, there was no significant difference between groups ($t(28) = 1.54$, $p = 0.13$), however, at late-EXP, the difference between between groups was significant ($t(28) = 2.26$, $p = 0.03$), with greater IDE in the shared-cursor group.

Interference at the end of the initial ballistic movement was then examined through IEE (Figure 3-4, C). The main effect of group was not significant ($F(1, 28) = 1.55$, $p = 0.22$), though the main effect of block was significant ($F(1, 28) = 11.49$, $p < 0.01$), with both groups increasing IEE over the course of the exposure period. The interaction was also not significant ($F(1, 28) = 2.59$, $p = 0.12$).

For both IDE and IEE, visual inspection of these variables over the course of the exposure period suggested that interference in these measures seemed to peak in the middle of the exposure period. As such, an *a posteriori* t-test examined group differences in these measures in a block of 30 trials where this peak occurred (trials 201-230). This showed that the shared-cursor group had significantly greater interference than the dual-cursor group in both IDE ($t(28) = 2.86$, $p < 0.01$) and IEE ($t(28) = 2.26$, $p = 0.03$) in this mid point of the exposure period.

Finally, FEE was examined (Figure 3-4, D), measuring interference at the end of the movement. Here, the main effect of block was significant ($F(1, 28) = 4.67$, $p = 0.04$), with FEE decreasing across the exposure period in both groups. The main effect of group ($F(1, 28) = 0.01$, $p = 0.91$) and the interaction ($F(1, 28) = 0.91$, $p = 0.35$) were not significant[§].

Taken together, these results show that more interference occurred in the left hand of the shared-cursor group, in measures that incorporated feed-forward movement control. This suggests that the coordinate system in which the perturbation occurred was shared between both hands in the shared-cursor group.

[§] See Appendix G for analysis of final endpoint directional error (FEDE), which measures the angle between a vector that runs from the home position to the target, and one that runs from the home position to the position of the hand at movement offset.

3.3.2 Kinetic measures

As in Chapter 2, a virtual force channel constrained movement to a straight line between the targets in a pseudorandom 20% of trials in the left hand. In this experiment, across participants and trials, the average point of peak velocity was calculated as 24% of the whole movement, while the average point of the end of the initial ballistic movement was calculated as 68% of the movement. As such, lateral force applied against the channel wall was evaluated between groups at early- and late-EXP at these points, as well as at the end of the movement.

At the average moment of peak velocity, early on in the reach, the mixed-design ANOVA showed no differences between group ($F(1, 28) = 0.02$, $p = 0.88$) or block, ($F(1, 28) = 1.89$, $p = 0.18$). The interaction was also not significant ($F(1, 28) = 0.90$, $p = 0.35$). Thus, both groups showed similar force applied against the force channel at peak velocity in both early and late-EXP (Figure 3-5). However, visual inspection of the force applied throughout the extent of the movement in Late-EXP showed a notable peak in force production in the shared-cursor group, at 19% of the way through the movement (5% earlier than the average point of peak velocity). As such, an *a posteriori* mixed-effects ANOVA was performed at this point. Here, a significant Group x Block interaction was present ($F(1, 28) = 6.47$, $p = 0.02$). The groups showed no difference in force applied against the force channel in early-EXP ($t(28) = -0.916$, $p = 0.37$), but at late-EXP, the shared-cursor group produced greater force than the dual-cursor group at a level that approached significance ($t(28) = 1.83$, $p = 0.08$).

At the end of the initial ballistic movement, ANOVA revealed significant a main effect of group ($F(1, 28) = 4.80$, $p = 0.04$), driven by lower force produced in the shared-cursor group than the dual-cursor group. A main effect of block ($F(1, 28) = 4.03$, $p = 0.05$) was also present, with both groups showing decreasing force produced at this point from early- to late-EXP.

However, post-hoc t-tests did not reveal significant differences between groups at early- or late-EXP ($p > 0.10$).

Finally, at the end of the movement, ANOVA showed significant main effects of group ($F(1, 28) = 7.81$, $p < 0.01$), with the shared-cursor group producing lower force than the dual-cursor group in both early- and late-EXP. The main effect of block was also significant ($F(1, 28) = 5.82$, $p = 0.02$), driven by decreased force produced in both groups from early- to late-EXP. The interaction term did was not significant ($F(1, 28) = 0.00$, $p = 0.95$). Post-hoc t-tests revealed that the shared-cursor group produced significantly less force at both early-EXP ($t(28) = -2.08$, $p = 0.05$) and late-EXP ($t(28) = -2.23$), $p = 0.03$).

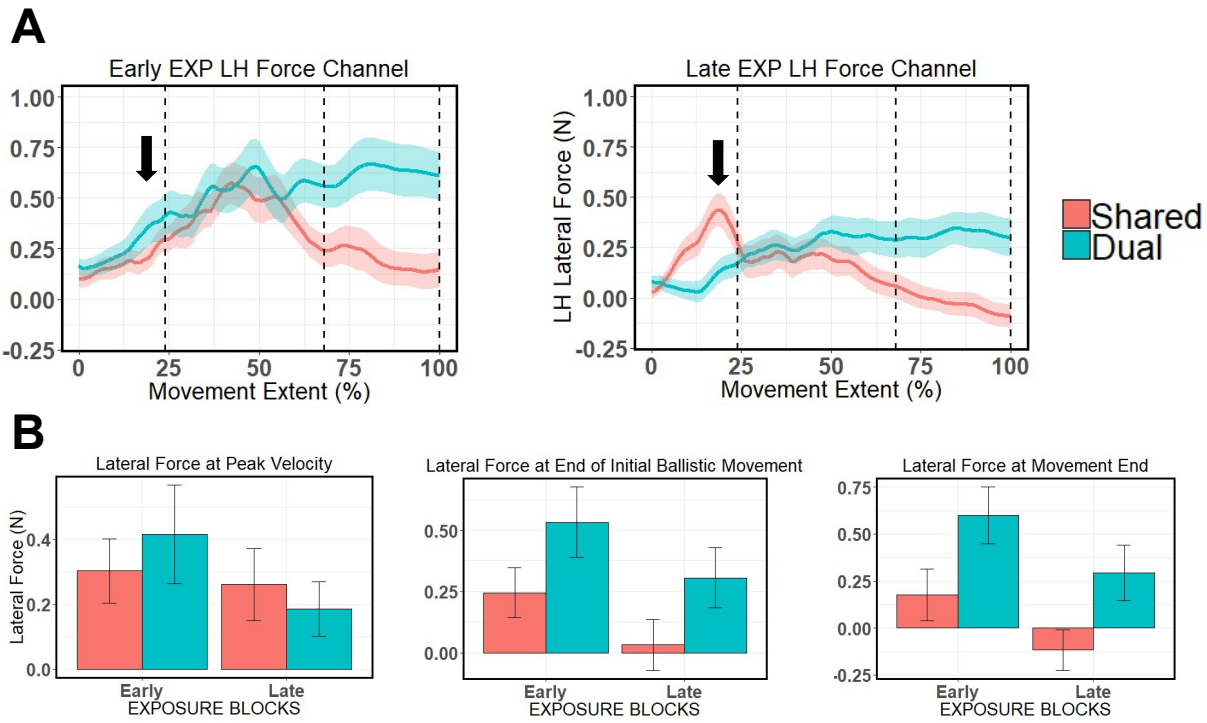

Figure 3-5: Left hand kinetic results during force channel trials for Chapter 3. Top row (A) shows the force applied against the force channel throughout the movement in early-EXP (left panel), and late-EXP (right panel). Dashed lines depict locations of peak velocity, end of the initial ballistic movements, and movement end (24%, 68%, and 100% of the way through the movement, respectively). Bottom row (B) depicts mean±SE at each of these locations. The arrow in the top panel shows the location of the *a posteriori* analysis due to the observed peak in the shared-cursor group in late-EXP.

3.4 Discussion

In this experiment, I investigated whether manipulating the controlled reference frame would increase interference during adaptation to a dynamic perturbation in the right hand. This manipulation was performed by asking participants to make two-handed reaching movements while controlling either a cursor with its control parameters shared between both hands, or by controlling independent cursors. By controlling a cursor that was shared between both hands, I hypothesized that this would cause participants to plan their movements in a coordinate space shared by both limbs, thereby increasing the interfering-effect of adaptation in one limb on the other. I found that in kinematic measures incorporating feed-forward control (IDE and IEE), interference was increased in the left hand in the group that received this manipulation. This suggests that, in a dynamic perturbation task, sharing the perturbed reference frame from one limb to the other resulted in increased interference between the limbs.

In a previous study, Diedrichsen (2007) applied a similar manipulation where participants were asked to make bimanual reaching movements under shared-cursor or dual-cursor conditions. In this experiment, the shared cursor's position was controlled in both the x- and y-directions by both hands. Diedrichsen hypothesized that since the goal of the movement was to achieve an accurate target reach, OFCT would predict that corrective actions would minimize some cost parameter – in this case, the distance of the cursor from the target. Importantly, only control parameters associated with this cost parameter would be controlled. Those not associated with the cost parameter would be left uncontrolled as the sensorimotor system flexibly modulates only those parameters which affect task success. As such, Diedrichsen found that in the shared-cursor condition, since control of the cursor was shared by both hands, both hands would respond to correct the movement of the cursor as one hand experienced a perturbation.

Conversely, during the dual-cursor condition, Diedrichsen found that only the perturbed hand would respond to the perturbation, since it was the only effector in which the cost parameter could be controlled. The study further showed that this behavior could be accurately modeled, in line with OFCT. Thus, he showed that the sensorimotor system will optimally control certain control parameters in a task- and goal-oriented manner.

In the present study, the shared-cursor group's control over the central cursor was builds on the manipulation introduced in the Diedrichsen (2007) study. Instead of the cursor being shared in both dimensions, control of the cursor in this study was only shared in the y-dimension. Meanwhile, control of the x-dimension, in which the perturbation occurred, was controlled only by the adapting hand. As such, movement parameters relevant to adaptation to the perturbation were controlled only by the adapting hand. The sensorimotor system readily detects and controls parameters relevant to a given task, while ignoring those that are irrelevant to the task or its goals (Dimitriou et al., 2013; Ranganathan et al., 2018; Scholz et al., 2000, 2001). Importantly, this capability is an integral component of theories of voluntary motor control including UCM and OFCT (Diedrichsen et al., 2010; Latash, 2012; Scholz and Schöner, 2014; Scott, 2004; Todorov and Jordan, 2002). In this study, since the dynamic perturbation was limited to the x-direction in the right hand, elevated interference in the left hand could not be explained by the motor system bilaterally controlling a task-relevant movement. Instead, I propose that since components of the cursor's control were still shared bilaterally (i.e., y-direction of the cursor) despite being irrelevant to the lateral position of the cursor, the sensorimotor system planned the movement in a coordinate system that was shared between hemisphere-hand systems, thus resulting in the observed interference.

Recent research suggests that the sensorimotor system utilizes a mixture of available coordinate systems during the planning of movements (i.e., intrinsic, extrinsic, object-centered). The gains of these coordinate systems can flexibly change depending on the movement context and task goals, in line with OFCT (Berniker et al., 2013; Brayanov et al., 2012; Franklin et al., 2016; Yeo et al., 2015). Control of bimanual movements when each limb has its own goals, as in the dual-cursor condition, may require the sensorimotor system to coordinate movement in a more intrinsic, joint centered coordinate system that operates independently for each limb. Thus, interference is reduced between limbs. However, if each hand is sharing a common coordinate system, due to the sensorimotor system flexibly modulating the reference frame across hemisphere-hand systems (as in the shared-cursor condition) perturbation of one hand would result in compensatory action of the opposing limb. Importantly, this may occur even if the control structure of the task is not directly relevant to the direction of the perturbation. Thus, this research extends the findings of Diedrichsen (2007), suggesting that the sensorimotor system will produce interference not just on the basis of task relevance, but also on the basis of a flexibly shared coordinate system.

How coordinate frames are shared between hemisphere-hand systems is an open question. One possibility is that the CNS independently controls the reference frame in each hemisphere. More likely, the CNS will transmit the representation of the hands between hemispheres using mechanisms of neural crosstalk. Interestingly, several studies have shown interference and neural crosstalk is dependent on the constraints on context of the task (Franz and McCormick, 2010; Franz et al., 2001; Kantak et al., 2016a; Shea et al., 2016). In these studies, though each hand must perform different movements, the ability to coordinate the movements well is dependent on the perception of the movements being unified. It is likely that

this “unified conceptualization” requires participants to encode and plan these movements in a shared coordinate system that, in this case, reduces interference between the hands.

Interestingly, measures incorporating feedback motor control processes (i.e., FEE) and overall interference (RMSE) did not show a difference between groups. This may suggest that, in this task, it was primarily feed-forward, planning components of a movement that were communicated between hemispheres. End-state control may be independently coordinated within the sensorimotor system once feedback is accessible to each hemisphere-hand system. Lack of differences between groups at the end of movement also represents a departure from findings of Diedrichsen (2007), who observed differences in end-state positions between dual- and shared-cursor groups. This suggests that end-state parameters of motor control may be less sensitive to changing coordinate systems and rely on optimization of task-relevant goals.

This study is not without drawbacks. Directional errors in the left hand, though statistically significant, were still quite small in magnitude. However, these errors were still larger than those seen in Diedrichsen (2007). This speaks to the robust ability of the sensorimotor system to coordinate independent movements of the hands. Additionally, though sharing of a coordinate system is a plausible explanation for increased interference during bimanual movements in the shared-cursor condition, whether the coordinate system was truly shared between hemispheres was not directly tested. Additionally, while shared control of the cursor was assumed to require a more extrinsic, object-centered coordinate system, the degree to which the coordinate system might have changed its point of reference (i.e., changing from intrinsic to extrinsic) was not directly assessed in this study. Future experiments could directly measure how specific reference frames might be shared between hands during joint control of an object by asking participants to generalize adaptation between hands during shared-cursor vs.

dual cursor movements. Alternatively, changing joint configurations of one or both arms during shared-cursor movements could assess how intrinsic representations are communicated between hemisphere-hand systems.

In summary, this experiment has shown that shared control of a cursor during dynamic perturbation of one hand may result in interference in the opposing hand in feed-forward components of a movement. This interference occurred despite the perturbation-relevant control of the cursor being contained only in one hand. Interference was absent during dynamic perturbation of one hand when each hand moves to independent targets. This may have been due to a coordinate system that became shared between hemisphere-hand systems when both hands contributed to the control of an object.

CHAPTER 4 – AIM 3: BIMANUAL INTERFERENCE AND UNDERLYING BRAIN DYNAMICS IN CERVICAL DYSTONIA

4.1 Introduction

Dystonia is a complex movement disorder characterized by irregular and involuntary movement patterns. These often involve co-contractions of muscles that lead to twisted postures, with or without a tremulous component (Albanese et al., 2013). Contractions can be sustained or intermittent and can affect a wide range of muscles and joints. Due to its complex etiology, dystonia can present focally (e.g., cervical dystonia, focal hand dystonia), multifocally, segmentally, or be generalized throughout the body. Such varying presentations make dystonia difficult to diagnose and treat.

In cervical dystonia (CD), the most comment subtype of dystonia in adults, involuntary contractions of the neck muscles cause abnormal twisting and posturing of the head. In addition to impaired control of the head movements (Anastasopoulos et al., 2014; De Pauw et al., 2017; Münchau et al., 2001; Shaikh et al., 2015), CD patients also display deficits in control of their upper limbs. Inzelberg and colleagues (1995) found that patients with dystonia in the neck, arms, and upper body had asymmetrical velocity profiles and were less accurate during simple reaching movements. The authors also noted that in dystonia patients, the feedback-controlled decelerating phase of reaching was more disturbed, as opposed to the feed-forward accelerating phase of movement. This effect was exacerbated by restricting visual feedback, forcing the subjects to rely on kinesthetic feedback only. In the decelerating phase, the motor system must integrate sensory and proprioceptive information into the internal model for movement, adjusting for any state-dependent error. Thus, the authors suggested that in addition to errors caused by

involuntary muscle contractions, central processing systems regulating reaching, particularly those involving integration of sensory information with the motor plan, were impaired. This is corroborated by other work in CD patients that shows atypical velocity profiles and error control, as well as increased variability, decreased velocity, prolonged movement duration, and increased co-contraction during their upper limb movements (Berardelli et al., 1996; van der Kamp et al., 1989; Katschnig-Winter et al., 2014).

Cervical dystonia patients also demonstrate deficits in other sensorimotor domains beyond movements themselves. For example, timing, thought to be highly dependent on the cerebellum, has been found to be impaired in dystonic individuals (Filip et al., 2013, 2017). CD patients also have impaired sensory capabilities, including spatio-tactile and temporal discrimination (Antelmi et al., 2016; Kägi et al., 2013; Molloy et al., 2003; Tinazzi et al., 2004). Spatial perception is also impaired in CD patients, who show inability to mentally rotate objects in space (Fiorio et al., 2007), difficulty discerning directions with reference to body orientation (Müller et al., 2004), and spatial memory deficits (Ploner et al., 2005). These findings also suggest that dystonia patients have disturbed egocentric reference frame perception and may rely more on coordinate systems anchored to the trunk or use more allocentric spatial representations. Finally, there exists a great deal of evidence that inhibitory networks are dysfunctional in dystonia (Hallett, 2011; Ridding et al., 1995). For example, Stinear and Byblow (2004) found abnormal intrahemispheric inhibition measured via TMS during a finger flexion task. Taken together, these findings demonstrate sensorimotor impairments that go beyond abnormal dystonic movements, and which influence the control of body segments not affected by dystonic contractions.

Another common clinical observation is the presence of motor overflow and mirror movements in dystonia. These are typically observed in focal hand dystonia (FHD), but also in other dystonia subtypes. In these movements, action of one part of the body causes involuntary actions in another effector (Cox et al., 2012; Sitburana and Jankovic, 2008; Sitburana et al., 2009). Mirror movements are thought to be the result of dysfunctional intra- and intercortical inhibition. A study using TMS showed that interhemispheric inhibition was substantially decreased in patients with mirror movements compared to controls and patients who did not display mirror movements (Sattler et al., 2013). Furthermore, weaker interhemispheric inhibition was correlated with disease severity. Similar effects were found during tasks of force production in the hands (Beck et al., 2009). Others have shown abnormal motor unit synchronization and motor overflow of a central command using intramuscular EMG in patients with FHD (Farmer et al., 1998). Taken together, atypical intra- and interhemispheric inhibition may allow for increased sharing of motor information for movement between the hemispheres, and thus leave dystonia patients more susceptible to interference between limb movements.

To treat dystonia, injections of *botulinum toxin* may be used to mitigate abnormal muscle contraction (Rosales and Dressler, 2010). *Botulinum toxin* blocks cholinergic activation of both extrafusal and intrafusal muscle fibers. In addition to blocking excess efferent contractile signaling, *botulinum toxin* may also allow for proper afferent muscle spindle activation. As muscles undergo sustained dystonic contractions, muscle spindles modulate their output, becoming less sensitive to contraction and demonstrating reduced firing rates. This leads to an inability to sense muscle dynamics and may contribute to lack of sensorimotor integration and proprioception (Bove, 2002; Lekhel, 1997; Rome and Grunewald, 1999; Yoneda et al., 2000). One very interesting study examined reaching movements before and after botulinum toxin

injections in CD patients (Pelosin et al., 2009). It showed that reaching movement trajectories, asymmetrical velocity profiles, path lengths, and reversal times were all improved by the treatment, suggesting that prior to injections, abnormal proprioceptive feedback altered the formation of internal models of reaching. Other evidence suggests that peripheral *botulinum toxin* injections may re-establish proper afferent signaling, decreasing CNS excitability and increasing inhibition to restore proper control of the head, neck, and non-dystonic body segments (Gregori et al., 2008; Kim et al., 2006; Pelosin et al., 2009; Trompetto et al., 2006).

There exist several critical gaps in our understanding of sensorimotor control in dystonia. First, to my knowledge, there has been no investigation of bimanual control in dystonia. Given that dystonia is a disorder of sensorimotor integration and reduced inhibition, bimanual movements offer a prime means of probing motor (dys)function in dystonia. Second, although mirror movements and abnormal inhibition exists in dystonia, no studies have investigated whether dystonia patients are more susceptible to interference during voluntary movements. Understanding how individuals with dystonia control bimanual movements, and whether they exhibit increased interference as compared to neurotypical individuals, could provide key information about the function of the sensorimotor system in dystonia patients. In particular, these movements could provide insight into the way in which motor information is communicated between brain areas, elucidate how movements are coordinated in dystonia, and provide information regarding the mechanisms by which the disorder manifests in the CNS.

The neural response to asymmetrical bimanual movements before and after treatment might be observed in the oscillatory activity of neural populations in the sensorimotor network. Neural oscillations during movement can be probed using EEG and MEG; however, investigations of neural oscillations in dystonia is lacking, and what work has been done has

been centered mainly on focal hand dystonia (FHD). In healthy individuals, event related desynchronization (ERD) in neural oscillations in the alpha (8-13 Hz) and beta (13-30 Hz) frequencies are associated with motor planning and motor performance (for review, Rueda-Delgado et al., 2014). ERD represents a drop in spectral power of oscillations due to asynchronous firing of neural populations during active processing of motor information. Conversely, event-related synchronization (ERS) represents resting state oscillations or post-movement sensorimotor integration (Neuper et al., 2006; Pfurtscheller et al., 1996; Tan et al., 2014, 2016). ERD/ERS has been shown to be related to voluntary movement and the acquisition of motor skills (Chung et al., 2017; Manganotti et al., 1998; Neuper et al., 2006; Pfurtscheller and Neuper, 1994; Pfurtscheller et al., 1996). Furthermore, EEG coherence, a measure of functional connectivity between brain areas, has also been related to motor control and skill learning (Chung et al., 2017; Ford et al., 1986; Kristeva et al., 2007; Manganotti et al., 1998; Rueda-Delgado et al., 2014).

Some research has investigated oscillatory activity in dystonia. Hummel and colleagues (2002) demonstrated a lack of event-related synchronization in EEG of dystonic individuals as compared to healthy controls in a task in which they had to observe but not execute a learned finger tapping sequence. They proposed that underlying neural populations were less adept at the inhibition of the motor command. Others have shown reduced amplitude of movement-related cortical potentials in FHD, which are associated with release of inhibitory influences on motor cortical activity during movement preparation (Deutchl et al., 1995; Kamp et al., 1995; Ruiz et al., 2009). The use of a "sensory-trick", which transiently relieves dystonic posturing in some patients, changes neural oscillations in cortical and subcortical regions (Tang et al., 2007). Focal hand dystonia patients have been shown to have a weaker preparatory desynchronization

and phase locking (Ruiz et al., 2009; Toro et al., 2000), and reduced functional connectivity (Jin et al., 2011). However, treatment using deep brain stimulation (DBS) is associated with normalization of oscillatory activity. Taken together, these studies show that EEG can be used to probe abnormal CNS activity in dystonia patients and can reveal specific associations between brain activation and the control of movement in this population.

In this study, patients and age-matched controls were invited to the lab on two occasions to perform a bimanual interference task while their brain activity was recorded via EEG. For the patients, one of the sessions occurred approximately three weeks following a scheduled *botulinum toxin type A* injection, at which time the effects of the treatment would be the strongest. The other session occurred approximately one week prior to a scheduled *botulinum toxin type A* treatment, when the effects of the previous injection had worn off. I predicted that more interference would be observed in the patients than in the controls, and particularly before the *botulinum toxin* injection. I also predicted that patients would show increased ERD as their sensorimotor system works to plan and execute movements, and increased coherence between the hemispheres due to reduced inhibition and increased neural crosstalk.

4.2 Methods

4.2.1 Participants

Nine cervical dystonia patients were recruited to participate in this study. Patients were first screened to confirm the absence of other neurological disorders, of concussion or loss of consciousness in the past year, and to establish a record of current medications and treatments. All patients were right-handed and had normal or corrected-to-normal vision. Patients were also asked about their cervical dystonia diagnosis and duration of the condition. Nine sex- and age-

matched (+/- 5 years) right-handed control participants were recruited. Control participants were free of any history of cognitive or neurological impairment, did not have sustained a concussion in the past year, and had normal or corrected to normal vision. Participants were compensated for their time with gift cards. Participant information is summarized in Table 4-1. All participants provided informed consent, and all procedures were approved by the Michigan State University Institutional Review Board.

	Age	***Sex***	***Handedness Score***	***Length of Diagnosis***	***Treatments (other than botulinum toxin)***	***Reported Pain***	***Reported Pulling***	***Sensory Trick***	***First Session***
Patients									
1	47	Female	100	11 years	Clonazepam	Yes	Yes	No	Post
2	21	Male	100	6 months	Propranolol, Procyclidine	Yes	Yes	No	Post
3	75	Male	100	20 years	None	Yes	Yes	Yes	Post
4	59	Female	100	6 months	Primidone, Gabapentin	Yes	Yes	No	Post
5	32	Female	100	2 years	Artane	Yes	No	No	Post*
6	55	Female	100	2 years	Baclofen	Yes	Yes	Yes	Pre
7	59	Female	100	6 years	Topiramate	Yes	Yes	Yes	Pre*
8	30	Female	100	10 years	Selective denervation	Yes	Yes	No	Pre*
9	58	Female	100	12 years	Baclofen	No	Yes	No	Pre+

	Age	***Sex***	***Handedness Score***	***First Session***
Controls				
1	49	Female	87.5	Post
2	21	Male	75	Post
3	74	Male	100	Pre
4	62	Female	100	Post
5	31	Female	100	Post
6	54	Female	100	Pre
7	58	Female	100	Pre
8	27	Female	100	Pre
9	58	Female	100	Post

Table 4-1: Demographic and diagnosis information for cervical dystonia patients and healthy controls

* Unfortunately, these participants did not return to the lab for the second session

+ Due to a scheduling issue on the part of the participant, the pre-injection session was collected 48 hours after botulinum toxin injection

4.2.2 Study design

Participants were invited to the lab for two sessions, which were counterbalanced between participants (Figure 4-1). For the patients, the pre-treatment session occurred in the week prior to a botulinum toxin injection, whereas the post-treatment session occurred approximately three weeks following the injection. Control participants also came to the lab

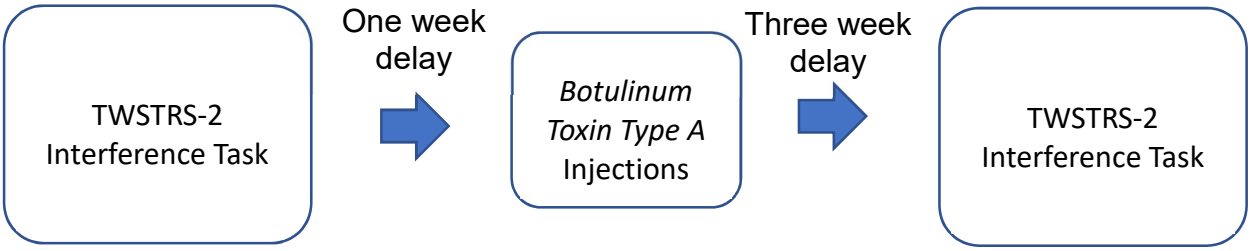

Figure 4-1: Study 3 design. Sessions were counterbalanced between participants

across two sessions, which were randomly assigned a pre-injection or post-injection designation. Of the nine patients recruited for the study, two did not return for their post-injection timepoint, while one patient did not return for the pre-injection timepoint.

	PRE-Injection			***POST-Injection***		
	Severity	***Disability***	***Pain***	***Severity***	***Disability***	***Pain***
	Max=24	Max=30	Max=40	Max=24	Max=30	Max=40
Patients						
1	5	18	25	4	13	15
2	4	16	20	1	12	15
3	16	17	25	12	8	17
4	10	9	17	4	6	8
5	-	-	-	11	6	17
6	16	14	25	12	15	23
7	8	2	13	-	-	-
8	6	12	17	-	-	-
9	4	1	0	0	1	0

Table 4-2: Results of the TWSTRS-2 evaluation of the severity, pain, and disability subscales for each session. Patients were asked to consider their experiences only within the past week when answering the pain and disability subscales. "Max" refers to the maximum score for each particular subscale.

In the first session, all participants completed the Edinburgh Handedness Inventory Short Form (Oldfield, 1971) where a score greater than 61 confirmed right-handedness. Additionally, during each session, patients were administered the TWSTRS-2 rating scale (Comella et al., 2016) to evaluate torticollis severity, disability and pain (Table 4-2). During the administration of the disability and pain subscales, participants were instructed to only consider their experiences within the past week when answering the questions.

4.2.3 Interference task

Participants were asked to perform a variation of the common "star-line" drawing task used to evaluate spatial interference in bimanual movements (Figure 4-2). Participants used the Kinarm endpoint robot to control white cursors on a screen that represented the spatial location of the hands while reaching to targets presented in a virtual workspace on a screen (Figure 4-2, A). The screen was positioned such that cursors and targets were presented at the veridical location and depth of the hands. Kinarm data were sampled at 1000 Hz. In a given trial, participants first positioned their hands in the "home" positions, which were 2cm in diameter and located 8.5 cm to the left and right of the midline. The home positions were positioned a comfortable distance from the participant, such that their elbows were approximately at a 90º angle. After holding in the home positions for 3000 ms, participants were given a "ready" cue via the appearance of the peripheral targets (green and red for the right and left hands, respectively), followed 1500 ms later by the "go" cue, at which point the targets turned yellow. Participants were instructed to then reach to the peripheral targets as straight, fast, and accurately as possible, and return directly to the home position. Successful target hits caused the targets to turn blue in color. Participants were instructed to continue reaching until they performed a

successful hit. The peripheral targets disappeared 2000 ms after returning to the home position (Figure 4-2, C, D).

Participants were familiarized with the Kinarm robot and interference task across visual baseline (VBL) and a kinesthetic baseline (KBL) blocks. In the VBL block, each hand was represented by a cursor, and movements were made from a home position to a straight-forward (0º) or straight backward (180º) peripheral target for each hand. Then, in the KBL block, cursor feedback for the left hand was removed at the presentation of the target and reappeared only when the participant returned to the home position.

After becoming familiar with the task, participants then performed bimanual reaches in the interference (INT) block. With the right hand, participants reached to one of eight target positions located 10 cm from the home position arranged in a circle about the home position at angles of 0°, 45°, 90°, 135°, 180°, 225°, 270°, and 315°. Twenty-five reaching movements were made to each of the eight targets in the right hand, for a total of 200 trials in the INT block. Right hand targets were cued in a pseudo-random order, with no location targeted more than twice consecutively, and all eight targets were cued once in a span of eight consecutive trials. With the left hand, participants continued to make reaching movements to either the 0° or 180° targets. Visual feedback was provided for the right hand, but was removed during movement of the left hand, leaving the left hand susceptible to interference.

4.2.4 Movement analysis

Movement onset and offset were semi-automatically identified using custom written Matlab scripts (Mathworks, Inc., Natick, MA), and onset/offset algorithms (Teasdale et al., 1993) that were subsequently checked for accuracy by trained experimenters. To evaluate motor

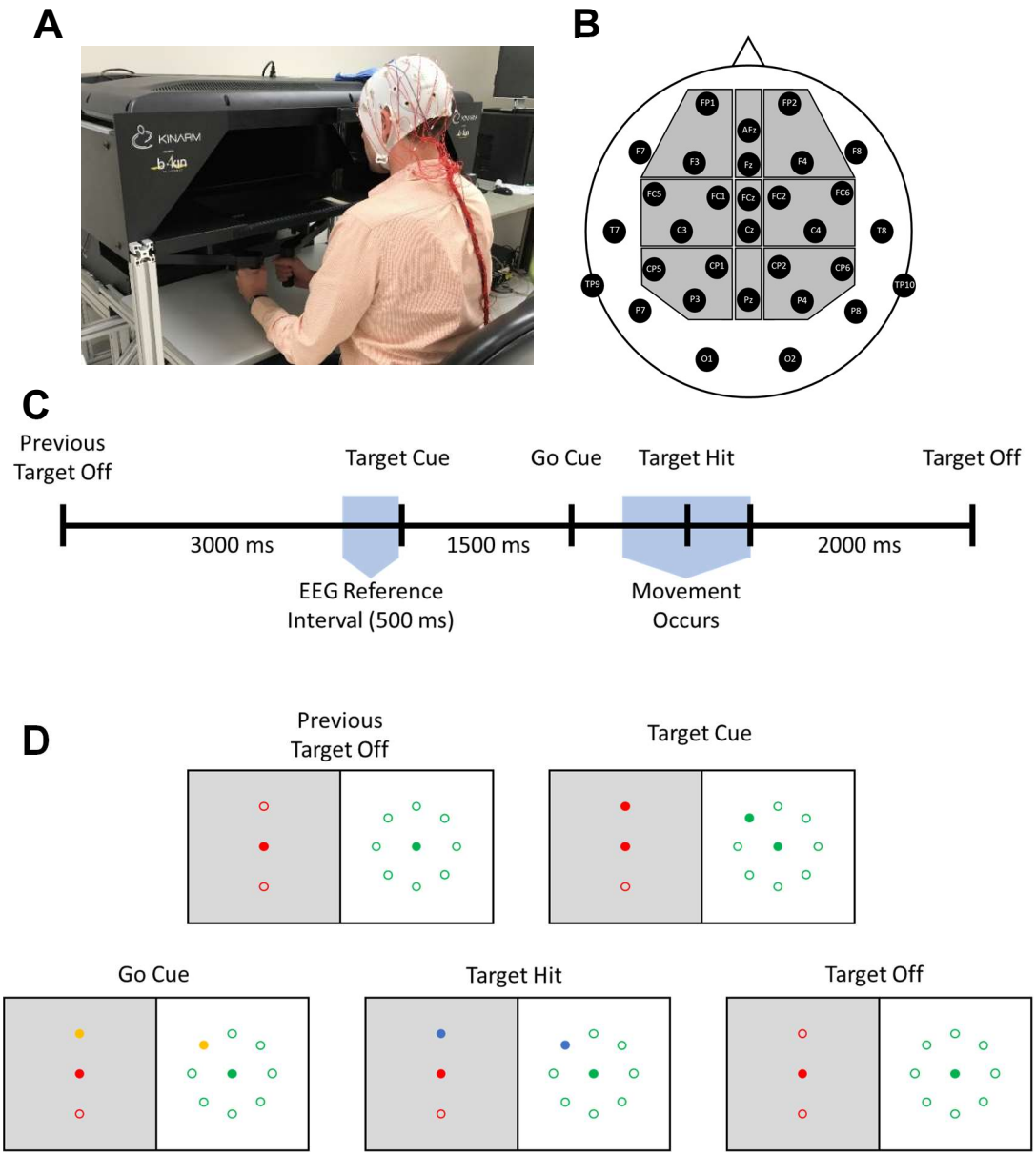

Figure 4-2: Trial protocol for Experiment 3. Participants performed the task at a Kinarm robot (A). Section B shows the channels and regions of interest for the EEG. Section C shows the timing for the trial, in addition to the relative locations of the EEG reference interval and movement period. Section B shows the cues and feedback that participants received during the task. Right hand targets (green) were arrayed in a circle about the home positions, while left hand targets (red) were cued either directly forward or backward. Target outlines were not visible to participants but are depicted here for the reader's reference.

performance in the right hand and interference in the left hand, kinematic error was assessed via three primary outcome interference measures (root mean square error (RMSE); initial directional error (IDE); apex directional error (ADE)), and four secondary interference outcome measures (normalized jerk; reaction time (RT), movement time (MT), and movement length) at each trial. The primary measures represented the most direct assessment of directional interference during reaching movement in the task. The secondary measures represented other temporal and kinematic measures that could capture interference between the actions of the hands.

First, RMSE was computed as a measure of movement straightness across the full out-and-back reach. RMSE was calculated with reference to a straight line between the targets and normalized to movement length. RMSE represented the movement error across the entirety of the movement.

Next, initial directional error (IDE) was computed at the moment of peak tangential velocity as the angle between a vector from the home position to the position of the cursor and a vector from the home position to the target. IDE represented a measure of feed-forward or predictive error of the motor plan, since the moment of peak velocity occurs at a time before sensory information could be processed by the CNS. Since different target directions could cause interference to either the left or right of the peripheral target in the left hand, we also evaluated the constant error (i.e., absolute value of the mean error to each target) of IDE.

Apex directional error (ADE) was computed as the angle between a vector from the home position to the target and a vector from the home position to the cursor at the maximal extent of the reach, during which the participant executed a reversal movement to head back to the home position. Like IDE, we also evaluated the constant error of ADE.

In addition to these three primary measures of interference (RMSE, IDE, ADE), we also examined several other kinematic measures to examine the basic movement patterns between patients and controls. Jerk was computed as the third derivative of displacement and normalized to movement length. Reaction time (RT), movement time (MT), and movement length were also assessed for both hands.

4.2.5 EEG data collection and analysis

EEG was collected and analyzed using BrainRecorder and BrainVision software on a 32-Channel electrode cap conforming to the international 10/20 coordinate system (BrainProducts Inc., Germany). During the task, EEG was recorded at 1000 Hz from a 32-channel electrode cap, and downsampled to 250 Hz during post-processing. The signals were then filtered with a 4-80 Hz fourth order dual-pass Butterworth filter and referenced to the T9 and T10 electrodes (located near the mastoid processes). Eyeblink artifacts were removed using an ocular ICA, and other artifacts were identified using semiautomatic artifact detection algorithms. The recordings were then segmented into two distinct windows time-locked to the onset of the reach from the home position to the targets. The "planning" window was computed from -1000 to 0 ms prior to movement onset, and the "execution" window was computed from 0 to 1000 ms following movement onset. Segments were baseline corrected, and those channels containing artifacts were rejected on a segment by segment basis. Regions of interest (ROIs; Figure 4-2, B) were created by averaging outputs from left frontal (LF; FP1, F3), right frontal (RF: FP2, F4), midline frontal (MF; Fz), left central (LC; FC1, C3, FC5), right central (RC; FC2, C4, FC6), midline central (MC; Fz, FCz), left parietal (LP; CP1, P3, CP5), right parietal (RP; CP2, P4, CP6), and midline parietal (MP; Pz) electrodes.

Changes in spectral power in the alpha (8-13 Hz) and beta (13-30 Hz) frequency bands was investigated to determine the engagement of underlying neural populations during the planning and execution windows. To evaluate event related (de)synchronization, power within target frequency ranges were isolated via an 8^{th} order zero phase shift Butterworth filter. Spectral power was then computed by squaring the raw activity values within the target frequency band. A percent change score was then computed relative to a baseline interval that occurred between -2500 to -2000 ms relative to movement onset. This interval was chosen because it was preceded by approximately 2500 ms of resting activity and was uninterrupted by visual cues. This result was averaged across the two 1000 ms windows (planning and execution) for each trial. The mean percent-change spectral power was then computed for each subject at each trial type (i.e., target direction) and evaluated in subsequent statistical analyses.

To examine functional connectivity during the task, magnitude-squared coherence was computed using the BrainVision Analyzer software within each target frequency band (see Appendix J for the formula used to compute magnitude-squared coherence). Coherence provides a statistical measure of the linear relationship between two oscillating signals. Coherence values were also computed as percent-change scores with reference to the baseline interval that occurred between -2500 to -2000 ms relative to movement onset. Due to the nature of the bimanual interference task, coherence between equivalent regions of interest in opposite hemispheres was investigated. As such, coherence was calculated between interhemispheric frontal, central, and parietal ROIs by averaging coherence between all combinations of channels between each ROI.

4.2.6 Statistical analyses

To simplify subsequent analyses, and because the interference effects of interest were between asymmetrical and symmetrical movements, measures were collapsed across the symmetrical (0º and 180º) and asymmetrical (45º, 90º, 135º, 225º, 270º, and 315º) targets[**]. Due to the small sample size and missing session data for some patients, a linear mixed-effects model (MEM; AKA multilevel model, hierarchical linear regression model) was chosen to analyze the relationship between the independent and dependent variables. MEM is a more flexible extension of a general linear model (GLM) and has several advantages over GLM (Baayen et al., 2008; Barr et al., 2013). First, MEM does not require the same number of observations per cell and does not necessitate listwise deletions due to missing within-subject data. Second, the covariance structure can be manipulated in terms of fixed and random effects, such that differences in the intercept and/or slope due to stochastic variation in one independent variable (random effect) can be accounted for in the model to better measure the effects of other independent variables of interest the experimenter (i.e., the fixed effects). Third, MEM can also be expanded to a repeated measures design, while also maintaining validity for non-normally distributed data. For this experiment, the basic model for interference measures was constructed with group (Controls vs. Patients), movement symmetry (Symmetrical vs. Asymmetrical), and session (Pre vs. Post) as fixed effects and subject as a random intercept effect. This means that the model intercept was allowed to vary by subject. Since the movement task was designed specifically to induce right-to-left interference, and since interference is, in right handers,

[**] Repeated-measures ANOVAs were performed for the primary measures of interference in the left hand to confirm that there were no significant differences between the six asymmetrical movements for each group and session. The same analysis was performed between the two symmetrical targets. No significant differences were observed between targets within each level of symmetry. As such, responses were collapsed across the symmetrical and asymmetrical levels of movement symmetry.

typically greater from right to left (Kagerer, 2015b, 2016a, 2016b), all models were constructed to analyze the movements of the left hand. For EEG power analyses, the model was applied to each ROI with fixed effects of group, symmetry, and session, with subject as the random intercept effect in each frequency band of interest. For coherence analyses, the model was constructed at each interhemispheric connection (frontal, central parietal) with fixed effects of group, symmetry, and session (frontal, central, parietal), with subject as the random intercept effect.

A Kenward-Roger approximation for degrees of freedom was used for subsequent significance testing on the mixed model (Judd et al., 2012). Across all analyses, the main effects of group, symmetry, and session were considered the primary effects of interest, due to their involvement in *a priori* hypotheses and the study design. Additionally, Group x Symmetry and Group x Session interaction terms were also examined. Statistical analyses were performed using custom written scripts that used the "afex" and "lme4" packages in R Studio software. Data visualization was performed using the "ggplot2" and "ggiraphExtra" packages in R Studio, in addition to EEG visualization tools in BrainVision Analyzer. For time-frequency plots, a Morlet wavelet transform with a 5^{th} order Morlet parameter was applied to the EEG data between 5 and 40 Hz across a window spanning -2000 to +2000 ms relative to movement onset. The plot was computed as a percent-change score relative to the -2500 to -2000 ms baseline window.

4.3 Results

4.3.1 CD severity, disability, and pain (TWSTRS-2)

Within the CD group, two-tailed paired-samples t-test was used to determine how severity changed for participants who completed both visits as evaluated by the TWSTRS-2. All

three scales showed improvement from the pre- to post-injection session. Dystonia severity in the pre-injection timepoint (M = 9.17±5.74) decreased significantly to the pre-injection timepoint (M = 5.5±5.28; $t(5) = 5.50$, $p = 0.003$). Likewise, patient reported disability also showed a moderate decrease from pre-injection (M = 12.5±6.47), to post-injection (M = 9.17±5.19; $t(5) = 2.56$, $p = 0.003$). Finally, patients' ratings of their pain decreased significantly from pre-injection (M = 18.67±9.72) to post-injection (M = 13.00±7.97; $t(5) = 3.44$ $p = 0.018$).

4.3.2 Kinematic measures

Table 4-3 summarizes significant findings from the mixed effects models for mean score and variability for each behavioral measure. For the primary interference measures in the left hand (RMSE, IDE, ADE; Figure 4-3), an effect of symmetry was only observed in RMSE, in which asymmetric movements showed greater error than symmetric movements. Interestingly, no differences between symmetrical and asymmetrical movements were observed in IDE or ADE. However, a significant effect of symmetry was found for the variability of IDE and ADE, with much greater variability in the asymmetrical movements, whereas no such effect was observed for variability of RMSE. A main effect of session was present for in RMSE and ADE, as well as the variability of RMSE, with slightly larger overall error in the post session.

Additionally, for the primary interference measures, there were no differences between the patient and control groups. Interestingly, however, an interaction between group and symmetry was observed for the variability of IDE and ADE, in which the control group showed higher variability in their directional error during asymmetrical trials than the patient group, indicating the possibility of more left hand trial to trial stability in the patient group than in the control group.

In secondary interference measures (Figure 4-4), several key differences were observed. Jerk showed a significant difference between asymmetrical and symmetrical movements, denoting smoother movements during reaches towards symmetrical targets. Jerk was also more variable in the post-injection session. RT was slightly higher for the left than for the right hand, suggesting that the right hand tended to initiate movements. Of note, RT was also higher in the post-injection session. Though the Group x Session interaction was not significant, the session effect seemed to be driven largely by the patient group. The variability showed a trending difference between groups, with the patient group showing marginally greater variability than the healthy controls. MT showed a significant effect of symmetry, with asymmetrical movement taking more time than symmetrical movements, and was marginally more variable in the post-injection session. This was driven mostly by the control group having greater variability in the post session and was captured by a marginal Group x Session interaction. Movement length was greater in the post-injection session, but this was mostly driven by the control group showing somewhat longer movements in that session. Movement length was also more variable for asymmetrical movements.

Measure and effect	Intercept	β Estimate	*F*(df)	*p* value
		Mean Score		
RMSE				
Symmetry	8.15 mm	-0.49	$F(1, 42.04) = 8.89$	0.005**
Session	8.15 mm	-0.44	$F(1, 44.37) = 6.58$	0.01*
IDE				
Session	2.71º	-0.33	$F(1, 45.04) = 5.21$	0.03*
ADE				
No significant effects				
Jerk				
Symmetry	102.86	-2.58	$F(1, 42.00) = 6.63$	0.01*
Session	102.86	-1.74	$F(1, 42.87) = 3.00$	0.09^{+}
RT				
Session	368.17 ms	-8.08	$F(1, 42.69) = 9.18$	0.004**
MT				
Symmetry	1140 ms	-32.13	$F(1, 45.01) = 6.06$	0.02*
Movement Length				
Session	23.13 cm	-0.33	$F(1, 44.00) = 3.62$	0.06^{+}
		Variability (SD)		
RMSE				
Session	4.14 mm	-0.30	$F(1, 45.34) = 6.25$	0.02*
IDE				
Symmetry	4.67º	-0.77	$F(1, 15.87) = 33.67$	<0.0001***
Group x Symmetry	4.67º	-0.34	$F(1, 42.11) = 6.78$	0.01*
ADE				
Symmetry	4.47º	-0.75	$F(1, 42.5) = 30.85$	<0.0001***
Group x Symmetry	4.47º	-0.32	$F(1, 42.15) = 5.58$	0.02*
Jerk				
Session	40.94	-3.29	$F(1, 43.52) = 4.09$	0.05*
RT				
Group	61.26 ms	-9.84	$F(1, 15.95) = 3.50$	0.08^{+}
MT				
Session	204 ms	-10.9	$F(1, 43.64) = 3.60$	0.06^{+}
Group x Session	204 ms	-10.2	$F(1, 46.64) = 3.20$	0.08^{+}
Movement Length				
Symmetry	2.17 cm	-0.16	$F(1, 42.02) = 11.14$	0.002**

Table 4-3: Results of mixed-effects models of mean kinematics scores and kinematic variability measures

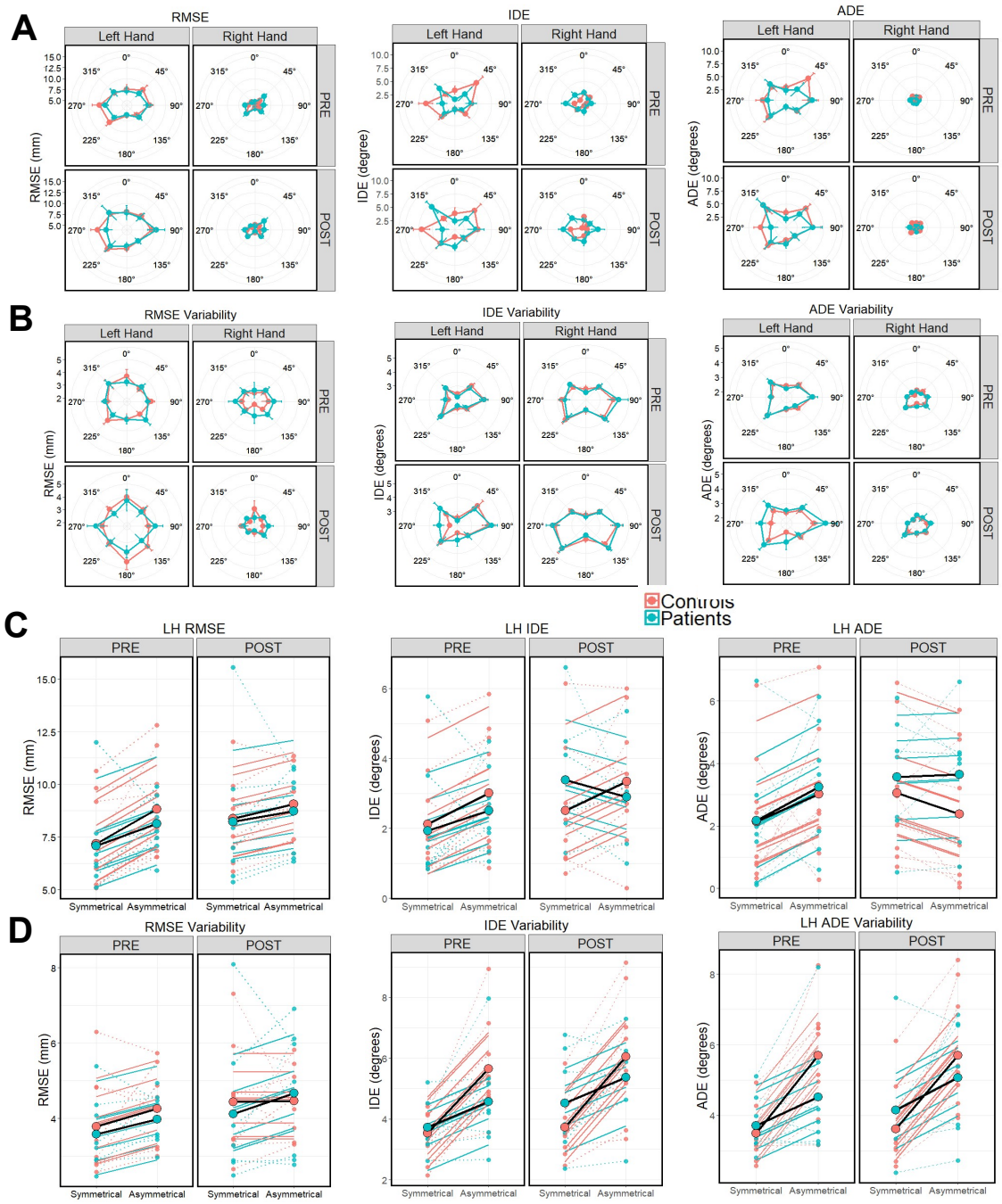

Figure 4-3: Results of primary interference measures. Top two rows depict polar plots for the main measures of interference (A) and variability of these measures (B). Polar angle corresponds to the cued target in the right hand; radius reflects the measure's magnitude. Error bars represent standard error. Bottom two rows show results of the mixed-effects models in the left hand for the mean scores (C) and variability (D). Points with dashed lines represent individual subjecs. Solid lines represent the mixed effects model, with Group, Symmetry, and Session as fixed effects and Subject as a random intercept effect. The large points connected by black lines show means for each session, group, and symmetry. These means are provided to assist the reader's interpretation but note that mixed effects models are not specifically examining differences between means.

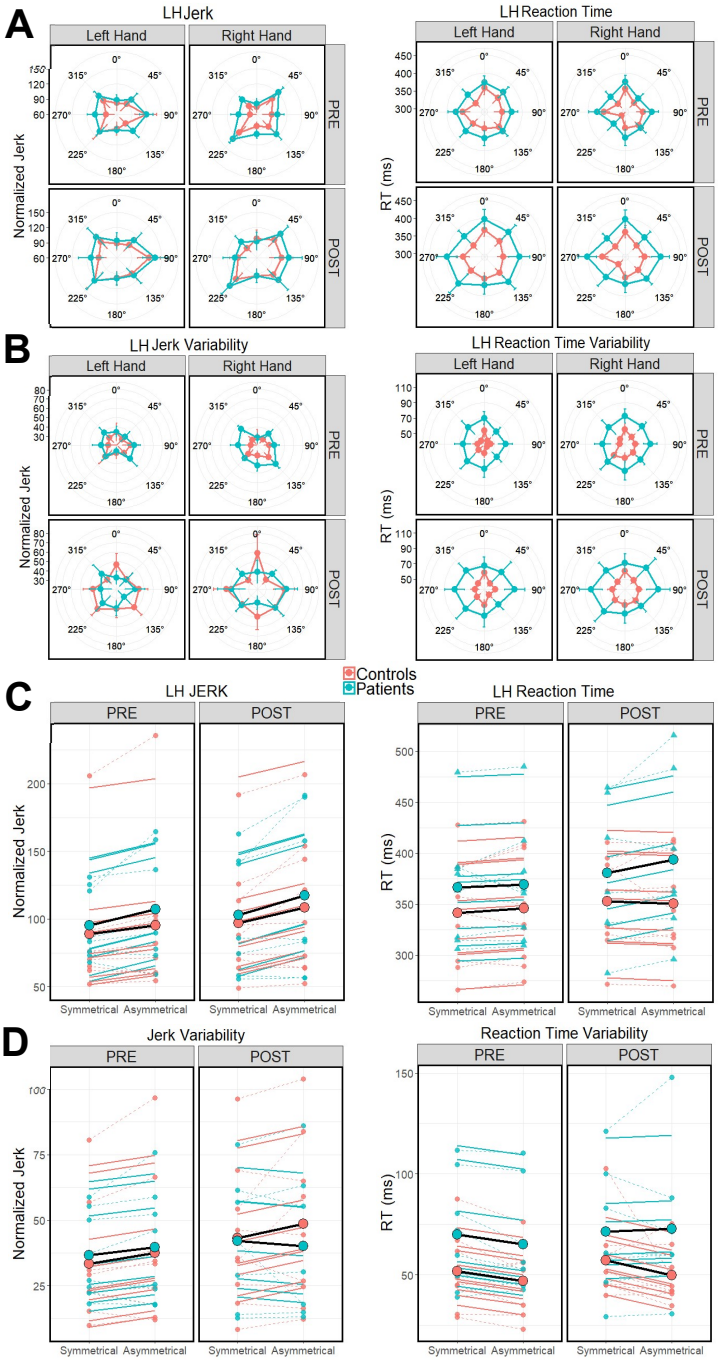

Figure 4-4: Results of secondary interference measures. Top two rows depict polar plots for Jerk and RT (A) and their variability (B). Polar angle corresponds to the cued target in the right hand, while radius reflects the magnitude. Error bars represent standard error. Bottom two rows show results of the mixed-effects model analysis in the left hand for the mean cores (C) and variability (D). Points with dashed lines represent individual subject data. Solid lines represent the mixed effects model, with Group, Symmetry, and Session as fixed effects and Subject as a random intercept effect. The large points connected by black lines denote the means for each session, group, and symmetry. These means are provided to assist the reader's interpretation but note that mixed effects models are not specifically examining differences between means.

4.3.3 Event-related desynchronization (ERD)

Table 4-4 summarizes the ERD findings (Figure 4-6). The mixed-effects model was applied at each ROI across the planning and execution windows in the alpha and beta frequencies. In the alpha band, a significant group difference was observed in the LF ROI during the planning window, while group differences approached significance in the MF ROI in the planning window, and in the MC ROI in both the planning and execution windows. In these regions, the patient group had greater desynchronization (i.e., a larger decrease in spectral power) than the control group.

Second, a consistent session effect was observed at the LF, MF, LC, MC, RC, LP, and RP ROIs in both the planning and execution windows, in which there was a larger desynchronization in the post-injection session compared to the pre-injection session. Visual inspection of the data suggested that this effect was mostly driven by the patient group, which seemed to have a substantial decrease in power from pre-injection to post-injection although there was no statistically significant Group x Session interaction in the alpha frequency.

In the beta frequency, a similar session effect was observed in the MF, MC, and RP ROIs in the planning window, and in the LF, MF, and MC ROIs in the execution window, with lower power in the post-injection session as compared to the pre-injection session. Visual inspection of the data suggested that this was driven by a greater ERD in the patient group at the post-injection session and Group x Session interactions approached significance in the RF, MC, and RC ROIs in the planning window, and at the RF ROI in the execution window (Figure 4-7). Main effects of group approaching statistical significance were found in the planning window in the MP ROI, with greater ERD in the patients. In the execution window, the group effect approached

Region and Effects	Planning				Execution			
	Intercept	β Estimate	*F*(df)	*p* value	Intercept	β Estimate	*F*(df)	*p* value
Alpha (8-13 Hz)								
Left Frontal								
Group			*No effects*		-2.13%	14.34	$F(1, 15.95) = 4.43$	0.05*
Session			*No effects*		-2.13%	4.97	$F(1, 45.66) = 5.67$	0.02*
Midline Frontal								
Group	-10.29 %	4.94	$F(1, 15.86) = 3.08$	0.10^{+}			*No effects*	
Session	-10.29 %	2.66	$F(1, 44.76) = 3.22$	0.08^{+}	-11.49%	3.68	$F(1, 45.57) = 3.80$	0.06^{+}
Left Central								
Session	14.74%	3.03	$F(1, 47.05) = 4.55$	0.04*	-15.53%	3.78	$F(1, 5.14) = 5.14$	0.03*
Midline Central								
Group	-12.40%	6.66	$F(1, 15.91) = 3.93$	0.07^{+}	-18.25%	10.83	$F(1, 15.95) = 4.13$	0.06^{+}
Session	-12.40%	2.89	$F(1, 46.83) = 4.05$	0.05*	-18.25%	3.08	$F(1, 45.68) = 3.44$	0.07^{+}
Right Central								
Session	-14.01%	2.56	$F(1, 46.43) = 3.61$	0.06^{+}	-14.59%	2.55	$F(1, 45.10) = 3.02$	0.09^{+}
Left Parietal								
Session	-19.38%	2.86	$F(1, 45.85) = 4.11$	0.05*	-19.36%	3.86	$F(1, 45.28) = 3.42$	0.07^{+}
Right Parietal								
Session	-19.86%	3.28	$F(1, 45.87) = 5.16$	0.03*	-20.02%	4.00	$F(1, 44.97) = 5.16$	0.03*
Beta (13-30 Hz)								
Left Frontal								
Session			*No effects*		-9.85%	2.83	$F(1, 46.53) = 3.39$	0.07^{+}
Midline Frontal								
Session	-15.80%	1.62	$F(1, 46.56) = 4.51$	0.04*	-14.74%	3.81	$F(1, 46.26) = 6.26$	0.02*
Right Frontal								
Group x Symmetry	-10.51%	1.53	$F(1, 44.08) = 3.04$	0.09^{+}			*No effects*	
Group x Session	-10.51%	1.61	$F(1, 47.35) = 3.30$	0.08^{+}	-8.05%	2.02	$F(1, 45.66) = 2.82$	0.10^{+}
Midline Central								
Group			*No effects*		-21.84%	8.14	$F(1, 15.95) = 4.17$	0.06^{+}
Symmetry	-20.53%	-1.43	$F(1, 44.02) = 5.01$	0.03			*No effects*	
Session	-20.53%	1.18	$F(1, 45.75) = 3.05$	0.09^{+}	-21.84%	2.48	$F(1, 45.86) = 3.59$	0.06^{+}
Group x Session	-20.53%	1.16	$F(1, 45.73) = 2.94$	0.09^{+}			*No effects*	
Right Central								
Group x Session	-17.43%	1.40	$F(1, 45.87) = 3.49$	0.07^{+}			*No effects*	
Midline Parietal								
Group	-21.40%	5.35	$F(1, 15.95) = 3.45$	0.08^{+}	-17.30%	16.31	$F(1, 15.96) = 5.47$	0.03*
Right Parietal								
Session	-20.11	2.53	$F(1, 45.19) = 3.93$	0.05*			*No effects*	

Table 4-4: Significant and trending results of mixed-effects models for event-related desynchronization across the nine ROIs, in the Alpha (8-13 Hz) and Beta (13-30 Hz) in the planning and execution windows

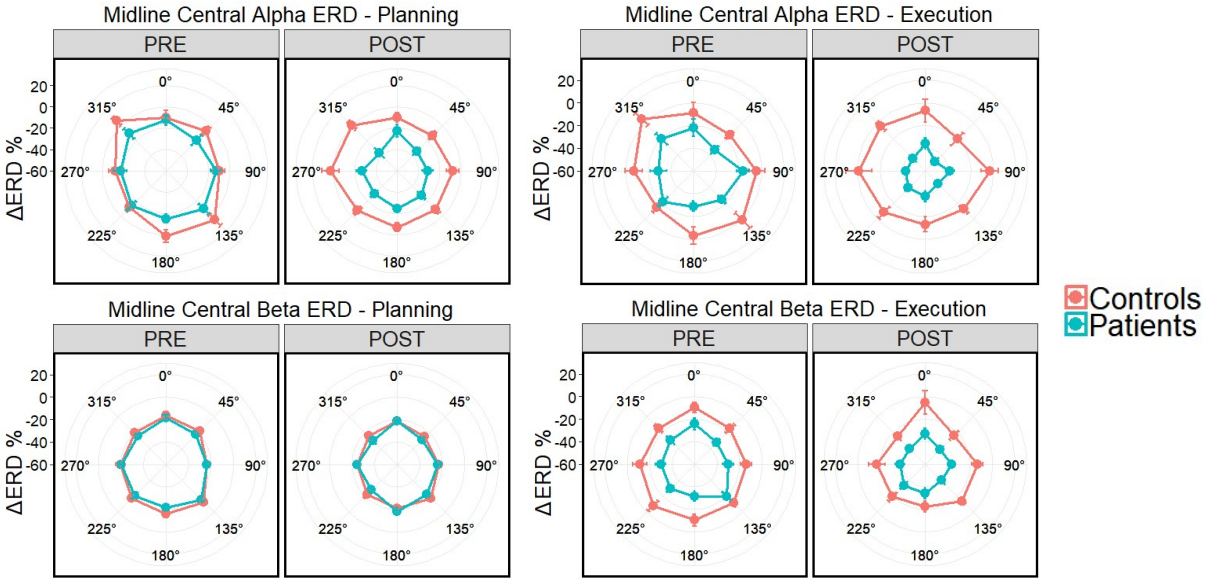

Figure 4-5: Polar plots of ERD for the midline central ROI. Polar angle represents reaching direction. Radius represents ERD. Note that values closer to the center of the circle represent greater ERD (lower spectral power)

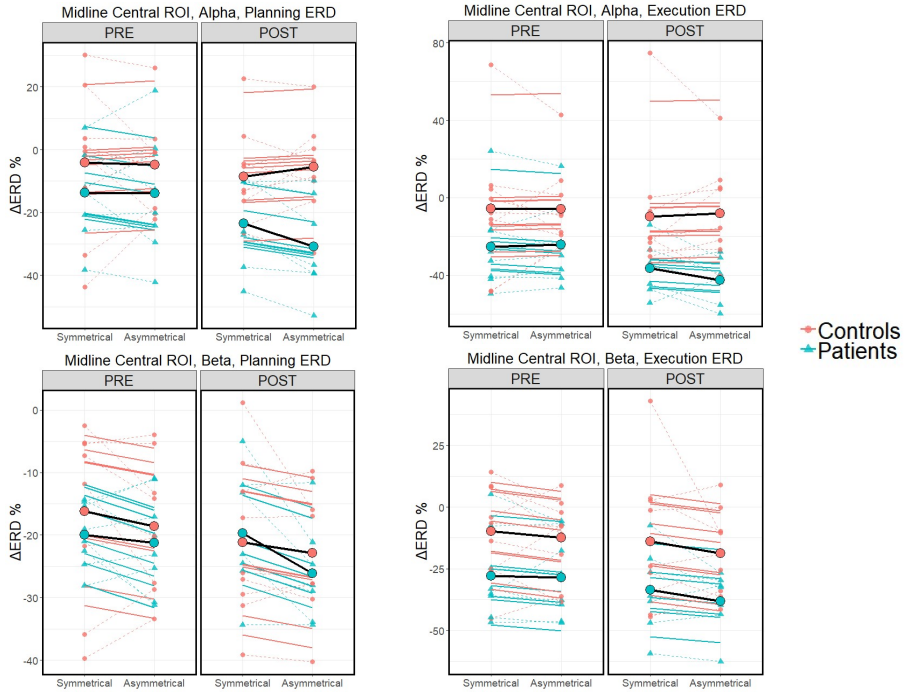

Figure 4-6: Results of the mixed-effects models for the midline central ROI. Points and dashed lines represent individual subject data. Solid lines represent the mixed effects model, with Group, Symmetry, and Session as fixed effects and Subject as a random intercept effect. The large points connected by black lines denote the means for each session, group, and symmetry. These means are provided to assist the reader's interpretation but note that mixed effects models are not specifically examining differences between means.

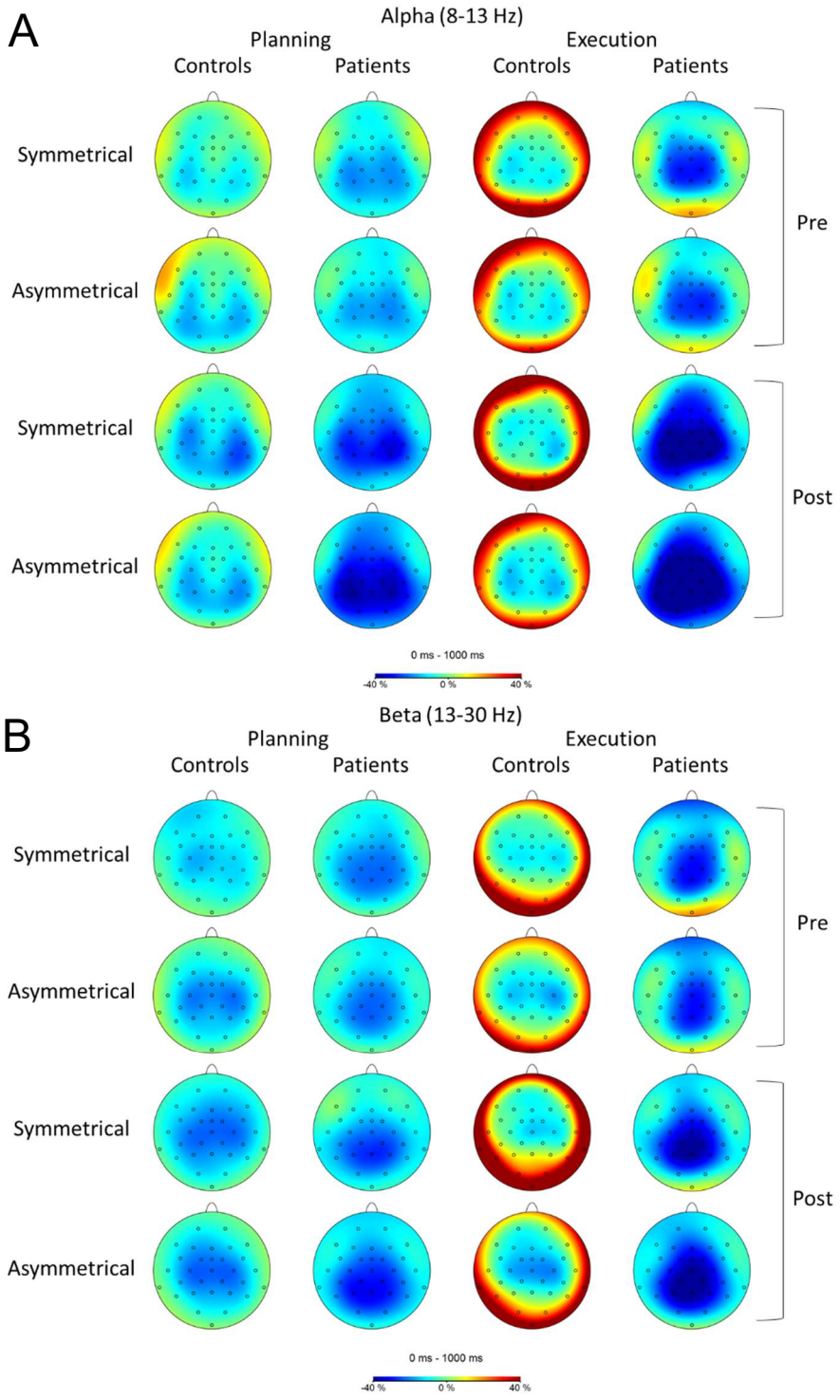

Figure 4-7: Head maps of average ERD across the alpha (A) and beta (B) frequency bands. Percent change scores relative to the -2500 -2000 ms pre-trial baseline period are interpolated across the 32 channels. Green colors represent no change from baseline, cool colors denote ERD, and warm colors denote ERS.

statistical significance in the MC ROI, and was significant in the MP ROI. Finally, a significant effect of symmetry was found in the MC ROI in the planning window, with greater desynchronization for symmetrical movements as opposed to asymmetrical movements. A Group x Symmetry interaction in the planning window also approached significance in the RF ROI, with greater desynchronization from symmetrical to asymmetrical movements in the control group and the opposite trend in the patient group.

4.3.4 Coherence

Interhemispheric coherence was computed between the left and right frontal, central, and parietal ROIs. Mixed effects models were used to evaluate the effects of group, symmetry, and session in the planning and execution windows in the alpha and beta frequency bands. Table 4-5 summarizes the coherence results. Findings that approached statistical significance were only observed in the execution window. Coherence between the frontal regions in the alpha frequency band showed a significant Group x Session interaction, such that the patient group showed less frontal coherence at the post-injection time point. Additionally, coherence between the central ROIs in the alpha frequency showed a Group x Symmetry interaction that approached significance, in which the control group showed a decrease in coherence from symmetrical to asymmetrical movements, while the patient group showed a slight increase. Additionally, in the beta frequency, a marginal main effect of symmetry was found, such that asymmetrical movements were accompanied by greater coherence than symmetrical movements.

	Execution			
Region and Effects	**Intercept**	**β Estimate**	***F*(df)**	***p* value**
		Alpha (8-13 Hz)		
Frontal				
Group x Session	-7.47%	-13.97	$F(1, 47.99) = 4.73$	0.03*
Central				
Group x Symmetry	18.82%	6.41	$F(1, 44.08) = 2.95$	0.09^{+}
		Beta (13-30 Hz)		
Central				
Symmetry	38.16%	-7.7	$F(1, 44.98) = 2.98$	0.09^{+}

Table 4-5: Significant and trending results of mixed model evaluating EEG Coherence at each ROI.

4.4 Discussion

This experiment examined interference and EEG brain dynamics during asymmetrical bimanual movements in individuals with cervical dystonia, before and after treatment with botulinum toxin injections, compared to healthy age- and sex-matched control participants. Overall, the patients showed similar amounts of directional interference compared to the healthy controls. Interestingly, patients showed a smaller increase in the variability of IDE and ADE from symmetrical to asymmetrical movements. This may suggest that patients made more consistently deviated movements than the healthy controls. Overall, participants' movements were less smooth, slower, and more variable during asymmetrical movements and in the post-injection session, which was captured by several secondary interference measures. These findings notably occurred separately from the focally affected segment, speaking to the more global effects of CD on sensorimotor control. Of importance, RT was greater in the post-injection timepoint, which seemed to be driven largely by the patient group. In the post-injection session, patients were also marginally more variable in their reaction time.

Importantly, the patients also showed greater ERD than the control participants in the alpha band, and in the beta band in the execution window. Across participants, ERD was

strongest bilaterally in the central and parietal ROIs but differed between groups in the frontal and central areas, with patients showing greater ERD in these regions. The ERD was also greater for participants in the post-injection session, particularly in the alpha frequency. Finally, EEG coherence in the execution window across frontal and central sites in both alpha and beta differed between the two groups, which may have been linked to interference observed during movements.

Greater ERD in the dystonia group in the alpha and beta frequencies suggests that neural populations controlling movement exhibit increased activity compared to those in healthy controls (Neuper et al., 2006). Group differences in the frontal ROIs may suggest increased engagement of frontal motor planning areas. These brain regions, particularly the SMA, are known to respond to increasing difficulty in bimanual movements (Garbarini et al., 2015; Jäncke et al., 2000; Toyokura et al., 1999; Tracy et al., 2001). Although the behavioral interference was roughly equivalent between the patient and control groups, this suggests that these movements were essentially more difficult for patients in terms of the neural resources recruited to coordinate their reaches. This is also supported by increased RT in the patient population, suggesting that, even though the targets were pre-cued, bimanual movements required greater processing time for patients.

Increased neural engagement and processing time is in line with emerging findings that suggest that motor control deficits in dystonia may, in part, be the result of dysfunctional integration between sensorimotor areas (Avanzino et al., 2015; Desrochers et al., 2019). In this context, research suggests that the CNS may have more difficulty integrating proprioceptive information (Bove, 2004; Frima et al., 2008; Grünewald et al., 1997; Yoneda et al., 2000) and visuospatial information (Filip et al., 2013, 2017; Fiorio et al., 2007) during movement planning

and execution. Indeed, connectivity between premotor and parietal areas has been found to be reduced in patients (Delnooz et al., 2012), suggesting that a compromised premotor-parietal loop may contribute to movement difficulties. In the current study, the simultaneous coordination of both hands likely requires greater cortical engagement to successfully integrate sensorimotor processes within and between hemispheres. Importantly, this study also shows that movement control relying on effectors not directly related to the dystonic segments is still associated with atypical neural processes, mirroring findings showing movement impairment in non-dystonic body segments (Pelosin et al., 2009). This study lends support to the growing literature suggesting that difficulties in sensorimotor integration may be a key component of the phenomenology of dystonia.

A consistent finding in this study was a difference between the pre- and post-injection sessions in the behavior and neurophysiology. Importantly, patients appeared to have larger RTs in the post-injection session, while in the EEG, more ERD was found in the post-injection session. Upon visual inspection of the data, this appeared to be mainly driven by the patient group, although there were no statistically significant Group x Session interactions (with the exception of MT variability). There were, however, a few ROIs during the planning window of the beta frequency band which trended towards an interaction. If one accepts that behavior and ERD changed in the patient group across sessions, it could indicate an effect of the botulinum toxin injections on both behavior and cortical processes, increasing processing demands on the system. While these injections act in the periphery to block efferent signaling to muscles affected by dystonia, the toxin also has upstream nervous system effects, through presynaptic reuptake and retroactive neuronal transport (Hallett, 2018; Kim et al., 2006; Weise et al., 2019). The toxin also modulates signaling of gamma motor neurons, changing the proprioceptive input

from infused muscles (Giladi, 1997; Rosales and Dressler, 2010). As such, researchers and clinicians are beginning to recognize the wider sensorimotor influence of botulinum toxin injections.

The results of this study suggest that the presence of botulinum toxin was associated with greater neural engagement of sensorimotor areas during movement. However, it is an open question whether this was a direct effect of the injection or a secondary effect of reduced efferent signaling ability and is deserving of additional research. Interestingly, these findings are in line with studies that have found increased sensorimotor activation in some motor areas following injection with botulinum toxin type A, particularly in botulinum toxin naïve participants (Nevrlý et al., 2018; Opavský et al., 2011). At the same time, the CD participants in this study exhibited longer reaction times after their injections as opposed to pre-injection, suggesting a deterioration in motor performance. This result is at odds with other studies that showed improvement on several motor control parameters after botulinum toxin injections (Pelosin et al., 2009; Walsh and Hutchinson, 2007). The increase in RT observed in the present study may instead represent central effects of botulinum toxin injections slowing descending motor commands or requiring extended time in motor planning stages (Hallett, 2018; Weise et al., 2019). However, in this context, and with a lack of statistically significant findings, the effects of session in this study should be interpreted with care and require further research to replicate and confirm this finding.

Surprisingly, few main effects of group or group x symmetry interactions were found in the interference measures, suggesting that the amount of interference was similar between groups at both levels. This was surprising, as it was hypothesized that interference would be greater for dystonia patients, who sometimes exhibit involuntary mirror movements in one effector during voluntary movements of the other effector (Beck et al., 2009; Cox et al., 2012; Sitburana and

Jankovic, 2008). While mirror movements are found in cervical dystonia, they are more often found in focal dystonias of the hands. Furthermore, mirror movements occur more strongly in patients with more severe dystonia and reduced inter hemispheric inhibition (Sattler et al., 2013; Sitburana et al., 2009). The patients tested for this experiment had a relatively low severity rating, with only two participants having scores greater than 12 out of a maximum score of 24. As such, it may be that the few dystonia patients tested in this study were not prone to mirror movements due to their dystonia subtype and lesser dystonia severity. Alternatively, the interference task may not have been sensitive enough to probe small differences in interference that may have existed between the less-affected patients and the healthy controls in this study. While interference did occur in both groups, its magnitude was generally small. In this task, we chose to pre-cue the locations of the targets prior to the "go" cue. This was done because greater predictability in discrete movements is associated with greater ERD (Alegre et al., 2003), a key measure outcome of this study. However, direct pre-cueing of target locations has been shown to mitigate interference effects, though primarily in RT measures (Diedrichsen et al., 2001; Hazeltine et al., 2003; Spijkers et al., 1997), and thus may have decreased interference. Finally, we modified a traditional star-line task to examine differences in the movement planning and execution windows associated discrete reaching movements. In the traditional task, participants make continuous, repetitive reaches, tracing the pattern of a star in one hand while tracing a line in the other, switching the direction of the star-drawing hand after a defined number of repetitions (Swinnen et al., 2002, 2003; Wenderoth et al., 2004, 2006). It is possible that the repetitive nature of these movements yields a greater interference effect than the discrete version of the task employed by this study.

Several other limitations exist for this study. First and foremost, the sample size is small, with three patients missing one of the sessions. The patient population was also very heterogeneous, with varying treatment types, length of diagnosis, and length of treatment. Though many of the findings in this study are in line with our *a priori* predictions, they should necessarily be interpreted with caution. Additional research could compare the effects seen in this CD population with another patient population that experience similar neck pain and muscle spasms but are free of neurological dysfunction (e.g., whiplash patients) to confirm that the findings are inherent to cervical dystonia. Second, there was wide variation in the age and length of diagnosis in the patient population. We sought to mitigate potential effects of age by matching age in the control group; however, the length of diagnosis represents an uncontrolled variable in this study, which has the potential to modulate results from patient to patient. This, however, should also be mitigated by the random intercept effect employed by the mixed effects models, which allowed us to probe our fixed effects while taking into consideration inherent variability between subjects. Additionally, we chose not to use other individual differences as covariates (e.g., age, length of diagnosis, length of treatment, severity, etc.) as fixed covariates in the model. This was because assigning subjects as a random variable in the mixed model would have accounted for overall inter-subject variability. However, using these variables as fixed covariates could have further specified the model and changed the observed pattern of results. Finally, the flexibility of these models is such that the model can be manipulated by the experimenter in a number of different ways. When constructing the model, we chose to allow subjects to have a random intercept in the model, but we did not specify whether their slopes should also be allowed to vary. This was because each fixed effect (i.e., group, session, symmetry) had explicit *a priori* predictions as to their direction. However, changing the models

to allow for variability in slopes between subjects (or other variables) has the potential to change the observed results.

This study has important implications for dystonia and opens several possible avenues of further study. First, to our knowledge, this study represents the first investigation of bimanual coordination in dystonia and suggests that bimanual movements are associated with discernable changes in the underlying neurophysiology and neural activity of dystonia patients. As such, bimanual movement paradigms could be valuable tools to probe the function of the sensorimotor system in dystonia. Bimanual movements of sufficient complexity could also be used to stratify dystonia severity or aid in the identification and diagnosis of the disorder. Second, dystonia is a heterogenous syndrome, occurring in different body segments and due to different etiologies. This methodology represents a valuable tool to probe potential differences between dystonia subtypes, furthering our underdeveloped understanding of the nature of this disorder. Finally, this study has implications for other disorders of movement, and the study of sensorimotor control as a whole. Mirror movements are found in other movement disorders including Parkinson's disease, essential tremor, Huntington's disease, and others (Cox et al., 2012). This paradigm could be equally valuable in these disorders to probe neural processes specific to those disorders. Were such disorders to show key differences in the neural processes underlying bimanual coordination, the distinct neurological functions could provide key insight into the processes by which the broad sensorimotor system coordinates bimanual movements.

CHAPTER 5 – GENERAL DISCUSSION

Performing coordinated bimanual actions is an important capability of the sensorimotor system. Understanding the neural processes controlling bimanual actions can yield important insights into its capabilities in both healthy and impaired states. The overall objective for this dissertation was to examine interference during bimanual movements in both neurotypical individuals, and those with movement impairment due to dystonia, a neurological movement disorder. I approached this through three aims; In Aims 1 and 2, two experiments explored how different kinds of perturbations during reaching movements of one hand caused interference in the opposing hand reaching simultaneously without a perturbation in healthy young adults. In Aim 3, the neurophysiological processes associated with interference were explored in a sample of individuals with cervical dystonia, a movement disorder characterized by aberrant muscle contractions in the head and neck, in addition to deficits in the integration and inhibition of information in the sensorimotor system (Desrochers et al., 2019). Together, these aims help to broaden the understanding of how the nervous system controls bimanual movements by assessing how different kinds of sensorimotor information are transmitted between hemispheres, and how these processes may be disrupted in individuals with movement disorders. While the implications of each study were discussed in depth in their respective chapters, this chapter will serve to summarize the results of this dissertation, discuss overall implications, and examine new questions and future directions generated by this research.

5.1 Aim 1: To determine the influence of visuomotor and dynamic perturbations in bimanual interference.

Previous research has shown that interference can occur during bimanual reaching movements when one of the hands experiences a visuomotor perturbation (Kagerer, 2015b; Brunfeldt et al., in prep). However, substantially less interference is observed when one hand experiences a dynamic perturbation (Desrochers et al., 2017). Interestingly, in unimanual studies, responses to a visuomotor perturbation are upregulated while adapting to a dynamic perturbation (Franklin et al., 2012). I thus hypothesized that simultaneous visuomotor and dynamic perturbations might result in increased interference from the perturbed to the non-perturbed hand. To evaluate Aim 1, I designed an experiment in which four groups of participants received either visuomotor, dynamic, or combined visuomotor and dynamic perturbation, or no perturbation. I found that interference in the visuomotor and combined perturbation groups was roughly equivalent in magnitude but was greater than the dynamic perturbation and control groups. This suggests that neural processes handling visuomotor information may cause interference more readily than those handling dynamic information, and that upregulated sensorimotor representations in one hemisphere-hand system may not necessarily be transmitted to the contralateral hemisphere-hand system. As such, each hemisphere may coordinate feedback gains in parallel with the other during bimanual actions.

5.2 Aim 2: To determine the contribution of reference frames on bimanual interference

While many have proposed that a sharing of sensorimotor information between hemisphere-hand systems underlies interference during bimanual movements, the extent to which reference frames could be shared between effectors remained unclear. It was possible that

the lack of interference due to dynamic perturbations in Aim 1 was due to adaptation occurring in an egocentric-intrinsic reference frame that was restricted to the adapting hand and arm. Therefore, if the reference frame could become shared between effectors, an increase in interference between the hands might be observed. As such, Experiment 2 tested whether the control of a shared cursor would result in more interference between the hands, as compared to when participants controlled two separate cursors with each hand. By sharing control of the cursor, it was assumed that the sensorimotor system might represent the action in a more unified manner, and thus, plan the movement within both hemisphere-hand systems. Indeed, more interference was found in the shared cursor group in measures that evaluated feed-forward control. This suggested that the reference frame did become shared between hemisphere-hand systems. As such, interference may be dependent on the reference frame in which the movements are controlled. Greater interference due to a shared reference frame explain a large body of studies that show that the manner in which a motor task is perceived/conceived has a large influence on the interference seen between hands (Blais et al., 2014; Franz, 2004; Franz et al., 2001; Ivry et al., 2004; Kovacs et al., 2010; Mechsner et al., 2001; Summers et al., 1993b). Changing the reference frame in which a motor action is planned and coordinated may be a major contributor to whether interference is generated or mitigated.

5.3 Aim 3: To determine the degree of interference and measure the underlying brain dynamics in individuals with cervical dystonia

Because bimanual coordination depends on a highly interconnected brain network, it represents an excellent means of assessing how the sensorimotor system might be disrupted in movement disorders. Cervical dystonia is a movement disorder characterized by involuntary,

extraneous movements of the head and neck (Albanese et al., 2013). In some patients, mirror movements are observed, in which voluntary actions of one hand trigger involuntary actions in the opposing hand (Cox et al., 2012; Sitburana et al., 2009). Dystonia is also associated with deficits in integration and inhibition processes within the sensorimotor system, which are essential to successful movement coordination (Avanzino et al., 2015; Desrochers et al., 2019). Treatment with *botulinum toxin* injections are often used to mitigate dystonic symptoms, but a few studies have also reported effects on the CNS and motor control beyond the local effects of the injections (Hallett, 2018; Pelosin et al., 2009). As such, Experiment 3 was designed to evaluate bimanual interference and its underlying neurophysiological processes before and after treatment with botulinum toxin injections. CD patients and healthy controls performed a bimanual interference task while their brain activity was recorded using EEG. While limited differences were observed in interference between the groups, there were changes in event-related desynchronization (ERD) in the patients. This signaled that neural populations controlling movement were more active and engaged in the patients during the bimanual control tasks. This was particularly evident in the post-injection session. Taken together, this suggests that although motor behavior was equivalent between groups, greater neural resources were recruited to maintain successful patterns of coordination, and that this was exacerbated by botulinum toxin injections. In other words, the sensorimotor system of patients treated bimanual movements as being more difficult than in healthy control participants. This may underlie reported difficulties in limb coordination experienced by some patients with cervical dystonia.

5.4 Broader implications for neuromotor control and future directions

Together, the studies in this dissertation produce several key findings relevant to the broader field of neuromotor control. First, these studies support the notion that all information within the sensorimotor system is not necessarily equal. The nervous system must integrate many different kinds of information during movement, including (but not limited to) visual, spatial, temporal, proprioceptive, dynamic, and perceptual information. The results of Experiment 1 suggest that visuomotor information dominates neural processes causing interference, while Experiment 2 demonstrates that the mental representation or the perception of the task can affect interference. Likewise, Experiment 3 indicates that underlying neural processing may be different in atypical populations despite the behavior being similar. Optimal feedback control theory (OFCT) suggests that the motor system will weight control parameters differently depending on the context of the task (Scott, 2004, 2008, 2012). It is important to recognize that in different contexts, different motor parameters can generate, or mitigate, interference between effectors.

Additionally, the studies in this dissertation expand the current understanding of how internal models are constructed and communicated within the central nervous system. To successfully adapt to a perturbation, internal models must be adjusted to account for introduced error (Kawato, 1999; Shadmehr and Mussa-Ivaldi, 1994; Wolpert et al., 1995a). Prior research, and the work done in this dissertation, suggest that interference between upper limbs can occur when internal models for one hemisphere-hand system influence those of the contralateral system (Brunfeldt et al., in prep; Kagerer, 2015b, 2016b). This dissertation suggests that the manner in which internal models may influence movement coordination is dependent on the type of information being shared. Further, it is possible that, depending on context, there may exist a

hierarchy of information within the motor system that influences whether movements are successfully coordinated or interfered-with.

These studies also highlight the importance of reference frames in the coordination of bimanual movement and the formation of internal models. The results of Experiment 2 suggest that the reference frame represents a key component of an internal model, and that modulating this reference frame can have a significant impact on the manner by which an internal model is represented and shared within the sensorimotor system. When a reference frame can be successfully shared between hemispheres (i.e., visuomotor information in Experiment 1 or a shared task representation in Experiment 2), asymmetrical movements within the same reference frame can cause interference. Meanwhile, it is possible that research which describes the elimination of interference into a meaningful "gestalt" may be because the motor system anchors the movements to a different frame of reference in which interference does not occur (Franz, 2004; Ivry et al., 2004; Kovacs et al., 2010; Swinnen and Wenderoth, 2004). Like with modes of sensorimotor information, this may suggest that there exists an organization or hierarchy of different frames of reference within the motor system, which allows for movement to be successfully coordinated in different contexts.

The notion of a hierarchy in the representation of motor actions is not new (Grafton and de C. Hamilton, 2007; Gurney et al., 2001; Todorov et al., 2005), and is in line with predictions made by OFCT (Scott, 2008). OFCT predicts that the sensorimotor system will selectively control different parameters that are associated with a certain cost during movement. These costs are often defined by the specific nature and goals of the task being performed. However, with movements occurring in a redundant system, the motor system may define high and low state-spaces in which to optimally control motor parameters. As such, the sensorimotor system

will not need to create a computationally demanding common reference frame in order to integrate all information. Neural optimal control hierarchy (NOCH; DeWolf and Eliasmith, 2011) is an extension of OFCT that posits how the motor system might hierarchically optimize actions. Hierarchical optimization allows the nervous system to optimize high-level, low dimension motor parameters, which in turn restrict the state space of lower-level, higher dimension parameters and allow for parallel optimization in a highly efficient manner. This process also can be roughly mapped onto specific neural structures and their function. For example, by creating a high-level optimal reaching trajectory in Cartesian space in in SMA and PMC, certain motor synergies can be isolated by the basal ganglia, allowing M1 to specify low-level muscle forces and joint torques within M1 (DeWolf and Eliasmith, 2011). At each level, the system specifies the optimal outputs based on the current state of the system and the movement goal.

In terms of interference, if the sensorimotor system is unable to correctly produce an optimal solution at high-order levels, lower-level movements will become unstable. Perturbations or highly complicated asymmetrical movement goals may tax the ability of the system to produce a well-defined solution. This could occur across many parameters of movement, such as the type of information being specified by the motor system (i.e., visuomotor vs dynamic information, as in Experiment 1), or the reference frame being utilized (i.e., shared or separate frames of reference, as in Experiment 2). Thus, as these processes are translated to lower level systems, involuntary interference may be the resulting output. In other words, interference between effectors in healthy people could be a failure in the ability of the motor system to hierarchically optimize motor commands.

Future research into bimanual control and its underlying neural mechanisms will be important for neuromotor control and atypical movements. These studies will help researchers and clinicians understand the mechanisms at work in the widely distributed brain network controlling simultaneous bimanual movements. Further, future work in this area will help to uncover further information about the etiology of specific movement disorders for therapeutic and rehabilitative uses.

Further research can continue to probe how different types of visuomotor and dynamic information may cause interference, and how the hands can be made to use a common reference frame. For example, as opposed to using a shared cursor, as in Chapter 2, perhaps other visual cues could be used to cause the motor system to plan the movements with a unified reference frame. For example, simply joining visual stimuli with a straight line has been shown to modulate intermanual interactions (Franz and McCormick, 2010). Further work could also directly assess how reference frames are shared between hemisphere hand systems. If dynamic perturbation of one hand causes more interference when contralateral joints are in equivalent positions as opposed to asymmetrical positions, this would support the notion that these reference frames are being shared based on the task context. Clever task designs using virtual reality or other technological means such as eyetracking could also examine how visual information delivered to a single visual field, and thus the reference frame within a single hemisphere, might eliminate interactions between the hands during visuomotor interference tasks.

This dissertation has key implications for the study of movement disorders. For dystonia, this research shows that bimanual movements are sensitive enough to show key differences in brain dynamics between patients and controls. Further, the findings of Chapter 3 fit into the

emerging picture of broad sensorimotor impairment in CD. As such, these results further motivate interference studies in cervical dystonia. Future studies to could examine other tasks that make use of other spatial, temporal, and perceptual manipulations to induce greater interference in both patients and controls. Additionally, future studies can investigate whether interference occurs in other dystonia subtypes and investigate possible differences in brain dynamics between these disorders. Such findings could yield key information regarding differences between dystonia subtypes. Distinguishing sensorimotor differences between dystonia subtypes is an integral step in understanding the heterogeneous nature of the disorder. Lastly, as not all patients display mirror movements, the presence of mirror movements, and perhaps the degree of interference exhibited by different patients, could be a valuable means of assessing the effects of different genetic contributions in both dystonia, and in the motor system of neuro-typical individuals. Currently, a large amount of resources have been devoted to understanding the genetic underpinnings of dystonia (Jinnah and Hess, 2018; Klein, 2014). If certain genetic mutations are associated with mirror movements and interference, this would suggest that these genes are important for bimanual control, neural communication, and sensorimotor control.

Finally, the studies in this dissertation could be valuable for the broader field of movement disorders and neurorehabilition. Bimanual movements are shown to be beneficial for stroke rehabilitation and can be used as a tool to probe the sensorimotor system for deficits in an array of movement disorders (Byblow et al., 2002; Kantak et al., 2017, 2016b; Nettersheim et al., 2018; Rose and Winstein, 2004). Understanding how information is transferred between hemispheres through interference processes could be beneficial for understanding the phenomenology of these conditions, particularly when impairments are lateralized (e.g.,

hemiplegia, lateralized bradykinesia). Additionally, in many lateralized movement disorders, the "bad" side may act to impair the "good" side during bilateral movements (Gosser and Rice, 2015; Kang and Cauraugh, 2017; Kishore et al., 2007; Rose and Winstein, 2005). Future research into interference and the neural crosstalk could be critical in understanding the mechanisms by which these phenomena occur.

5.5 Summary

The experiments in this dissertation aimed to expand the understanding of how complex bimanual actions are coordinated, both in healthy humans and in patients with dystonia. Experiments 1 and 2 allowed for better conception of the ways in which visuomotor vs. dynamic components of the motor system are encoded and cooperate within frames of reference to form coordinated movements. Experiment 1 examined whether an over-additive relationship exists between dynamic and visuomotor perturbations and found that only visuomotor information is primarily responsible for interference. Experiment 2 examined whether observed interference may be due to different levels of reference frame processing, and found that when the reference frame is shared, interference increases. Experiment 3 provided key insights into dysfunction in the bimanual control network in CD patients. It investigated how interference occurs in individuals with a dysfunctional motor control system and probed how these differences are related to brain dynamics. Here, it was found that CD patients did not show greater interference than neuro-typical controls but did show differences in patterns of neural activation as a result of bimanual movements. Together, these studies have important implications for understanding the mechanisms by which motor information is shared between hemispheres in healthy individuals as well as in patients with dystonia.

APPENDICES

MICHIGAN STATE
UNIVERSITY

Initial Study APPROVAL
Revised Common Rule

February 25, 2019

To: Florian A Kagerer

Re: **MSU Study ID:** STUDY00002078
IRB: Biomedical and Health Institutional Review Board (BIRB)
Principal Investigator: Florian A Kagerer
Category: Expedited 4, 5, 6, 7a
Submission: Initial Study STUDY00002078
Submission Approval Date: 2/25/2019
Effective Date: 2/25/2019
Study Expiration Date: None; however modification and closure submissions are required (see below).

Title: Upper limb interactions in dystonia

This submission has been approved by the Michigan State University (MSU) BIRB. The submission was reviewed by the Institutional Review Board (IRB) through the Non-Committee Review procedure. The IRB has found that this study protects the rights and welfare of human subjects and meets the requirements of MSU's Federal Wide Assurance (FWA00004556) and the federal regulations for the protection of human subjects in research (e.g., 2018 45 CFR 46, 21 CFR 50, 56, other applicable regulations).

How to Access Final Documents
To access the study's final materials, including those approved by the IRB such as consent forms, recruitment materials, and the approved protocol, if applicable, please log into the Click™ Research Compliance System, open the study's workspace, and view the "Documents" tab. To obtain consent form(s) stamped with the IRB watermark, select the "Final" PDF version of your consent form(s) as applicable in the "Documents" tab. Please note that the consent form(s) stamped with the IRB watermark must typically be used.

Expiration of IRB Approval: The IRB approval for this study does not have an expiration date. Therefore, continuing review submissions to extend an approval period for this study are not required. **Modification and closure submissions are still required (see below).**

Modifications: Any proposed change or modification with certain limited exceptions discussed below must be reviewed and approved by the IRB prior to implementation of the change. Please submit a Modification request to have the changes reviewed.

Office of Regulatory Affairs
Human Research Protection Program

4000 Collins Road
Suite 136
Lansing, MI 48910

517-355-2180
Fax: 517-432-4503
Email: irp@msu.edu
www.hrpp.msu.edu

New Funding: If new external funding is obtained to support this study, a Modification request must be submitted for IRB review and approval before new funds can be spent on human research activities, as the new funding source may have additional or different requirements.

Immediate Change to Eliminate a Hazard: When an immediate change in a research protocol is necessary to eliminate a hazard to subjects, the proposed change need not be reviewed by the IRB prior to its implementation. In such situations, however, investigators must report the change in protocol to the IRB immediately thereafter.

Reportable Events: Certain events require reporting to the IRB. These include:

- Potential unanticipated problems that may involve risks to subjects or others
- Potential noncompliance
- Subject complaints
- Protocol deviations or violations
- Unapproved change in protocol to eliminate a hazard to subjects
- Premature suspension or termination of research
- Audit or inspection by a federal or state agency
- New potential conflict of interest of a study team member
- Written reports of study monitors
- Emergency use of investigational drugs or devices
- Any activities or circumstances that affect the rights and welfare of research subjects
- Any information that could increase the risk to subjects

Please report new information through the study's workspace and contact the IRB office with any urgent events. Please visit the Human Research Protection Program (HRPP) website to obtain more information, including reporting timelines.

Personnel Changes: Key study personnel must be listed on the MSU IRB application for expedited and full board studies and any changes to key study personnel must to be submitted as modifications. Although only key study personnel need to be listed on a non-exempt application, all other individuals engaged in human subject research activities must receive and maintain current human subject training, must disclose conflict of interest, and are subject to MSU HRPP requirements. It is the responsibility of the Principal Investigator (PI) to maintain oversight over all study personnel and to assure and to maintain appropriate tracking that these requirements are met (e.g. documentation of training completion, conflict of interest). When non-MSU personnel are engaged in human research, there are additional requirements. See HRPP Manual Section 4-10, Designation as Key Project Personnel on Non-Exempt IRB Projects for more information.

Prisoner Research: If a human subject involved in ongoing research becomes a prisoner during the course of the study and the relevant research proposal was not reviewed and approved by the IRB in accordance with the requirements for

research involving prisoners under subpart C of 45 CFR part 46, the investigator must promptly notify the IRB.

Site Visits: The MSU HRPP Compliance office conducts post approval site visits for certain IRB approved studies. If the study is selected for a site visit, you will be contacted by the HRPP Compliance office to schedule the site visit.

For Studies that Involve Consent, Parental Permission, or Assent Form(s):

Use of IRB Approved Form: Investigators must use the form(s) approved by the IRB and must typically use the form with the IRB watermark.

Copy Provided to Subjects: A copy of the form(s) must be provided to the individual signing the form. In some instances, that individual must be provided with a copy of the signed form (e.g. studies following ICH-GCP E6 requirements). Assent forms should be provided as required by the IRB.

Record Retention: All records relating to the research must be appropriately managed and retained. This includes records under the investigator's control, such as the informed consent document. Investigators must retain copies of signed forms or oral consent records (e.g., logs). Investigators must retain all pages of the form, not just the signature page. Investigators may not attempt to de-identify the form; it must be retained with all original information. The PI must maintain these records for a minimum of three years after the IRB has closed the research and a longer retention period may be required by law, contract, funding agency, university requirement or other requirements for certain studies, such as those that are sponsored or FDA regulated research. See HRPP Manual Section 4-7-A, Recordkeeping for Investigators, for more information.

Closure: If the research activities no longer involve human subjects, please submit a Continuing Review request, through which study closure may be requested. Closure indicates that research activities with human subjects are no longer ongoing, have stopped, and are complete. Human research activities are complete when investigators are no longer obtaining information or biospecimens about a living person through interaction or intervention with the individual, obtaining identifiable private information or identifiable biospecimens about a living person, and/or using, studying, analyzing, or generating identifiable private information or identifiable biospecimens about a living person.

For More Information: See the HRPP Manual (available at hrpp.msu.edu).

Contact Information: If we can be of further assistance or if you have questions, please contact us at 517-355-2180 or via email at IRB@msu.edu. Please visit hrpp.msu.edu to access the HRPP Manual, templates, etc.

Expedited Category. Please see the appropriate research category below for the full regulatory text.

Expedited 1. Clinical studies of drugs and medical devices only when condition (a) or (b) is met.
(a) Research on drugs for which an investigational new drug application (21 CFR Part 312) is not required. (Note: Research on marketed drugs that significantly increases the risks or decreases the acceptability of the risks associated with the use of the product is not eligible for expedited review.)
(b) Research on medical devices for which (i) an investigational device exemption application (21 CFR Part 812) is not required; or (ii) the medical device is cleared/approved for marketing and the medical device is being used in accordance with its cleared/approved labeling.

Expedited 2. Collection of blood samples by finger stick, heel stick, ear stick, or venipuncture as follows:
(a) from healthy, nonpregnant adults who weigh at least 110 pounds. For these subjects, the amounts drawn may not exceed 550 ml in an 8 week period and collection may not occur more frequently than 2 times per week; or
(b) from other adults and children, considering the age, weight, and health of the subjects, the collection procedure, the amount of blood to be collected, and the frequency with which it will be collected. For these subjects, the amount drawn may not exceed the lesser of 50 ml or 3 ml per kg in an 8 week period and collection may not occur more frequently than 2 times per week.

Expedited 3. Prospective collection of biological specimens for research purposes by noninvasive means.
Examples: (a) hair and nail clippings in a nondisfiguring manner; (b) deciduous teeth at time of exfoliation or if routine patient care indicates a need for extraction; (c) permanent teeth if routine patient care indicates a need for extraction; (d) excreta and external secretions (including sweat); (e) uncannulated saliva collected either in an unstimulated fashion or stimulated by chewing gumbase or wax or by applying a dilute citric solution to the tongue; (f) placenta removed at delivery; (g) amniotic fluid obtained at the time of rupture of the membrane prior to or during labor; (h) supra- and subgingival dental plaque and calculus, provided the collection procedure is not more invasive than routine prophylactic scaling of the teeth and the process is accomplished in accordance with accepted prophylactic techniques; (i) mucosal and skin cells collected by buccal scraping or swab, skin swab, or mouth washings; (j) sputum collected after saline mist nebulization.

Expedited 4. Collection of data through noninvasive procedures (not involving general anesthesia or sedation) routinely employed in clinical practice, excluding procedures involving x-rays or microwaves. Where medical devices are employed, they must be cleared/approved for marketing. (Studies intended to evaluate the safety and effectiveness of the medical device are not generally eligible for expedited review, including studies of cleared medical devices for new indications.)
Examples: (a) physical sensors that are applied either to the surface of the body or at a distance and do not involve input of significant amounts of energy into the subject or an invasion of the subject's privacy; (b) weighing or testing sensory acuity; (c) magnetic resonance imaging; (d) electrocardiography, electroencephalography, thermography, detection of naturally occurring radioactivity, electroretinography, ultrasound, diagnostic infrared imaging, doppler

blood flow, and echocardiography; (e) moderate exercise, muscular strength testing, body composition assessment, and flexibility testing where appropriate given the age, weight, and health of the individual.

Expedited 5. Research involving materials (data, documents, records, or specimens) that have been collected, or will be collected solely for nonresearch purposes (such as medical treatment or diagnosis). (NOTE: Some research in this category may be exempt from the HHS regulations for the protection of human subjects. 45 CFR 46.101(b)(4). This listing refers only to research that is not exempt.)

Expedited 6. Collection of data from voice, video, digital, or image recordings made for research purposes.

Expedited 7. Research on individual or group characteristics or behavior (including, but not limited to, research on perception, cognition, motivation, identity, language, communication, cultural beliefs or practices, and social behavior) or research employing survey, interview, oral history, focus group, program evaluation, human factors evaluation, or quality assurance methodologies. (NOTE: Some research in this category may be exempt from the HHS regulations for the protection of human subjects. 45 CFR 46.101(b)(2) and (b)(3). This listing refers only to research that is not exempt.)

Expedited 8. Continuing review of research previously approved by the convened IRB as follows:
(a) where (i) the research is permanently closed to the enrollment of new subjects; (ii) all subjects have completed all research-related interventions; and (iii) the research remains active only for long-term follow-up of subjects; or
(b) where no subjects have been enrolled and no additional risks have been identified; or
(c) where the remaining research activities are limited to data analysis.

Expedited 9. Continuing review of research, not conducted under an investigational new drug application or investigational device exemption where categories two (2) through eight (8) do not apply but the IRB has determined and documented at a convened meeting that the research involves no greater than minimal risk and no additional risks have been identified.

MICHIGAN STATE
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Modification and Continuing Review APPROVAL
Pre-2018 Common Rule

March 23, 2019

To: Florian A Kagerer

Re: **MSU Study ID:** LEGACY15-1348
IRB: Biomedical and Health Institutional Review Board (BIRB)
Category: Expedited 4, 6
Submission: Modification and Continuing Review MODCR00000639
Submission Approval Date: 3/21/2019
Effective Date: 3/21/2019
Study Expiration Date: 3/20/2020

Title: Neurophysiological correlates of upper limb movements

This submission has been approved by the Michigan State University (MSU) BIRB. The submission was reviewed by the Institutional Review Board (IRB) through the Non-Committee Review procedure. The IRB has found that this study protects the rights and welfare of human subjects and meets the requirements of MSU's Federal Wide Assurance (FWA00004556) and the federal regulations for the protection of human subjects in research (e.g., pre-2018 45 CFR 46, 28 CFR 46, 21 CFR 50, 56, other applicable regulations).

This renewal included changes to personnel. IRB approval expired on 3-15-19. Project granted renewed approval on 3-21-19 after PI confirmed no research activities occurred during the expired period.

How to Access Final Documents
To access the study's final materials, including those approved by the IRB such as consent forms, recruitment materials, and the approved protocol, if applicable, please log into the Click™ Research Compliance System, open the study's workspace, and view the "Documents" tab. To obtain consent form(s) stamped with the IRB watermark, select the "Final" PDF version of your consent form(s) as applicable in the "Documents" tab. Please note that the consent form(s) stamped with the IRB watermark must typically be used.

Continuing Review: IRB approval is valid until the expiration date listed above. If the research continues to involve human subjects, you must submit a Continuing Review request at least one month before expiration.

Modifications: Any proposed change or modification with certain limited exceptions discussed below must be reviewed and approved by the IRB prior to implementation of the change. Please submit a Modification request to have the changes reviewed. If changes are made at the time of continuing review, please submit a Modification and Continuing Review request.

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New Funding: If new external funding is obtained to support this study, a Modification request must be submitted for IRB review and approval before new funds can be spent on human research activities, as the new funding source may have additional or different requirements.

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Closure: If the research activities no longer involve human subjects, please submit a Continuing Review request, through which study closure may be requested. Human subject research activities are complete if there is no further interactions or interventions with human subjects and/or no further analysis of identifiable private information.

For More Information: See the HRPP Manual (available at hrpp.msu.edu).

Contact Information: If we can be of further assistance or if you have questions, please contact us at 517-355-2180 or via email at IRB@msu.edu. Please visit hrpp.msu.edu to access the HRPP Manual, templates, etc.

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Examples: (a) physical sensors that are applied either to the surface of the body or at a distance and do not involve input of significant amounts of energy into the subject or an invasion of the subject's privacy; (b) weighing or testing sensory acuity; (c) magnetic resonance imaging; (d) electrocardiography, electroencephalography, thermography, detection of naturally occurring radioactivity, electroretinography, ultrasound, diagnostic infrared imaging, doppler blood flow, and echocardiography; (e) moderate exercise, muscular strength testing, body composition assessment, and flexibility testing where appropriate given the age, weight, and health of the individual.

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(b) where no subjects have been enrolled and no additional risks have been identified; or
(c) where the remaining research activities are limited to data analysis.

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APPENDIX B – Experiment 1 and 2 Consent Form

Principal Investigator: Dr. Florian Kagerer

Consent Form for Adults

Michigan State University, Movement Neuroscience Laboratory

Project	Neurophysiological correlates of upper limb movements
Statement of Age of Participant	You are over 18 years of age and willing to participate in a research project conducted by Dr. Florian Kagerer at the Department of Kinesiology, Michigan State University, East Lansing.
Purpose	The purpose of this research is to investigate arm and hand coordination under changing movement conditions. The experiment is designed in a way that makes it possible to determine the influence of different task conditions, such as movement direction, distance, and velocity, on arm and hand movements.
Procedures	You will first be asked to fill out a brief handedness questionnaire. For the experiment, you will sit comfortably in a chair with your hands resting on a table. You will perform arm movements with one, or both hands, moving joysticks, a pen on a digitizing tablet, or robotic handles. A computer will store information about the position of your hand(s) during the movement task. You may be asked to participate in one to three sessions. Portions of the session may be video recorded for coding or demonstration purposes, using a small camcorder next to the setup. In that case, small markers may be placed on your arms and torso, allowing cameras to record your movements. Each session will last about 45-60 min.
Confidentiality	All information collected in the study is strictly confidential (except as you specify on the signed permission form for video and image illustrations), and your name will not be identified at any time. Your data will be grouped with data others provide for reporting and presentation. Data will be stored in a locked file cabinet and on a password protected computer. Only the principal investigator, his collaborators, as well as the MSU Human Research Protection Program (HRPP) will have access to the project data. Your confidentiality will be protected to the maximum extent allowable by law. The consent form, your participant code, or videos made will be retained securely for at least three years after the close of the study.
Risk	As a result of your participation in this study, you may experience a modest degree of fatigue from the concentration required during the performance of the test, but there are no other known risks and no long-term effects associated with participation in this study.
Benefits	The experiment is not designed to help you specifically, but it may have substantial impact on understanding how the brain controls visually-guided movement.
Freedom to Withdraw and to Ask Questions	Your participation is voluntary. You are free to ask questions or to withdraw permission for your participation at any time without penalty. You may refuse to participate in certain procedures or answer certain questions. **INJURY Statement:** If you are injured as a result of your participation in this research project, Michigan State University will assist you in obtaining emergency care, if necessary, for your research related injuries. If you have insurance for

medical care, your insurance carrier will be billed in the ordinary manner. As with any medical insurance, any costs that are not covered or are in excess of what are paid by your insurance, including deductibles, will be your responsibility. The University's policy is not to provide financial compensation for lost wages, disability, pain or discomfort, unless required by law to do so. This does not mean that you are giving up any legal rights you may have. You may contact Dr. Florian Kagerer at 517-432-9907 with any questions or to report an injury.

Cost and Compensation: As Kinesiology student, you can earn extra credit (equivalent to one quiz/session) by participating; if you do not wish to participate, other ways to earn extra credit will be provided. Psychology students can earn extra credit according to the department's 'Participation in Psychological Research: Information for Students' guidelines.

Principal Investigator

If you have questions about the study, or want to report an injury, please contact: Dr. Florian Kagerer, Dept. of Kinesiology, Michigan State University 308 West Circle Drive, Suite 126, East Lansing, MI 48824, Ph: 517-432-9907, email: fkagerer@msu.edu

If you have questions or concerns about your role and rights as a research participant, would like to obtain information or offer input, or would like to register a complaint about this study, you may contact, anonymously if you wish, the Michigan State University's Human Research Protection Program at 517-355-2180, Fax 517-432-4503, or e-mail irb@msu.edu or regular mail at 4000 Collins Rd, Suite #136, Lansing, MI 48910.

Informed Consent Requirements

You are voluntarily making a decision whether or not to participate in the research study described above. Your signature indicates that you have read the information provided above, and have had all of your questions answered. You will be given a copy of this consent form to keep.

We will not share your contact information with anyone outside this project.

You voluntarily agree to allow videotaping or to be photographed during the experiment.

☐ Yes ☐ No Initials_____

You voluntarily agree to allow the videotapes or photos to be used later in publications.

☐ Yes ☐ No Initials_____

Name of Participant: _____ **DOB:**_____

Contact Email & Phone: _____

Signature: _____ **Date:** _____

Approved by a Michigan State University Institutional Review Board effective 3/21/2019.
This version supersedes all previous versions. MSU Study ID LEGACY15-1348.

Principal Investigator: Dr. Florian Kagerer
Graduate Assistant: Phillip Desrochers

Research Participant Information and Consent Form
Michigan State University, Movement Neuroscience Laboratory

You are being asked to participate in a research study. Researchers are required to provide a consent form to inform you about the research study, to convey that participation is voluntary, to explain risks and benefits of participation, and to empower you to make an informed decision. You should feel free to ask the researchers any questions you may have.

Study Title: **Upper limb interactions in dystonia**

1. PURPOSE OF RESEARCH

The purpose of this research study is to examine bimanual coordination during upper limb movements in individuals with dystonia and individuals without dystonia. We also wish to measure underlying brain activity associated with differences in bimanual coordination using electroencephalography (EEG) while you do the motor task. The experiment is designed in a way that makes it possible to determine the influence of different task conditions, such as movement direction, distance, and velocity on arm and hand movements.

2. WHAT YOU WILL DO

First, we will ask you some questions to determine your eligibility for the study (this may already have been accomplished). These questions will include a brief medical history and demographic information. If you have been diagnosed with dystonia, we will ask you about your dystonia, including your dystonia subtype, how long you have been diagnosed, and what your treatments are. You are free to withhold responses to any questions that you don't want to answer.

Next, we will ask you to complete the TWSTRS-2 rating scale to evaluate dystonia symptoms and their severity. We'll do this even if you haven't been diagnosed with dystonia. We will also ask you to complete a handedness questionnaire to measure your hand dominance. Again, you are free to withhold responses to any questions that you don't want to answer.

After this, we will apply the EEG cap to your head that will measure your brain activity through sensors in the cap. We will also place electrodes above your left eye (near the eyebrow) and to the side of your eye. We will then use q-tips to clean the skin under the electrodes with rubbing alcohol. We'll then fill each electrode with a conductive gel, which will allow the electrodes to read the electrical activity coming from your brain.

We will then record your brain activity while you do the motor task. During this, you will sit comfortably in a chair in front of a robotic device with two handles, which you'll grasp and move around. These handles will track your hand movements, and also allow you to interact with virtual objects on a computer screen. Sometimes, the robot may gently move one of your arms for you. After the experiment we will provide you a place to wash the gel out of your hair.

The whole experimental session should not last more than two hours. You will be given breaks during the experiment and may request additional breaks for any reason.

We will then ask you to return to the lab approximately 4 weeks from your first visit for a second experimental session. During this time, we will again obtain your consent to do the experiment, and you may still withdraw or withhold any information. In the second session, we will again do the TWSTRS-2 evaluation, and you will be asked to do the motor task once again while we record EEG. Throughout the experiment, if we discover highly unusual movement or EEG characteristics, we will share this information with you.

Across the whole experiment, we plan to collect data from 8-12 neurologically typical individuals and 8-12 individuals with cervical dystonia.

Continue to next page →

3. POTENTIAL BENEFITS
You will not directly benefit from being in this study. The results of the study, however, will advance knowledge about movement coordination, which might benefit people with movement disorders in the future.

4. POTENTIAL RISKS
As a result of participation in this study, you may experience a modest degree of fatigue while doing our task, or from the concentration required during your performance. You may also experience slight irritation from either the EEG cap or gel. The cap can also sometimes feel uncomfortable if worn for extended periods of time. If you have dystonia, there may be times where your dystonic contractions make it difficult to complete the task. We do not anticipate that this task will cause you any discomfort above that which you may typically experience. There are no other foreseeable risks associated with this experiment. If these or any other situations occur, let your experimenter know.

5. PRIVACY AND CONFIDENTIALITY
All information collected in the study is strictly confidential (except as you specify on this form for video and image illustrations). Your name will not be identified at any time, and all your data will be assigned a unique, anonymous identifier that is not tied to your identity. Your data will be grouped with data others provide for reporting and presentation. Data will be stored in a locked filing cabinet or on a password protected computer. Only the principal investigator, his collaborators, and the MSU Human Research Protection Program (HRPP) will have access to the project data. The data collected from this study will be published in scientific journals or used in presentations to the public about dystonia. Your confidentiality will be protected to the maximum extent allowable by law. This consent form, your participant code, and your data will be retained securely for at least three years after the close of the study. Identifiers (name, age, etc.) will be removed from your identifiable private information and, after such removal, the information may be used for future research studies or distributed to another investigator for future research studies without additional informed consent from you or other authorized representative.

6. YOUR RIGHTS TO PARTICIPATE, SAY NO, OR WITHDRAW
Your participation in this study is completely voluntary. You have the right to say no to participate in the research. You can stop at any time after it has already started. You may also refuse to participate in certain procedures or answer certain questions. There will be no consequences if you stop and you will not be criticized. You will not lose any benefits that you normally receive.

7. COSTS AND COMPENSATION FOR BEING IN THE STUDY
As a thank-you for participating in our study, you will receive a $20 gift card.

8. CONTACT INFORMATION
If you have concerns or questions about this study, such as scientific issues, how to do any part of it, or to report an injury, please contact the principal investigator for this study: Dr. Florian Kagerer, Dept. of Kinesiology, Michigan State University, 308 West Circle Drive, Suite 126, East Lansing, MI 48824. Phone: (517) 432-9907. Email: fkagerer@msu.edu

If you have questions or concerns about your role and rights as a research participant, would like to obtain information or offer input, or would like to register a complaint about this study, you may contact, anonymously if you wish, the Michigan State University's Human Research Protection Program at 517-355-2180, Fax 517-432-4503, or e-mail irb@msu.edu or regular mail at 4000 Collins Rd, Suite 136, Lansing, MI 48910.

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Approved by a Michigan State University Institutional Review Board effective 2/25/2019.
This version supersedes all previous versions. MSU Study ID STUDY00002078.

9. DOCUMENTATION OF INFORMED CONSENT.

Your signature below means that you voluntarily agree to participate in this research study.

Name of Participant	Date of Birth
Signature	Date
Email	Phone Number

- I voluntarily agree to allow photography/videotaping of my performance in the experiment.

  ☐ Yes ☐ No Initials_____

- I voluntarily agree to allow the videotapes or photos to be used later in publications or presentations

  ☐ Yes ☐ No Initials_____

Approved by a Michigan State University Institutional Review Board effective 2/25/2019.
This version supersedes all previous versions. MSU Study ID STUDY00002078.

APPENDIX D – Experiment 3 HIPAA Release

MSU AUTHORIZATION TO USE OR DISCLOSE
HEALTH INFORMATION FOR RESEARCH

Name: _____

Date of Birth: _____

If you sign this document, you give permission to all health care providers at the MSU HealthTeam to use or disclose (release) your health information that identifies you for the research study described below.

Title: Upper limb interactions in dystonia

Purpose of Research: The purpose of this research study is to examine bimanual coordination during upper limb movements in individuals with dystonia and individuals without dystonia. We also wish to measure underlying brain activity associated with differences in bimanual coordination using electroencephalography (EEG) while you do the motor task. The experiment is designed in a way that makes it possible to determine the influence of different task conditions, such as movement direction, distance, and velocity on arm and hand movements.

DESCRIPTION OF INFORMATION TO BE USED OR DISCLOSED (RELEASED) FOR THIS RESEARCH INCLUDES: Your medical history, medication/treatment schedule, and health information regarding your diagnosis.

THE HEALTH INFORMATION LISTED ABOVE MAY BE USED AND/OR DISCLOSED (RELEASED) TO:

- The Motor Neuroscience Laboratory at Michigan State University
  - Dr. Florian Kagerer, Principle Investigator
  - Phillip Desrochers, Graduate Student researcher
- Michigan State University Human Research Protection Program

You may refuse to sign this authorization and your refusal will not affect your ability to obtain treatment, however, it may affect your ability to participate in this research study.

You may change your mind and revoke (take back) this Authorization at any time, except to the extent that MSU HealthTeam has already acted based on this

V17-01 (12-3-2017)

Authorization. To revoke this Authorization, you must write to: The MSU privacy officer at Michigan State University, 965 Fee Road, A130 East Fee Hall, East Lansing, MI 48824.

MSU HealthTeam is required by law to protect your health information. By signing this document, you authorize MSU HealthTeam to use and/or disclose (release) your health information for this research. Those persons who receive your health information may not be required by Federal privacy laws (such as the Privacy Rule) to protect it and may share your information with others without your permission, if permitted by laws governing them.

EXPIRATION: Your Authorization to disclose the above information expires January 1, 2020

_____

Signature of individual participant or personal representative Date

_____

Printed name of individual participant or personal representative

_____

If applicable, a description of personal representative's authority to act for the individual participant

YOU WILL BE PROVIDED A COPY OF THE SIGNED FORM

A COPY OF THE SIGNED FORM MUST BE PROVIDED TO MSU HEALTHTEAM

APPENDIX E – Experiment 3 Screening Form

Principal Investigator: Dr. Florian Kagerer
Graduate Assistant: Phillip C. Desrochers

Upper Limb Interactions in Dystonia

Thank you for calling the motor neuroscience lab regarding our research on arm movements in dystonia. I would like to ask you a few questions in order to determine whether you may be eligible for the research. Before I begin the screening, I would like to tell you a little bit about the research. The purpose of this research study is to examine bimanual coordination during upper limb movements in individuals with dystonia and individuals without dystonia. We also plan to measure brain activity associated the bimanual coordination using electroencephalography (EEG) while you do the motor task.

Would you like to continue with the screening? The screening will take about 15 minutes. I will ask you questions about your demographics and your medical history, including any neurological disorders you may have, and any treatments you are undergoing. You do not have to answer any questions you do not wish to answer or are uncomfortable answering, and you may stop at any time. Your participation in the screening is voluntary.

Your answers will be confidential. No one will know your answers except for the research team. If you qualify for the study, and choose to participate by signing the informed consent form, we will keep your answers in a locked cabinet and/or password protected computer with other study data. If you don't qualify for the study, or choose not to participate, your answers to this screening will be destroyed.

Would you like to continue with the screening?

If no: No problem, thanks for speaking with me.
If yes: Wonderful. Let's begin.

Questions for all participants:

1) What is your name? _____
2) What is your DOB? _____
3) Would you be willing to provide your contact information so that we may get in touch with you if you qualify for the study?

   Email: _____

   Phone: _____
4) What is your sex? Male Female
5) What is your age? _____
6) What is your dominant hand? Right Left
7) Have you been diagnosed with a neurological disorder? Y/N

Approved by a Michigan State University Institutional Review Board effective 2/25/2019.
This version supersedes all previous versions. MSU Study ID STUDY00002078.

8) Have you had a concussion in the past year? Y/N

9) Do you have normal or corrected-to-normal vision? Y/N

Questions for Dystonia participants

10) What subtype(s) of dystonia do you have? _____

11) How long have you been diagnosed with dystonia? _____

12) Do you have pain associated with your dystonia?

_____

13) Have you been diagnosed with any neurological disorders besides dystonia?

_____

14) Over the course of your diagnosis, what treatments have you had to treat your dystonia?

_____

15) What are your current treatments?

_____

16) What is the treatment schedule and dose for your medications?

_____

_____

17) Are you taking any other medications? Y/N If so, what?

_____

18) Do you have a sensory trick (aka alleviating maneuver)? Y/N If so, what?

_____

19) If you are being treated with Botox injections, when is your next injection?

_____

20) Is there anything else that you can think of that you think I should know?

Thank you for answering the screening questions.

[Indicate whether the person is eligible, requires additional screening, or is not eligible and explain why.]

Do you have any questions about the screening or the research? If you have concerns or questions about this study, such as scientific issues, how to do any part of it, or to report an injury, please contact the Principal Investigator: Dr. Florian Kagerer, Dept. of Kinesiology, Michigan State University, 308 West Circle Drive, Suite 126, East Lansing, MI 48824. Phone: (517) 432-9907. Email: fkagerer@msu.edu.

If you have questions or concerns about your role and rights as a research participant, would like to obtain information or offer input, or would like to register a complaint about this study, you may contact, anonymously if you wish, the Michigan State University's Human Research Protection Program at 517-355-2180, Fax 517-432-4503, or e-mail irb@msu.edu or regular mail at 4000 Collins Rd, Suite 136, Lansing, MI 48910.

Thank you again for your willingness to answer our questions.

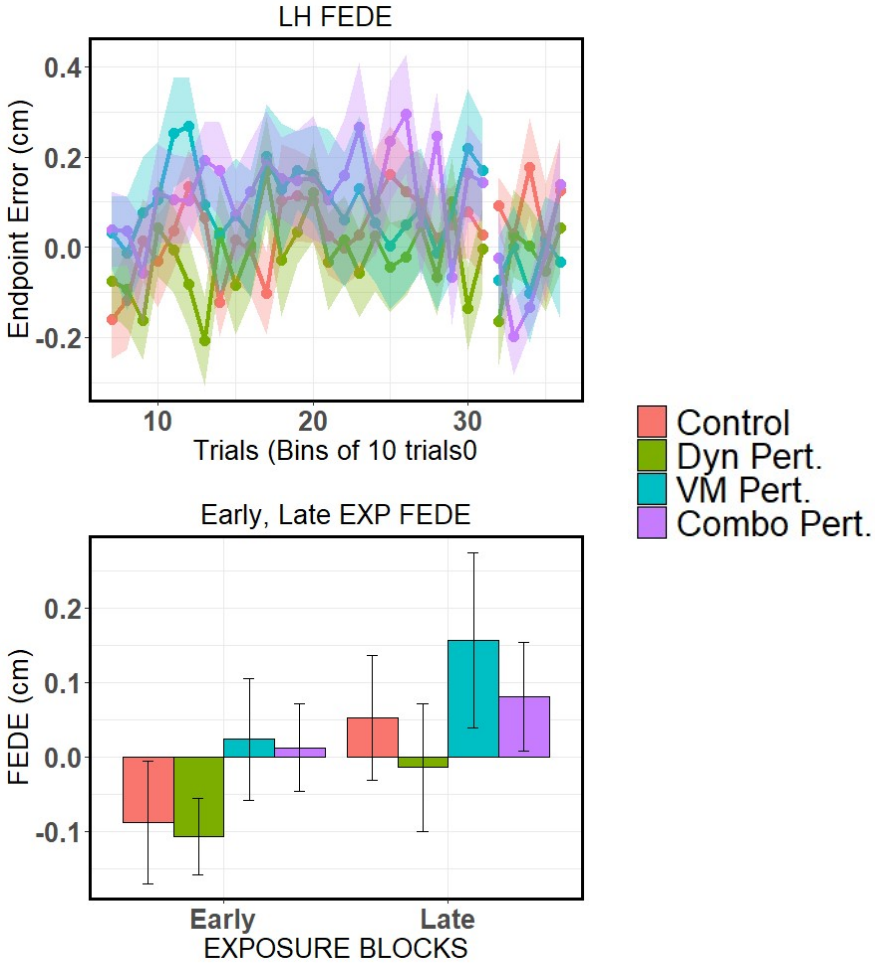

Figure 6-1: Exp 1 Final Endpoint error. In Experiment 1, Final Endpoint Directional Error (FEDE) was computed as the angle between a vector from the home position to the target and a vector from the home position and the position of the left hand at the end of the movement. Analysis with a 2 (Block: Early, Late) x 4 (Group: Control, Dynamic Perturbation, Visuomotor Perturbation, Combined Perturbation) mixed-design ANOVA showed a significant main effect of block ($F(1, 56) = 6.55$, $p = 0.01$). The main effect of group and the Group x Block interaction were not significant.

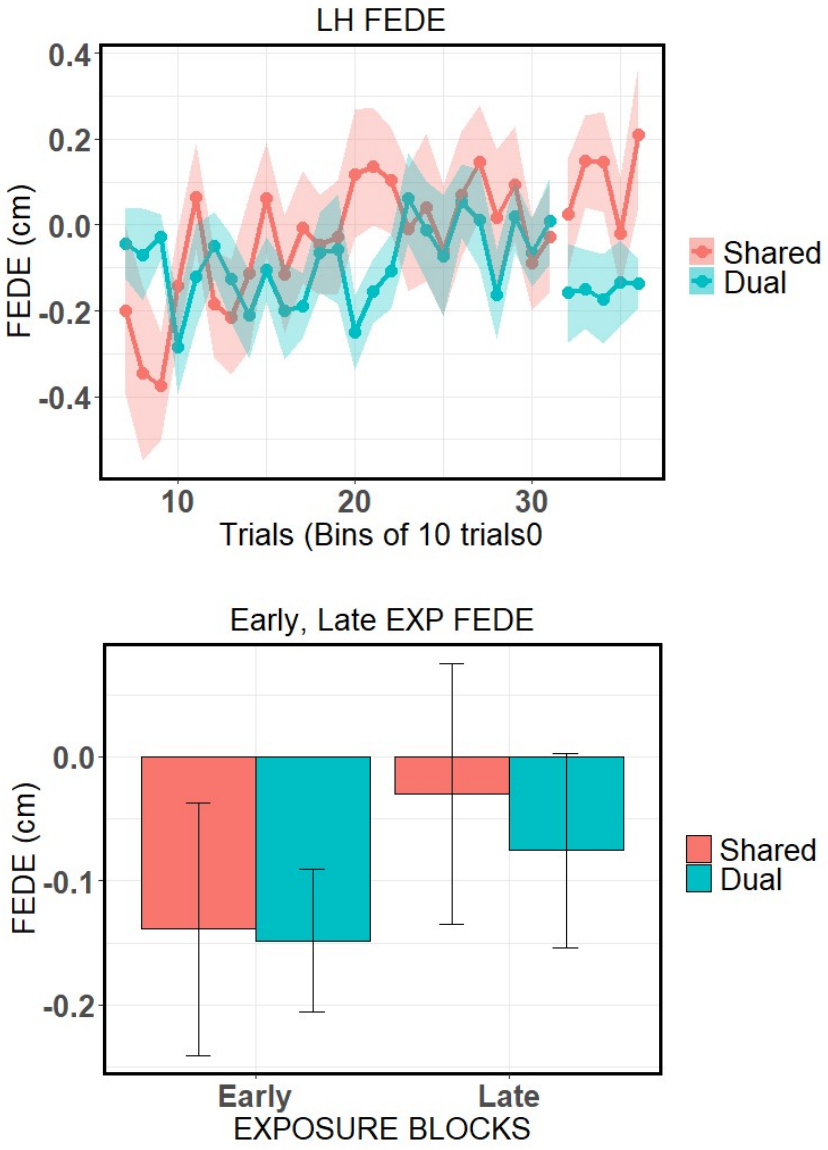

Figure 6-2: Exp 2 Final Endpoint Error. In Experiment 2, Final Endpoint Directional Error (FEDE) was computed as the angle between a vector from the home position to the target and a vector from the home position and the position of the left hand at the end of the movement. Analysis with a 2 (Block: Early, Late) x 2 (Group: Shared cursor vs. Dual cursor) mixed-design ANOVA showed no significant effects.

Toronto Western Spasmodic Torticollis Rating Scale, second edition (TWSTRS-2)

Severity Subscale

This scale is used to assess the severity of cervical dystonia and the success of its treatment. A total score of 0 to 35 can be achieved; this is made up of various subscores (A-F).

The first section of the Severity scale is maximal excursion. This section has rating items for the amplitude of excursion with patients allowing their head and neck to assume the spontaneous abnormal posture, without opposing the movement, during the manoeuvres indicated by the videotape examination protocol. The angle of the movement is determined for each axis of head movement, shifting of the neck on the shoulders in a forward or backward direction, and shoulder movement.

In scoring each item, it is important to score only for that particular posture. For example, the score for rotation would only include the degree of horizontal deviation separate from the other components of movement observed.

- For each item, full range is considered the range that a normal person without dystonia can achieve at maximal effort in a particular direction
- If a rating lies between two scores, the greater score is marked. There are no 0.5 scores accepted.

1. Rotation (horizontal turn: right or left)

Rotation is defined as the movement of the head along the horiztonal axis. The movement of the chin from the midline position to the right or left is best seen in the frontal view. In the mid-position, the chin is positioned directly over the sternum, midway between the attachments of the clavicles. Rotation is scored by the greatest degree of deflection from the mid-position.

0	None
1	Slight (1-22°; less than 25%)
2	Mild (23-45°, 25% to 50%)
3	Moderate (46-67°; 50% to 75%)
4	Severe (68-90°; greater than 75%)

2. Laterocollis (tilt right or left, exclude shoulder elevation)
Laterocollis refers to the angle of tilting of the head to the right or left but excludes shoulder elevation. As in rotation, the maximm deviation in a lateral direction is the score to be recorded. A technique for determining head tilt or laterocollis is to draw a line between the eyes or the ears and compare this line to the horiztonal plane.

0	None
1	Slight (1-22°; less than 25%)
2	Mild (23-45°, 25% to 50%)
3	Moderate (46-67°; 50% to 75%)
4	Severe (68-90°; greater than 75%)

3. Shoulder elevation/anterior displacement
This category inclues an assessment of the severity of shoulder movement, as well as a duration factor for the shoulder. Shoulder elevation is best evaluated from a frontal or posterior view. Anterior or posterior displacement of the shoulder is best viewed from a lateral or profile view.

0	Absent
1	Slight (<25% full range) intermittent or constant
2	Mild (greater than 25% but less than 50% of full range) intermittent or constant
3	Moderate (greater than 50% but less than 75% of full range) intermittent or constant
4	Severe (greater than 75% of full range) intermittent or constant

4. Range of Motion of the head and neck

The range of motion category assesses the ability of the patient to move from the abnormal posture through the midline to the extreme position without the aid of a sensory trick. Range of motion is assessed for each of the three axes of head movement: horizontal rotation, flexion/extension, and lateral tilting. The score for the most severely limited direction of movement is the final range of motion score.

0	Able to move to extreme opposite position
1	Able to move head well past midline but not to extreme opposite position
2	Able to move head barely past midline
3	Able to move head toward but not past midline
4	Barely able to move head beyond abnormal posture

5. Time holding head in midline

This item assesses the ability of the patient to hold the head within 10 egrees of the midline, normal head position. Obtaining midline position may be done using verbal direction. Obtaining midline marks the beginning of the time measure. The ability to remain in midline is obtaned twice, and the mean duration up to 60 seconds for each attempte is averaged to obtain the score. If the patient cannot reach mideline, the score is 4.

Attempt 1: _____ Attempt 2: _____ Average: _____

0	> 60 sec
1	46-60 sec
2	31-45 sec
3	16-30 sec
4	<15 sec

6. Duration of cervical dystonia during entire examination. Duration is determined during the course of the entire exam session and is an assessment of head deviation in any direction. Consists of two components: (a) the percentage of time during the entire examination AND b) the relative intensity of the head deviation during the examination (e.g., when present during the session, the head deviation was mote often submaximally or maximally present)

Note that the duration of shoulder movement is not consideredin the category, but is rated below in another section

0	None
1	Occasional deviation (<25% of the time), either maximal or submaximal
2	Intermittent deviation (25-50% of the time), either maximal or submaximal OR Frequent deviation (50-75% of the time), most often submaximal
3	Frequent deviation (50-75% of the time), most often maximal OR Constant deviation (>75% of the time), most often submaximal
4	Constant deviation (>75% of the time), most often maximal

Disability Subscale

On a scale of 0-5, how affected is the patient in each of the following scenarios)

1. Work	0	1	2	3	4	5
2. Activities of Daily Living	0	1	2	3	4	5
3. Driving	0	1	2	3	4	5
4. Reading	0	1	2	3	4	5
5. Television	0	1	2	3	4	5
6. Activities Outside of the Home (e.g., Shopping, walking about, movies, dining, and other recreational activities)	0	1	2	3	4	5

Total Disability (Sum Items 1-6. Maximal Score = 30): _____

Pain Subscale

1. Rate the **severity** of neck pain during the last week on a scale of 0-10 where a score of 1 represents a minimal ache and 10 represents the most excrutiating pain imaginable.

A. Best	0	1	2	3	4	5	6	7	8	9	10
B. Worst	0	1	2	3	4	5	6	7	8	9	10
C. Usual	0	1	2	3	4	5	6	7	8	9	10

Subtotal Severity :_____

2. Rate the duration of neck pain

0	None
1	Present <10% of the time
2	Present 10% to <25% of the time
3	Present 25% to <50% of the time
4	Present 50% to 75% of the time
5	Present >75% of the time

3. Rate the degree to which pain contributes to **disability**

0	No limitation or interference from pain
1	Pain is quite bothersome but not a source of disability
2	Pain definitely interferes with some tasks but is not a major contributor to disability
3	Pain accounts for some (less than half) but not all disability
4	Pain is a major source of difficulty with activities; separate from this, head pulling is also a source of some (less than half) disability
5	Pain is the major source of disability; without it most impaired activities could be performed quite satisfactorily despite the head pulling

Total Pain (Sum Items 1-3. Maximal Score = 40): _____

APPENDIX I – Experiment 3 time-frequency plots of electrode CZ

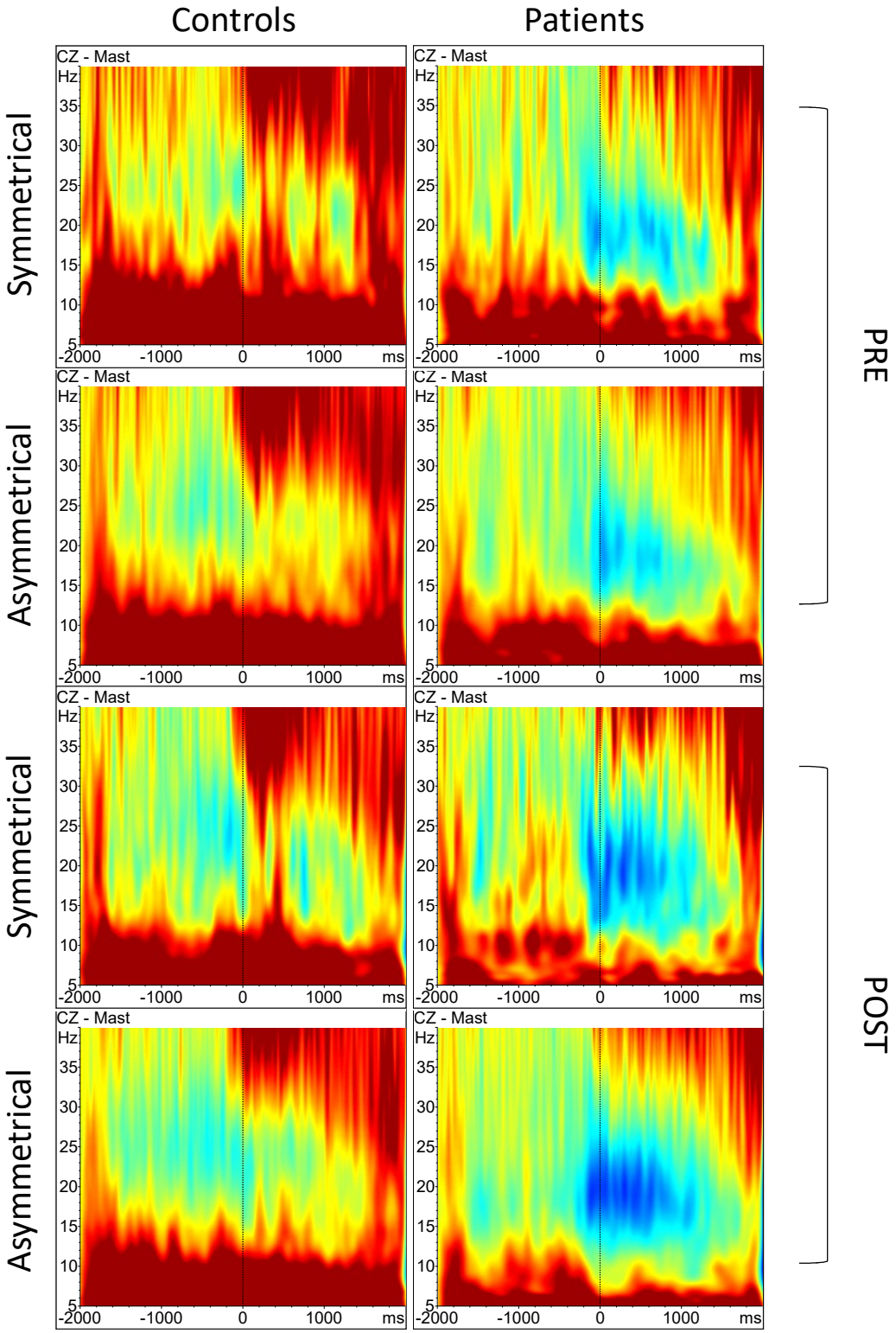

Figure 6-3: Experiment 3 Time-Frequency plots for electrode Cz. Note the large beta desynchronization in the patient group, particularly in the post-injection session

APPENDIX J – Magnitude squared coherence formula

The formula for magnitude-squared coherence (MSC):

$$MSC = |C^{X,Y}(t,f)|^2 = \frac{\left|\sum_{k=1}^{K} X_k(t,f) Y_k^*(t,f)\right|^2}{\sum_{k=1}^{K}|x_k(t,f)|^2 \sum_{k=1}^{K}|y_k(t,f)|^2}$$

Where:

$X_k(t, f)$ and $Y_k(t, f)$ are complex spectral fourier transform coefficients at segment k, time t and/or frequency f for input channels x and y

k is the free-of-artifact segment index

K is the number of free-of-artifact segments across all channel pairs

$C^{X,Y}$ is the coherency between channels

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REFERENCES

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