The Pennsylvania State University

The Graduate School

LATERALIZATION OF CENTRAL AND PERIPHERAL INFLUENCES ON BIMANUAL COORDINATION

A Dissertation in

Kinesiology

by

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Submitted in Partial Fulfillment

of the Requirements

for the Degree of

Doctor of Philosophy

August 2020

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Abstract

Bimanual movements, requiring fine coordination between the hands, make up a large portion of the tasks we perform every day. Neurophysiological evidence suggests that such bimanual movements recruit specialized neural circuits that do not appear to be a simple summation of dominant and non-dominant unimanual control networks. In addition, substantial asymmetries in coordination between the dominant and non-dominant limbs are well-known, and are thought to reflect lateralized cortical mechanisms of control between the hemispheres. This dissertation examines how a lateralized brain coordinates movements of both hands together, and what mechanisms allow for the fine coordination between the limbs necessary for functional bimanual movements. We first assessed whether bilateral feedback mechanisms involved in bimanual movements were asymmetric. We found that bilateral responses to perturbations during bimanual movements were expressed asymmetrically, such that non-dominant arm responses to perturbations to the dominant arm were stronger than dominant arm responses to non-dominant arm perturbations. We then studied two separate clinical populations to assess how central and peripheral mechanisms contribute to bimanual coordination. We found that stroke-related damage to one hemisphere affected certain aspects of bimanual control, specifically that predictive mechanisms that govern bilateral coordination are dependent on the left hemisphere (in right-handers). These findings indicate that assessment and training in cooperative bimanual tasks should be considered as part of an intervention framework for post-stroke physical rehabilitation. We also studied the effect of proprioception in bimanual coordination by studying movements of an individual who lacked somatosensory feedback due large fiber sensory

neuropathy (LFSN). The results indicated that loss of proprioception had differential effects on each aspect of control in the two limbs. The non-dominant left hand of the deafferented participant showed substantial deficits in trajectory coordination, but was better able to stabilize position at the end of motion, whereas the dominant right hand showed better trajectory control, but demonstrated greater drift at the end of movement. These asymmetries were not apparent in the movements of age-matched control participants, suggesting that somatosensory signals from the two moving arms might be critical for synchronized bimanual movements. Lastly, we examined mechanisms by which activity from one hemisphere can influence the other. To do this, we tested how components of reflexes are altered by muscle activity on the contralateral side. Isometric force generation in one hand facilitated long-latency but not short-latency reflexes in the opposite wrist, suggesting that a facilitatory mechanism involving transcortical pathways may mediate interhemispheric interactions. Taken together, these studies show evidence of lateralization of bimanual control mechanisms and provides methodological considerations that may inform research on identifying and treating bimanual deficits in clinical populations.

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Introduction

Bilateral Coordination

Neurophysiology of Bimanual Coordination

Bilateral coordination is crucial for activities of daily living, including preparing and eating food, donning and doffing clothing, and many other work, self-care, and leisure-related activities. Previous research has established that over the course of daily living, people use their hands significantly more in bimanual activities than in unimanual activity (Kilbreath & Heard, 2005). In addition, a wealth of evidence has shown that specialized neural resources are recruited during control of bimanual coordination that are not recruited during unimanual movements (Brinkman, 1984; Sadato et al., 1997; Donchin et al., 1998; Jäncke et al., 1998; 2000; Debaere et al., 2001). In other words, bimanual movements are not controlled by a simple summation of left and right unimanual control patterns. For example, neuroimaging studies have indicated a specialized role of the supplementary motor area in bimanual coordination (Sadato et al., 1997; Jäncke et al., 1998; 2000; Debaere et al., 2001) . In addition, Jäncke and colleagues reported that the left hemisphere is more active during bimanual movements than the right, specifically in the left supplementary motor area (Jäncke et al., 2000). Brinkman found that monkeys with supplementary motor area lesions showed specific deficits in the ability to coordinate both hands to solve a food retrieval task, but no deficits in the unimanual component tasks (Brinkman, 1984).

Studies using neurophysiological recordings have shown that some neurons in the primary motor cortex have activities that are specifically correlated with bimanual movements (Donchin et al., 1998). Zhuang et al. (2005) showed that bimanual movements recruit cortical interactions between left and righ primary motor cortices. The cingulate cortex also demonstrates bimanual-specific activity (Debaere et al., 2001), and lesions to cingulate cortex in humans appear to disrupt the ability to coordinate rhythmic bimanual movements (Stephan et al., 1999). Specifically, Stephan et al. (1999) found that patients with cingulate cortex damage had problems with bimanual movements in which the hands performed two different movements, such as tying shoes or fastening buttons. Evidence for a specialized role of the cerebellum in bimanual coordination has been supported by the finding of specific bimanual coordination deficits in patients with cerebellar dysfunction that impair the temporal ordering of bimanual movements (Brown, et al., 1993; Serrien & Wiesendanger, 2000). Behavioral studies showing little or no transfer of learning between bimanual and unimanual conditions have also suggested separate representations for unimanual and bimanual coordination (Nozaki, et al., 2006; Yokoi, et al., 2017). Taken together, this line of research indicates that coordination of bimanual movements recruits specific neural mechanisms that are not associated with unimanual coordination (Walsh, et al., 2008).

In addition, although most descending projections from the cortex cross over via the lateral corticospinal tract to innervate the contralateral side of the body, there are some projections that descend bilaterally or ipsilateral via the anterior corticospinal tract or through the brainstem via reticulospinal tracts (Brinkman & Kuypers, 1972; Kuypers,

1964). The anterior corticospinal tract, which descends ipsilaterally does have collateral projections bilaterally to pontine and medullary reticular nuclei, which have robust projections to the bilateral medial ventral horn, affecting predominantly proximal muscular of the trunk and limb girdles (Brinkman & Kuypers, 1972; Kuypers, 1964). However, more recent studies have also shown ipsilateral projections play a role in very complex movements or movements requiring high amounts of force, even in more distal muscles (Chen et al., 1997; Ziemann et al., 1999). It has also been shown that ipsilateral MEPs elicited in proximal muscles by TMS are asymmetric, such that the strength of ipsilateral MEPs evoked by stimulation of the dominant hemisphere is greater than MEPs evoked by stimulation of the non-dominant hemisphere (MacKinnon et al., 2004).

In addition to ipsilateral projections, there is also communication between the hemispheres via the corpus callosum, a white matter commissural tract connecting the left and right hemispheres. Several studies have identified an important role of the corpus callosum in coordinating bimanual movements (Preilowski, 1972; Franz et al., 1996; Eliasson et al., 2000; Kennerley et al., 2002), as well as transferring lateralized information between the hemispheres (Gazzaniga, Bogen, & Sperry, 1962; Risse et al., 1989; Gazzaniga, 2000). Studies on split brain patients, who have had their corpus callosum sectioned have provided much of the information on the role of the corpus callosum. Many functions, such as visual processing cannot be integrated across hemispheres without the corpus callosum (Gazzaniga, Bogen, & Sperry, 1962; Gazzaniga, 2000). Some somatosensory functions such as perception of light or deep touch can be detected by either hemisphere from both sides of the body, however,

stereognostic information processed by one hand is not available to the ipsilateral hemisphere (Gazzaniga, Bogen, & Sperry, 1963). Split hemispheres exert some control over both contralateral and ipsilateral movements, however, there are deficits in ipsilateral control, especially for more distal musculature (Gazzaniga, Bogen, & Sperry, 1967). More recent studies using fMRI to measure functional connectivity have shown that the corpus callosum plays a crucial role in maintaining functional connectivity between the hemispheres (Quigley et al., 2003; Roland et al., 2017). These studies highlight the importance of transcallosal pathways in integrating signals from each hemisphere. Examples of mechanisms of interhemispheric interactions will be discussed in later chapters.

Cyclical Bimanual Movements

As the neurophysiological data suggests, there are also interesting differences in behavior in bimanual movements compared to unimanual movements. When discussing bimanual movements, it should be noted that there are different categories of bimanual movements. The first category that has been the topic of extensive research is bimanual cyclical movements. This line of research started with the seminal study of Kelso (1984). This study examined cyclical bimanual finger oscillations during symmetrical, or in-phase mode, and asymmetrical, or out-of-phase mode. Kelso showed that as the frequency of asymmetrical cyclical movements increased, participant transitioned to the symmetrical mode unintentionally. This result spurred extensive research into cyclical movements in a variety of different effector systems studying phase transitions and coordination modes of bimanual coordination. Franz and colleagues (1996) showed that

spatial constraints of bimanual movements as well as temporal constraints were important in the coordination of cyclical bimanual movements. They showed that when subjects made continuous circular movements in one hand while simultaneously making straight line movements with the other, the movements became more similar to each other. It was hypothesized that the "coupling" observed in many of the bimanual paradigms may be due to a coupled motor program that tends to activate homologous muscles (Heuer, 1993). However, in a series of experiments, Mechsner et al. (2001) showed that spatial and perceptual symmetry was more important for stabilizing movements than activation of homologous muscles. One of the experiments in this study was a finger oscillation paradigm similar to that of Kelso and others, however in this case one of the hands was flipped such that in one hand the palm was facing down and the other palm was facing up. This meant that when performing spatially symmetrical finger oscillations there was not homologous muscle activation. Subjects showed a preference for the spatially symmetrical movements rather than co-activation of homologous muscles, suggesting that a shared motor program between homologous muscles was not what was causing the coupling. In addition, although certain aspects of cyclical bimanual movements appear synchronous, limitations to this coupling have been seen, specifically relating to the ability of each arm to control interaction torques in multijoint movements (Dounskaia et al., 2010). Although a shared motor program in bimanual movements is unlikely, there is evidence that ipsilateral pathways may be contribute to the stability of bimanual cyclical movements (Kagerer et al., 2003). Instability during antiphase cyclical movements was shown to be increased for people in which a distal ipsilateral MEP could be elicited,

suggesting that greater involvement of the ipsilateral cortex was contributing to the instability (Kagerer et al., 2003).

Goal-Oriented Bimanual Movements

Although much work has been done and continues to be done on cyclical bimanual movements, functional, goal-oriented bimanual movements have been studied less extensively. These types of movements make up a large portion of activities of daily living, yet have been less focused on by researchers. This may be due to the complexity of such tasks and the technical difficulties involved in attempting to study them (Obhi, 2004). Obhi states that studying these types of bimanual movements can uncover "new coordination rules and principles that will improve our general understanding of how the rich variety of bimanual coordination tasks that humans routinely perform are planned and controlled." These goal-oriented tasks, which are the focus of this dissertation, are made up of a variety of subcategories, which Kantak et al. (2017) have outlined, as shown in Figure 1.

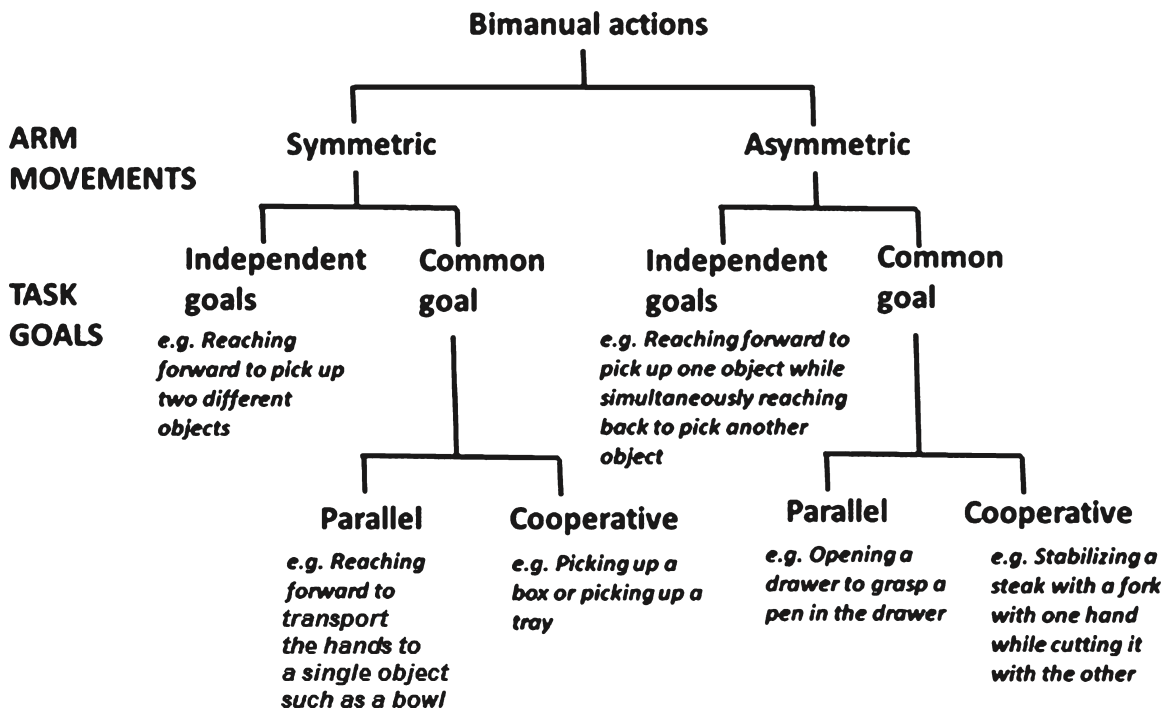

Figure 1- Subcategories of goal-oriented bimanual movements (Kantak et al., 2017)

Symmetric

Symmetric movements involve tasks in which both hands are required to move in the same way. Lateralization of control between the hemispheres presents a unique challenge to symmetrical bimanual movements, given the differences in movement qualities between dominant and non-dominant unimanual movements and differences in control between the dominant and non-dominant hemispheres (reviewed by Sainburg, 2014). Yet, one feature of symmetric bimanual movements that has been well-established is the tendency for the limbs to be tightly correlated in spatial and temporal measures, regardless of whether the two limbs are moving toward a common goal or they are moving to two separate targets of equal distance, similar to the coupling observed in symmetrical cyclical movements. The temporal parameters of movements, such as

movement start, peak velocity, and movement end, have been shown to be particularly tightly linked between the limbs even if some differences in spatial measures are observed (Wiesendanger et al., 1994; Nguyen et al., 2017). Although neural crosstalk effecting the control of each arm may contribute to this, it has also been suggested that somatosensory feedback plays an important role in temporal coupling and coherence between homologous muscles (Nguyen et al., 2017). As the neurophysiological data suggests, bimanual movements are not simple summations of right and left hand movements (Brinkman, 1984; Sadato et al., 1997; Donchin et al., 1998; Jäncke et al., 1998; 2000; Debaere et al., 2001). It is possible that one hemisphere dominates certain aspects of bimanual movements. Blinch et al. (2019) show that the left hemisphere may be dominant for symmetrical reach-to-grasp movements; a finding backed up by similar findings in cyclical bimanual movements (Byblow, Carson, & Goodman, 1994; de Poel, Peper, & Beek, 2007).

The task goal, and whether it is shared between the limbs or independent does play an important role in bimanual movements, particularly in adaptation to various perturbations (Diedrichsen, 2007; Diedrichsen & Dowling, 2009; Mutha & Sainburg, 2009; Dimitriou et al., 2012; Omrani et al., 2013). Diedrichsen (2007) found that in a symmetric bimanual reaching task that participants responded to a force field applied to one of the arms in a very different way depending on whether each arm moved to its own independent target simultaneously, the two arms shared a cursor and moved to one shared target. In the independent condition, the arm that was not perturbed did not respond to the perturbation of the other arm, but when the task was shared between the arms both arms

responded in in a way that was optimal for the overall task, showing that feedback circuits are modulated in bimanual movements based on task demands. More recent studies have shown that even rapid feedback mechanisms such as reflexes can be modulated in a task-specific way during bimanual movements (Mutha & Sainburg, 2009; Dimitriou, et al., 2012; Omrani, et al., 2013).

Asymmetric

Many of the bimanual tasks that we perform every day are movements in which each hand has distinct actions. This includes tasks in which the goals of each arm are independent, such as simultaneously picking up to different objects at different locations. Much research has been done on these types of movements, most of it looking into how the movements of each arm can interfere with the other, but also what movement constraints are tightly synchronized. Another seminal study by Kelso and colleagues (1979) examined how participants simultaneously initiated and terminated bimanual movements to targets of widely disparate difficulty. They found that although the hands moved at different speeds when moving to different targets, the times to peak velocity and acceleration were synchronized between the hands. The authors believed this to be an organizing principle of bimanual coordination. Marteniuk et al. (1984) showed bimanual interference in a similar task, such that movements to 10 cm targets were overshot in one hand when the other hand was reaching to 30 cm targets and movements to 30 cm targets were undershot when the other hand reached to 10 cm targets. Their findings also differed from Kelso's, showing significant asymmetry in temporal coupling.

This research has sparked much interest into studying the source of bimanual interference and coupling. Swinnen et al. (1991) postulated that bimanual interference may be the result of a bilaterally distributed motor system, which mainly activates proximal musculature, and the ability to perform asymmetric bimanual tasks depends on the ability to suppress such activity. This idea was challenged, however, by the finding that direct cueing of asymmetric bimanual tasks can largely eliminate interference (Diedrichsen et al., 2001). This suggested that interference may be due to issues with stimulus identification and response selection (Hazeltine et al., 2003). Blinch et al. (2014) found increased reaction times associated with asymmetric bimanual movements in choice conditions compared to unimanual and symmetric bimanual movements. They attributed this asymmetric cost to interference during response programming. The question remains whether interference occurs at the afferent or efferent level of motor control. Swinnen et al. (2003) studied this question in a bimanual interference paradigm while manipulating afferent inputs such as vision and proprioception. They found no significant changes in interference when afferent inputs were manipulated, suggesting that interference occurs at the efferent level. In contrast, Kazennikov and Wiesendanger (2005) found in a similar paradigm that synchronization of the two hands during a bimanual reach and grab task was disrupted by altering proprioception via tendon vibration applied to one of the arms. Both studies manipulated proprioception using tendon vibration, which alters but does not eliminate proprioceptive input, leaving some uncertainty about the effect of proprioception on bimanual movements.

Many daily tasks involve movements in which the two hands do different tasks to achieve a common goal. These bimanual movements include movements in which the two limbs perform acts in parallel, such as reaching to pull out a drawer with one hand and picking up an item in the drawer with the other. In these cases, even though the movements have different functions, movements of both hands are temporally linked (Perrig et al., 1999; Kazennikov et al., 2002). The hand that is picking up the object tends to prolong its trajectory compared to unimanual movements, so that the velocity peaks are linked to the velocity peaks or velocity changes of the other hand (Kazennikov et al., 2002). Although the movements were separate, the two limbs covaried in a task-dependent way. Domkin et al. (2002) studied the covariation between the two limbs in a bimanual task using Uncontrolled Manifold analysis. They found that the kinematic variability was structured to stabilize the performance of both limbs together, suggesting that the bimanual synergy was not simply a simultaneous execution of two unimanual synergies.

Asymmetric bimanual movements can also be cooperative, such as holding down a loaf of bread with one hand while cutting with the other. These types of tasks often reflect the specialization of each hemisphere. For example, Woytowicz et al. (2018) designed a task to recreate an experimental equivalent of cutting bread. The two hands were connected with a spring and one hand was to maintain a position while the other had to make smooth and accurate movements to a target. They showed that the non-dominant hand performed better in maintaining a position, while the dominant hand made straighter reaches, reflecting the specialization of each side shown in unimanual movements

(Sainburg, 2002). Sainburg and colleagues have reported extensive differences in movement characteristics between the dominant and non-dominant side in a variety of unimanual tasks (Bagesteiro & Sainburg, 2002; Sainburg, 2002; Sainburg, 2014). They have suggested that these differences arise because of differences in mechanisms of control between the dominant and non-dominant hemispheres, specifically that the dominant hemisphere relies on predictive control of body and environmental dynamics and the non-dominant hemisphere relies on impedance control to stabilize positions and minimize errors.

In bimanual movements, the nervous system must tightly constrain certain aspects of control between the limbs in order to maintain symmetrical or cooperative movements, but this is complicated by the asymmetry of our motor system. One of the main goals of this dissertation is to examine how these differences in control between the hemispheres persist during bimanual movements, and the neural mechanisms that allow the two hemispheres to communicate and control each side cooperatively. Specifically, the dissertation will ask:

1) Are rapid bilateral feedback responses elicited asymmetrically, reflecting the lateralized mechanisms of cortical control?
2) What is the role of central contributions to bimanual movements and are certain aspects of cooperative bimanual movements driven by one hemisphere or the other?
3) What is the role of peripheral contributions in interlimb coordination during cooperative bimanual tasks?

4) What are the mechanisms involved in facilitatory bilateral interactions between the upper limbs?

Literature Review

Bilateral Reflexes

Given the specialization of motor-related brain regions for bilateral coordination, it is not surprising that reflexes might be differentially modulated by descending commands for unilateral and bimanual movements (Diedrichsen, 2007; Diedrichsen & Dowling, 2009; Mutha & Sainburg, 2009; Dimitriou, et al., 2012; Omrani, et al., 2013). Reflexes in which one limb responds to stimulation of the other limb, such as the crossed-extension reflex have been well described over century ago (Sherrington, 1910). However, task specific bilateral reflexes that emerge only during bimanual tasks and involve cooperative task goals, such as moving a single object with both hands, have more recently been described (Diedrichsen, 2007; Diedrichsen & Dowling, 2009; Mutha & Sainburg, 2009; Dimitriou et al., 2012; Omrani et al., 2013). In a seminal study, Diedrichsen (2007) applied a velocity-dependent force field to one arm during bimanual forward reaching movements and reported error corrections in the non-perturbed arm that occurred late in the movement, but were only expressed when a single cursor was shared between both arms, but not when each arm carried its own cursor to its own target. Mutha and Sainburg (2009) extended these findings to reflex responses at the shoulder joint that occurred within 50 milliseconds of perturbation onset, a latency associated with the transcortical component of the stretch reflex (Kurtzer, et al., 2008; Omrani et al., 2013). This study was done by applying an unpredictable 50 Newton force perturbation of 50 millisecond duration to one of the arms, under two task conditions: 1) Two targets and cursors were displayed for each arm, and the cursors were to be brought to the targets

simultaneously. 2) A single cursor displayed between the hands that depended on the position of both hands was to be brought to a single target. Reflex responses occurred in both the perturbed dominant arm and the contralateral non-dominant arm when the task and cursor were shared between the arms, but only in the perturbed arm when the task and cursor were not shared. However, this study only examined responses to dominant arm perturbations, and not to non-dominant arm perturbations. The long-latency nature of bilateral reflexes suggests the involvement of transcortical loops (Evarts & Tanji, 1976; MacKinnon, et al., 2000; Pruszynski, et al., 2014).

We have previously reported substantial asymmetries in cortical mechanisms of control, throughout the posterior frontal and parietal lobes (Mutha, et al., 2014). We hypothesize that this asymmetry in the cortical control of movement might be reflected in long-latency reflexes. Thus, we predict that long latency bimanual reflexes might be expressed asymmetrically in a manner that reflects neural lateralization for motor control. Previous research has suggested that the hemisphere contralateral to the non-dominant arm is specialized for feedback mediated control mechanisms that are important when performing movements in unpredictable mechanical environments and to stabilize the limb against loads applied by the dominant arm (Duff & Sainburg, 2007; Schabowsky et al., 2007; Yadav & Sainburg, 2014; Woytowicz et al., 2018). In contrast, the hemisphere contralateral to the dominant arm appears specialized for predictive control of limb and task dynamics, which is particularly effective when performing movements in consistent environmental conditions (Sainburg, 2002; Yadav & Sainburg, 2014). As a result of this asymmetry in control, participants adapt more effectively using the dominant arm when

performing in predictable and consistent force environments, but adapt better to unpredictable force fields, using the non-dominant arm (Yadav & Sainburg, 2014). A simplified view of this asymmetry can be expressed as dominant hemisphere/limb specialization for predictive control, and non-dominant hemisphere/limb specialization for reactive control mechanisms.

We hypothesize this asymmetry in cortical control of movement should be reflected in cortical modulation of reflexes during bimanual activities. We thus test whether bimanual reflex mechanisms are lateralized during cooperative bimanual movements. We predict that the non-dominant responses to dominant arm perturbations will be more robust than dominant arm responses to non-dominant arm perturbations.

To test these predictions, we used a shared bimanual task similar to that of Mutha and Sainburg (2012), in which participants were instructed to move a bar with both hands to a target trough. On random trials either the dominant or non-dominant arm was perturbed and the kinematic and EMG response to the perturbation on both arms were analyzed. We examined whether the responses of the arm ipsilateral to the perturbation as well as the arm contralateral to the perturbation differed depending on which arm (dominant or non-dominant) was perturbed.

Unimanual and Bimanual Deficits in Stroke

While the motor deficits that result from contralesional hemisphere stroke can be devastating and include complete loss of voluntary control, the idea that deficits might

also occur in the arm ipsilateral to the brain lesion has also been demonstrated. Many studies have found that damage to one hemisphere causes deficits in the ipsilesional arm (Haaland, et al., 1977; Haaland & Delaney, 1981; Fisk & Goodale, 1988; Haaland & Harrington, 1989;), and that these deficits are different depending on the side of the damage. Haaland and Harrington (1989) showed that in a simple aiming task done with the ipsilesional arm of both right hemisphere damaged and left hemisphere damaged patients, the left hemisphere damaged group was slower and the initial movement was less accurate than controls. The right hemisphere damaged group was not significantly impaired on any measure. Winstein and Pohl later (1995) supported these findings in an alternating tapping task, showing that left hemisphere damage resulted in deficits in the open-loop components of movement and right hemisphere damage affected the closed-loop components. Haaland et al. (2004) found a similar distinction between open-loop and closed-loop components as left hemisphere damaged patients suffered deficits in the initial components of movement and right hemisphere damaged patients suffered in final position error. Studies that have applied more detailed kinematic and kinetic analyses have indicated a similar dichotomy. While left hemisphere damage produces ipsilesional deficits in predictive aspects of control that affect trajectory and multi-joint coordination, right hemisphere damage produces deficits in the ability to achieve and stabilize final steady state positions (Schaefer, et al, 2007; 2009). Similar results have been seen in contralesional movements for patients with mild paresis (Mani et al., 2013).

Sainburg and colleagues (2002) have proposed a bihemispheric model of motor control, as a foundation for undertanding the nature of ipsilesional deficits in stroke. Each

hemisphere is specialized for different aspects of control, as stated above, and thus lesions to one hemisphere will produce hemisphere-specific deficits in control in both arms of patients. In patients with severe paresis, such deficits may only be apparent in the ipsilesional arm because the paretic arm is too impaired to observe such deficits. As discussed above, bilateral coordination recruits unique neural mechanisms, including cortical circuits. We hypothesize that the same hemispheric specializations that predict deficits in unilateral motor control should predict specific deficits in bimanual coordination. Thus, we predict that temporospatial coordination between the hands early in movement, determined by predictive mechanisms should be disrupted by left but not right hemisphere damage in unilateral cortical stroke patients. In contrast, we predict that lesions to right hemisphere should disrupt coordination during the stabilization phase of reaching movements. It should be stressed that we are not simply predicting that the deficits previously shown for unilateral movements should be expressed during bimanual movements, but rather that hemisphere specific deficits in bimanual coordination will occur.

It is, in fact, important to understand the effect of specific brain lesions on bimanual coordination because of the importance of bimanual movements to activities of daily living and functional recovery in stroke patients (Kilbreath & Heard, 2005). There is substantial evidence that in addition to unimanual training following stroke, it is important to also specifically train bimanual activities in which both hands must move cooperatively (Waller, et al., 2008; Sainburg, et al., 2014). McCombe Waller et al. (2008) showed that improvement after stroke was specific to the method of training,

such that patients who received bilateral training improved more in bilateral performance and patients who received unilateral training improved more in unilateral movements. This highlights the need for a greater focus on bilateral mechanisms of control in stroke rehabilitation. In addition, the need for more research on functional, goal-directed bimanual tasks, specifically ones that involve cooperation between the hands, is important for understanding these mechanisms (Obhi, 2004; Sainburg et al., 2014). Some work has been done on identifying functional deficits in bimanual coordination in stroke patients. For example, Kang and Caraugh (2014) found that stroke patients showed increased bimanual force variability, mostly driven by the paretic arm, in a force control task. In addition stroke patients have shown an inability to coordinate both hands efficiently during cooperative tasks such as picking up boxes (Kantak, et al., 2016). However, these studies did not the effect of specific lesion locations, including the damaged hemisphere, factors that could be critical in identifying bimanual coordination deficits and ultimately designing intervention based on this information.

We hypothesize that predictive processes that are involved in coordinating bimanual movements may be dependent on left hemisphere processes, and therefore predict that LHD patients will show more deficits in a bimanual task, specifically early in the movement. We tested the contribution of each hemisphere to bimanual coordination using a shared bimanual task in which participants move an object (bar) to targets. We examined performance differences in patients with left hemisphere damage

and right hemisphere damage compared to age-matched controls to see what specific deficits resulted from left or right hemisphere damage.

Deafferentation

The role of sensory information in motor control and coordination is reflected by the common use of terms such as sensorimotor control and sensorimotor cortices. The specific role of proprioception in motor control has been studied since the beginning of motor control research, and is emphasized by the extensive innervation of muscles with specialized sensors, including the muscle spindle and the Golgi tendon organ. Information from these sensors is transmitted to the CNS through the fastest neurons in the mammalian system, including the type IA, IB, and II sensory axons, emphasizing the critical nature of proprioception to motor processes. One of the first approaches to study the role of proprioception in motor control was to deafferent parts of the body, like the forelimb, through surgical dorsal rhizotomy, and observe the effects on movement. Mott and Sherrington (1895) found that after complete dorsal rhizotomy, monkeys were unable to perform purposeful movement, with the exception of some random movements that occurred under certain stressful situations. This finding led to the conclusion that afferent feedback is necessary for purposeful movements. This view was largely persistent, as corroborated by Lassek (1953) and Twitchell (1954), even though Munk (1907), in Germany, showed that bilaterally deafferented monkeys could be trained to perform functional movements, although they were somewhat impaired. Munk's findings were not supported until a series of studies by Taub and colleagues showed that deafferented monkeys could learn newly conditioned responses (1965), regain movements that were

conditioned prior to deafferentation (1966), and could accurately point to targets with and without visual feedback (1975). These studies showed that voluntary movements could be performed in the absence of afferent feedback, although significant deficits in movement were present.

These findings were not confirmed in humans until Rothwell et al. (1982) studied the effects of large fiber sensory neuropathy (LFSN). LFSN results in loss of proprioception and discriminative touch sensations, and has been shown to produce deficits in intralimb coordination and in the ability to stabilize the limb, in the absence of visual feedback (Rothwell et al., 1982; Sainburg & Ghez, 1993; Sainburg, et al., 1995). Specifically, deafferentation has been found to result in an inability to maintain constant motor output without visual feedback (Rothwell et al., 1982; Sanes, et al., 1985). Gordon et al. (1995) found large drifts and secondary movements at the end of movements, again showing deficits in maintaining a stable motor output. However, deafferented patients are able to perform fast, single-joint movements similar to controls (Forget & Lamarre, 1987). Deafferented patients have also been shown to be able to appropriately scale forces (Gordon, et al., 1987). In more complex tasks, which involve multi-joint movements, Sainburg and colleagues have found deficits in interjoint coordination, as shown by their inability to compensate for interaction torques during movement (Sainburg & Ghez, 1993; Sainburg et al., 1995). They suggested that proprioception is required to compensate for the mechanical effects arising from dynamic interactions between motions of linked limb segments. Other studies involving multi-joint movements

in deafferented patients have found similar deficits in inter-joint coordination (Messier, et al., 2003; Sarlegna, et al., 2006).

A few studies have also examined the effect of deafferentation on bimanual movements. Bimanual movements add another layer of complexity to the system as they require not only accurate inter-joint coordination but also inter-limb coordination. Many studies have found a coupling effect in bimanual movements in healthy people that link certain aspects of each arm's movement (Kelso, et al., 1979; Swinnen, et al., 2002). Studies have specifically shown a strong correlation of the temporal aspects of bimanual movement (Bozzacchi, et al., 2017), with some even showing a "bimanual advantage" in timing of movements (Helmuth & Ivry, 1996). Interestingly, Drewing et al. (2004) showed that this timing advantage for bimanual movements was persistent in a finger tapping task, and actually even stronger for deafferented patients compared to controls, showing that this effect is not due to sensory feedback. Spencer et al. (2005) also showed strong temporal coupling for deafferented patients in a bimanual circle drawing task, even though deafferented patients showed much larger deficits in spatial consistency and position.

It should be stressed that studies that have demonstrated intact or even superior interlimb coordination have focused predominantly on temporal coordination, as opposed to spatial coordination. Seminal research by Diedrichsen and colleagues has previously demonstrated context dependent factors in bimanual coordination (Diedrichsen, 2007) . When presented with a task requiring simultaneous reaching to two separate targets with

each arm, the presentation of a disturbing force to one arm had no effect on the opposite arm. However, when moving a single cursor between the arms, the opposite arm corrected for the disturbing force, even though the limbs were not mechanically coupled. Mutha and Sainburg, showed similar, but shorter latency effects, in response to discrete force pulses applied to one, but not the other arm. During bimanual cooperative task of moving a single cursor, reflexes were elicited in the opposite arm, but during a non-cooperative task of moving both cursors, bimanual reflexes were not elicited. Schaffer and Sainburg (in press) recently corroborated these findings in a study that showed asymmetries in such responses. We thus expect that, in contrast to studies examining temporal coordination between the arms during repetitive bimanual motions, proprioception should be critical for bimanual spatiotemporal coordination during a cooperative bimanual task.

As previous studies have suggested an important role of proprioception in interjoint coordination (Sainburg & Ghez, 1993; Sainburg et al., 1995; Messier et al., 2003; Sarlegna et al., 2006), we hypothesize that proprioceptive information is also important for interlimb coordination during bimanual movements. We predict that a deficit in interlimb coordination from sensory deafferentation will result in movements that are poorly coordinated between the arms and more asymmetric.

We examined the role of proprioception on bimanual coordination by observing performance of a sensory deafferented individual in a bimanual task. An individual with large fiber sensory neuropathy (LFSN) performed bimanual movements in two

conditions: one in which both arms moved a shared object to a target area, and a two-cursor task in which participants moved both arms simultaneously to two separate targets. Performance in these two tasks for the deafferented patient was compared to age-matched controls.

Bilateral Interactions

Bilateral interactions between the upper limbs have been well-documented, however, the neural mechanisms underlying these interactions are not well-understood. A consistent feature of bimanual coordination is the tendency for people to prefer symmetrical movements. In cyclical bimanual movements, it has been shown that people are more stable when the movements of the right and left side are in phase with each other (Kelso, 1984; Mechsner, et al., 2001). In addition, people perform better in discrete bimanual movements if the movements are symmetrical between the limbs, and when performing asymmetrical movements there is a tendency for the movements to become similar to each other (Swinnen, et al., 2001). Mirror movements during unimanual movements are also observed during development and in clinical populations (Mayston, et al., 1999). In healthy adults, mirror movements are mitigated to some degree by the presence of inter hemispheric inhibition (IHI).

IHI refers to inhibitory effects that occur in one hemisphere when the opposite hemisphere is activated. Cracco et al. (Cracco, et al., 1989) was one of the first groups to show these inhibitory effects in humans using brain stimulation techniques. Ferbert et al. (1992) expanded on these results, using what is now the classic IHI technique. This

technique involves use of transcranial magnetic stimulation (TMS) on the motor cortex to apply a test stimulus and a resulting motor evoked potential (MEP), which is often done on first dorsal interosseous muscle. Then they apply a conditioning stimulus to the opposite hemisphere, which inhibits the size of the MEP coming from the test stimulus. Studies on patients with callosal damage have shown that inhibition is mediated by transcallosal pathways (Meyer, et al., 1995), which is likely through excitatory axons that cross the corpus callosum to act on local inhibitory neurons in the contralateral motor cortex (Berlucchi & Antonini, 1990). Functionally, interhemispheric interactions are important in facilitating communication between the hemispheres necessary for bimanual coordination as well as preventing mirror movements during unimanual movements. Fling and Seidler (2012) showed that IHI correlates with unimanual and symmetric bimanual force tasks, but increased IHI also limits performance on independent bimanual force tasks. Musicians, such as guitarists and pianists, who are required to perform two different dexterous movements simultaneously with each hand show reduced IHI (Ridding, et al., 2000).

Interhemispheric interactions also can be altered in a task-specific manner. Although IHI via transcallosal pathways is a well-known phenomenon, there are some cases in which these pathways can yield facilitation of the other hemisphere. The increased excitability of motor pathways resulting from muscle contraction on the opposite side, termed motor irradiation, has been documented in a variety of situations. For example, while low force levels produced by one hand lead to a decrease in MEP amplitude in the homologous contralateral muscle (Liepert, et al., 2001), high force levels

(25–50% MVC) lead to increased responses (Hess, et al., 1986; Muellbacher, et al., 2000). Other studies have found that when forces exceed approximately 70% of MVC, interhemispheric interactions can result in increased cortical excitability in the opposite hemisphere (Perez & Cohen, 2008; Long, et al., 2016)

Thus, facilitation, or increased excitability via contralateral force production has been well documented, but the neural pathways that mediate it are not known. A number of pathways, both at the cortical and subcortical level, have been suggested as candidates for being involved in this phenomenon. Evidence for a cortical influence on facilitation was provided by Stedman et al. (1998), who showed the facilitatory effect when stimulating the cortex, but not when stimulating the spinal cord. Specifically, it has been suggested that uncrossed ipsilateral corticofugal pathways may be involved (Carson, 2005). Although ipsilateral pathways mostly innervate more proximal muscles (Brinkman & Kuypers, 1972) subjects in which ipsilateral MEPs could be elicited at distal muscles have shown greater instability in bimanual movements, suggesting ipsilateral projections could be involved in bimanual coupling (Kagerer, et al., 2003). Muellbacher et al. (2000) also reported increased excitability in ipsilateral M1 during unimanual forceful hand muscle activation which may contribute to the facilitation of MEPs. It is also possible that this effect is elicited via interhemispheric transcallosal pathways (Carson, 2005). Although interhemispheric inhibition was shown to be absent or delayed in patients with corpus callosum abnormalities, the facilitatory effect brought on by strong contraction of contralateral hand muscles persisted in the patients, suggesting that transcallosal pathways are not responsible for this effect (Meyer et al., 1995). This finding may also be

interpreted as evidence that the facilitation occurs at a subcortical level. It has been shown that during walking, H-reflexes can be modulated by active contraction of contralateral leg muscles (Brooke, Misiaszek, & Cheng, 1993; McIlroy, Collins, & Brooke, 1992). Muellbacher et al. (2000) also showed changes in motor neuron excitability resulting from contralateral activation, as shown by contralateral F-wave facilitation. This evidence suggests subcortical mechanisms of facilitation are involved.

Clearly there is conflicting evidence as to where and by what mechanisms the contralateral facilitation occurs. In order to test whether this interaction is occurring at the spinal or supraspinal level, we designed an experiment to examine how reflexes were modulated by strong contralateral force. Specifically, the experiment was designed to test whether the short or long-latency components of a reflex elicited in the wrist flexors of one arm were differentially modulated by strong isometric wrist flexion on the contralateral side. Whereas the short-latency component of the stretch reflex involves spinal circuitry, long-latency responses are thought to reflect cortical involvement, based on findings showing changes in motor cortex activity that precede the long-latency reflex (MacKinnon et al., 2000; Spieser et al., 2010) as well as the ability for the long-latency reflex to be modified in a task-dependent manner that can account for variations in limb dynamics (Evarts & Tanji, 1976; Pruszynski et al., 2014; Kurtzer, 2015). Thus, if contralateral force facilitates a stronger reflex response to a perturbation in the short-latency component of the reflex, then the facilitation is likely due to spinal mechanisms. Alternatively, if the long-latency components of the reflex are facilitated, then that provides evidence that supraspinal mechanisms are involved.

Studies

Interlimb Responses to Perturbations of Bilateral Movements are Asymmetric

We have previously reported substantial asymmetries in cortical mechanisms of control, throughout the posterior frontal and parietal lobes (Mutha, et al., 2014). We hypothesize that this asymmetry in the cortical control of movement might be reflected in long-latency reflexes. Thus, we predict that long latency bimanual responses might be expressed asymmetrically in a manner that reflects neural lateralization for motor control. We now ask whether these interlimb responses are expressed symmetrically. We tested this question in a virtual reality environment: a cursor representing each hand was used to 'pick up' each end of a virtual bar and place it into a target trough. Near the onset of occasional, unpredictable trials, one arm was perturbed. Regardless of which arm was perturbed, ipsilateral responses were significant during the perturbation. However, responses in the arm contralateral to the perturbation were asymmetric. While the non-dominant arm showed a significant kinematic response to correct the bar orientation when the dominant arm was mechanically perturbed, the dominant arm did not respond when the non-dominant arm was perturbed. We also saw an asymmetric response in early EMG activity, in which only the non-dominant anterior deltoid showed a significant reflex response within 100 milliseconds of perturbation onset in response to dominant arm. This response was consistent with correcting the bar position, but not with correcting its orientation. We conclude that responses to perturbations during bilateral movements are expressed asymmetrically, such that non-dominant arm responses to

perturbations to the dominant arm are stronger than dominant arm responses to non-dominant arm perturbations.

Experimental Procedures

Participants

Participants were 10 healthy right-handed adults (5 male, 5 female) aged 18-25 years old. All participants were screened for handedness using the Edinburgh Inventory (Oldfield, 1971) with a mean handedness score of 68.85 across all participants, indicating moderate right-handedness. Each participant provided informed consent before participation in this study, which was approved by the institutional review board of Penn State University.

Experimental Setup

Participants were seated at a 2-D virtual-reality workspace in which stimuli from a TV screen were reflected by a mirror, with the participants' arms under the mirror. Figure 2 shows this experimental set-up. Participants' arm movements were tracked using 6 DOF magnetic sensors (Ascension TrackStar) placed on the hand and upper arm. All joints distal to the forearm were splinted. We digitized the location of the tip of the index finger, as well as multiple locations on the hand, and upper arm, and used custom software to estimate the locations of the wrist, elbow, and shoulder joints, relative to these digitized landmarks. Vision of the participants' arms was occluded while position of the index finger was provided as a cursor on the screen. Participants' arms were supported on air sleds that reduced the effects of friction, and eliminated gravitational torques at the joints. Attached to each air sled was a metal rod that glided through a low-

friction vinyl sleeve on a swivel. During baseline movements of the arms, the rods glided through the low friction sleeve, allowing for unhindered motion. A friction-instantiated brake, attached to a solenoid clamped the rod when triggered, restricting motion of one arm, predominantly in the antero-posterior direction for perturbations. It is important to note that there was no mechanical connection between the arms, and thus there was no mechanical stimulus applied to the non-perturbed arm. The solenoid clamp was mounted on a low friction ball-bearing swivel, which when clamped restricted motion of the arm about an arc with a radius defined by the location of the hand along the anterior posterior axis (Y-Axis). While the perturbation occurred in time, relative to the start in movement (10 ms after movement onset), it always occurred prior to the hand traversing midway between the start and the target location. This midpoint was 50 centimeters from the center of the swivel.

The geometry of this set-up allowed us to approximate the perturbation as arresting forward motion, but allowing perpendicular displacement. Specifically, an excursion along an arc of 10 cm is associated with a displacement parallel to the target direction of just 0.99 cm, and a displacement perpendicular to the target direction of 9.93 cm. We thus approximate the perturbation as braking motion along the target direction. The trial started when both hands, and thus sides of the virtual bar, left the start circles. The onset of movement was defined by the last minimum (below 5% maximum tangential velocity) prior to the maximum in the index finger's tangential velocity profile. The perturbation was triggered 10 ms after the start of the trial. We used kinematic data to confirm the onset of perturbation. This was determined as the time at which the

tangential acceleration of the perturbed hand deviated from the average of all unperturbed trials by 1 standard deviation. EMG activity was recorded from the biceps, triceps, and anterior and posterior deltoid of both arms with active electrodes (35 mm electrode distance, 500 Hz low pass filter, Biopac Systems inc).

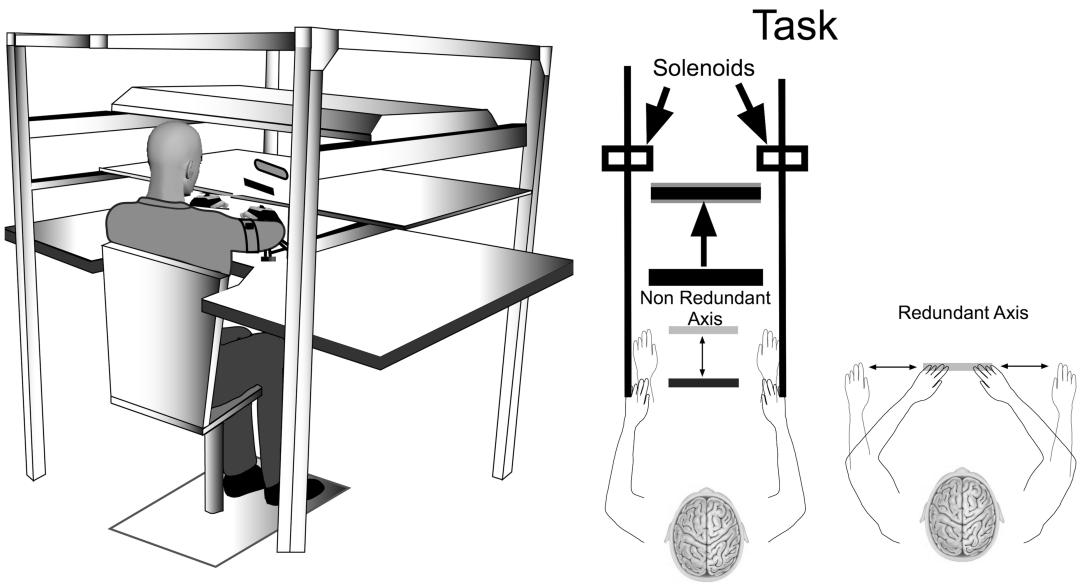

Figure 2- Experiment 1 Task Setup

Experimental Task

The experimental session consisted of 171 total bimanual movements. Participants were first required to "grab" a virtual bar (20 cm across) by moving cursors representing the position of each hand to each end of the bar. Once the cursors locked on to each end of the bar, participants controlled the movement of the bar with both hands. Next, participants moved the bar into the start position, with each end of the bar placed in the small green circles. Once in the start position, after 100 ms**,** participants were given an auditory start signal, and the cursors disappeared, giving subjects only visual feedback of the bar during the trial. The task required participants to move the bar with both hands quickly to a target "trough" that was 25 cm away from the start position, and stay there

until the end of the trial. Points were given for accuracy, as long as participants reached the target speed of at least 0.8 m/s. After each trial, participants were shown the velocity of their movement compared to the minimum requirement on a velocity meter in order to inform them if they needed to move faster. Participants were instructed to be as accurate as possible in the final position while maintaining the velocity requirement, and to respond as quickly as possible to maintain accuracy through any perturbations.

Accuracy required displacement of the bar the correct distance, as well as stopping with the bar parallel to the trough, requiring control of both bar displacement and bar orientation. As shown in Figure 2, movement along the long axis of the bar was redundant, allowing the hands to move outside of the bar. The perturbation device acted as a clutch that prevented motion primarily along the antero-posterior axis for one of the arms, and locked in position for 200 milliseconds. There was no specific load applied to the arm, but rather an increased resistance to movement of the hand in the direction of the target for 200 milliseconds. After 20 baseline non-perturbed trials, a perturbation was applied 10 ms after movement onset approximately every 10th trial, resulting in 16 total perturbation trials (8 right, 8 left). The perturbations alternated between the dominant and non-dominant arms. The relatively low number of perturbations was done in an effort to prevent participants from anticipating perturbations and to ensure a consistent baseline. Increased muscle activity and co-contraction during adaptation to many different environments has been shown (Milner, 2002; Franklin et al., 2003), and these changes can persist for several trials even when the perturbation is removed. In addition, long-latency reflex responses can be sensitive to the predictability of the perturbation

(Rothwell et al., 1980). Thus, we attempted to limit changes in muscle activity and co-contraction brought on by anticipating the perturbation during the session by having more non-perturbed trials in between perturbed trials.

Kinematic Analysis

We calculated arm segment positions and angles from digitized locations relative to the Trackstar 6-DOF sensors. Data were collected from each sensor at 116 Hz. We digitized multiple positions on the hand, wrist and upper arm. Using custom software, we calculated 10 degrees of freedom per arm, however, because this task was restricted to the horizontal plane by air sled support, and all joints distal to the forearm were splinted, we report only planar motion of the hand, as well as horizontal flexion/extension of the shoulder and elbow joint flexion/extension. All kinematic data were low-pass filtered at 8 Hz (3rd order, dual pass Butterworth) and differentiated to yield velocity and acceleration. Trials in which the subjects failed to make a corrective response were excluded. This typically meant that the participant stopped movement in response to or prior to the perturbation. We analyzed kinematic responses immediately after the perturbation to characterize the mechanical effect of the perturbation. We also analyzed the kinematic response in the recovery phase, which included 100 ms after the end of the perturbation. We chose this interval as it shows the immediate voluntary responses of each arm after the perturbation and it is consistent with the timing of previously reported bilateral kinematic responses to perturbations (Diedrichsen, 2007).

EMG Analysis

EMG data was collected at 1 KHz for the biceps, triceps, anterior deltoid, and posterior deltoid, and high-pass filtered with a cutoff of 5 Hz. Collection began one second prior to the start of the trial and ended two seconds after the trial ended. EMG signal was then full-wave rectified, low-pass filtered at 400 Hz using a third-order dual-pass Butterworth filter, and normalized to the maximum EMG recorded during the experiment for that muscle for each subject. It should be noted that EMG in the figures are low-pass filtered at 10 Hz for a clearer presentation. Trials in which there was no discernable response in perturbed arm electrodes were eliminated from analysis. Out of the 160 perturbation trials across all subjects, 13 trials were excluded. Similar to previous studies (Kurtzer et al., 2008; Omrani et al., 2013) we binned muscle activity into three intervals, relative to the initiation of the perturbation: 1) R1 (20-45 ms), 2) R2 (45-75 ms), and 3) R3 (75-105 ms) to reflect the latencies of the short-latency, early long-latency and late long-latency components of the stretch reflex. We also examined EMG activity in each muscle 100 ms prior to the perturbation (pre-perturbation interval) to insure a consistent baseline activity for each muscle, and we looked at activity in the voluntary interval (105-200 ms after perturbation onset). In order to examine the effect of the perturbation on muscle activity, for each muscle we calculated the integral of the EMG in each of these intervals. We compared muscle activity in these intervals in the arm ipsilateral and contralateral the perturbation with the corresponding activity in matched non-perturbed trials.

Statistical Analysis

Statistical analysis of the kinematic measures was done using a two-way mixed-factor ANOVA, with perturbation condition (non-perturbed, ipsilateral perturbed, contralateral perturbed) and hand (dominant and non-dominant) as the independent factors. Significant interactions and main effects were adjusted for multiple comparisons and subjected to post hoc analysis using Tukey HSD. A separate two-way ANOVA (hand by interval) was done only on the intervals during the perturbation, to assess potential asymmetries in the kinematic effect of the perturbation in the perturbed arm. For all statistics, our alpha value was set at 0.05 and only p values less than or equal to 0.1 will be reported.

For statistical analysis of the EMG within the reflex interval, we compared muscle activity for each muscle using a 3 by 3 mixed-factor ANOVA with perturbation condition (no perturbation, dominant arm perturbation, non-dominant arm perturbation) and reflex interval (R1, R2, R3) as the within subject variables. We also conducted separate one-way ANOVAs for the pre-perturbation and voluntary intervals with perturbation condition as the independent variable. We used the Shapiro-Wilks test to test for the normality of the data and the Levene's test of unequal variances. If these criteria were not satisfied we performed Box-Cox transformations of the data. Significant interactions and main effects were subjected to post hoc analysis using the Tukey HSD test, which adjusts for family-wise multiple comparisons (JMP Statistical Software, SAS Software).

Results

Subjects were asked to quickly move the virtual bar with both hands along the anteroposterior axis and to bring the bar to a stop in a target trough. A successful trial required the participants to reach the end with the bar horizontally oriented, requiring accurate displacement and accurate orientation of the bar. The perturbation arrested motion of the hand, primarily in the anteroposterior direction for 200 ms. Figure 3 shows an example of a perturbed movement along with example velocity (center) elbow and shoulder displacement profiles (left and right columns, top) and velocity and acceleration profiles for each hand (left and right columns, bottom). The lines representing stick figures of the arm are drawn between every 2 collected data points (17.2 ms). The virtual black bar was moved from the starting location to the gray trough, and the path of the middle of the bar is shown in between the hands. Near the beginning of the movement, the perturbation arrested motion, predominantly along the axis of movement for 200 ms. Because the rod attached to hand was free to swivel, arc motion was not impeded, allowing the observed medial displacement of the dominant hand-path. Only one arm was perturbed at a time, thus the left arm was not perturbed in this trial. We identify two phases of the perturbation: 1) perturbation phase, shown in Figure 3 inside the open rectangles on the example trials and 2) Recovery phase, shown in Figure 3 within the cross-hatched rectangles, which included the 100 ms immediately following the perturbation.

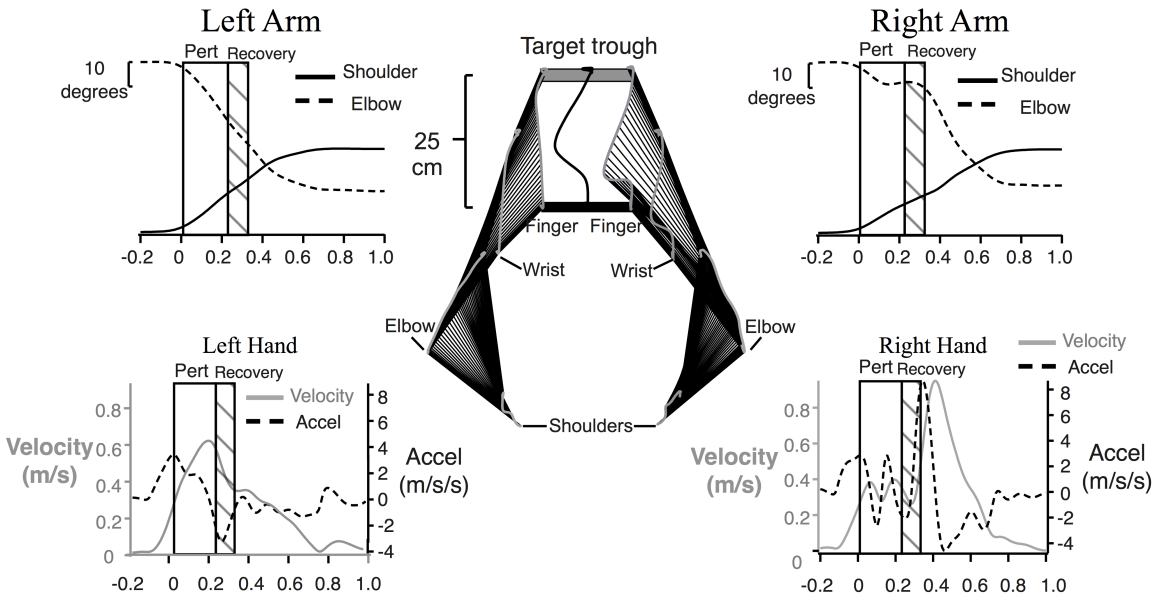

Figure 3- Example Perturbed Movement

Perturbation phase kinematics

We conducted an analysis to test for a potential confound of an asymmetry in the direct effect of the perturbation on dominant and non-dominant arm kinematics. This could have occurred due to asymmetrical variations in limb configurations and/or muscle activations at the onset of the perturbation. To do this, we separated the 200-millisecond perturbation period into four 50-millisecond intervals. We then calculated the average tangential hand acceleration, elbow joint acceleration, and shoulder joint acceleration, shown in Figure 4 as the gray bars, along with acceleration for the 200 milliseconds preceding the perturbation. Baseline trial acceleration intervals are shown as open bars. We conducted a three-way ANOVA (limb) by interval (4 50-millisecond intervals within the 200-millisecond perturbation) by perturbation condition (no perturbation, left perturbation, and right perturbation)) for hand acceleration, elbow joint acceleration, and

shoulder joint acceleration during the four 50-millisecond intervals that comprised the perturbation for each perturbed and baseline arm.

As expected, ANOVA indicated an interaction between perturbation and interval for hand acceleration ($F(3,27)= 4.9082$, $p= .0075$), elbow acceleration ($F(3,27)= 8.4381$, $p= .0004$), and shoulder acceleration ($F(3,27)= 4.1958$, $p= .0147$). There was also a main effect of perturbation for hand acceleration ($F(1,9)= 36.7594$, $p= .0002$) elbow acceleration ($F(1,9)= 70.4034$, $p< .0001$), and for shoulder acceleration ($F(1,9)= 14.1591$, $p= .0045$, as well as a main effect of interval for hand acceleration ($F(3,27)= 18.8494$, $p< .0001$), elbow acceleration ($F(3,27)= 20.6454$, $p<.0001$), and shoulder acceleration ($F(3,27)= 37.4683$, $p<.0001$). However, there were no main effects nor interactions with hand (left, right) for any of these dependent variables. Thus, we conclude that the kinematic effects of the perturbations did not differ between the hands.

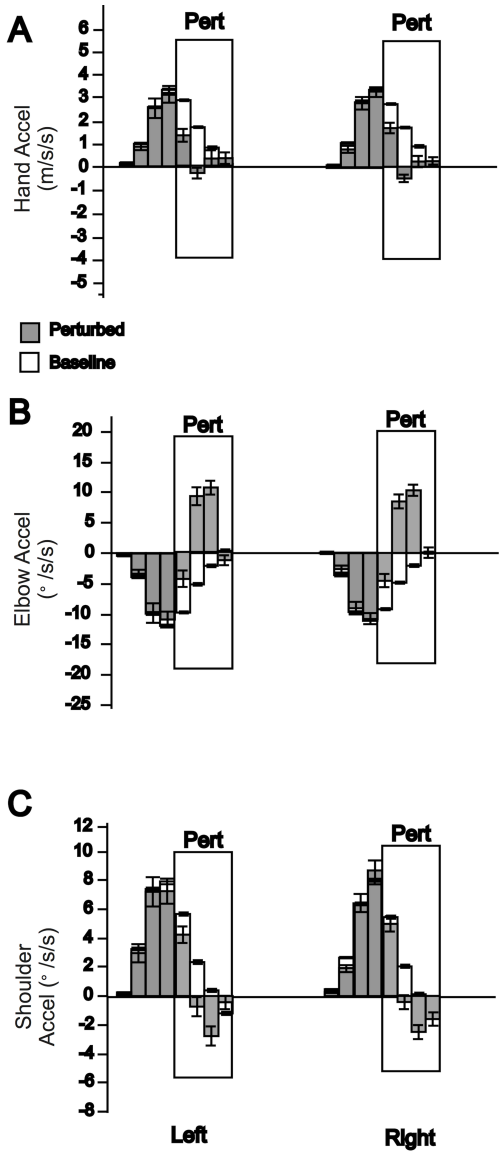

Figure 4- Effect of Perturbation

Response Kinematics of the Recovery Phase.

Ipsilateral Arm: Intralimb Response

We examined the kinematic response that occurred in the 100 ms period immediately following the perturbation. This recovery period is shown in the trials of Figure 3 by the cross-hatched rectangles Extension of the elbow and flexion of the shoulder are impeded during the perturbation phase, requiring corrections in the recovery

phase to move the hand toward the target. Kinematic analysis showed asymmetric responses of the perturbed dominant and non-dominant arms in the recovery phase.

The bar graphs in Figure 5 show these responses across trials and subjects. The bars represent the mean acceleration across the 100 ms interval, following the perturbation (ipsi perturbation) for the perturbed arm (right bars), and the same time period for the same arm, but during unperturbed trials (left bars). For the unperturbed trials (left), there were no differences between hand acceleration (a), elbow acceleration (b), or shoulder acceleration (c). Our two-way ANOVA (perturbation by hand) revealed a significant interaction between hand and perturbation ($F(2,18)=11.8134$, $p=.0005$) for hand acceleration. There was also a main effect of perturbation ($F(2,18)= 23.5242$, $p< .0001$), but no main effect of hand. Both hands accelerated after the perturbation in order to recover, but post-hoc analysis revealed that the perturbed non-dominant hand accelerated significantly more than the perturbed dominant hand immediately following the perturbation ($p= .0028$).

Joint angular accelerations also showed significant differences between the hands. The ANOVA for mean elbow acceleration during the 100 ms post-perturbation (Figure 5b) showed an interaction between hand and perturbation ($F(2,18)=11.4452$, $p=.0006$), as well as a main effect of perturbation ($F(2,18)= 103.3875$, $p<.0001$), but no main effect of hand. The perturbed non-dominant arm accelerated in the extension direction significantly more than the perturbed dominant arm ($p= .0117$), which contributed to the rapid forward motion of the hand.

Average shoulder acceleration (Figure 5c) showed an interaction between hand and perturbation ($F(2,18)=19.2873$, $p<.0001$), and a main effect of the perturbation ($F(2,18)= 9.7342$, $p=.0014$), but no main effect of hand. Post-hoc analysis showed that the perturbed dominant shoulder accelerated significantly more into extension than the perturbed non-dominant shoulder ($p=.0011$). In addition, the perturbed non-dominant shoulder showed significantly less acceleration into extension than baseline trials ($p= .0007$), while the perturbed dominant shoulder showed no significant difference from baseline.

Overall, the kinematic data from the perturbed arms showed increased acceleration of the perturbed arms, effectively recovering both the position of the bar, as well as the orientation of the bar. This recovery response, however, was somewhat asymmetric in that the non-dominant hand showed greater forward hand acceleration, which was associated with greater elbow extensor acceleration, and lower shoulder extensor acceleration.

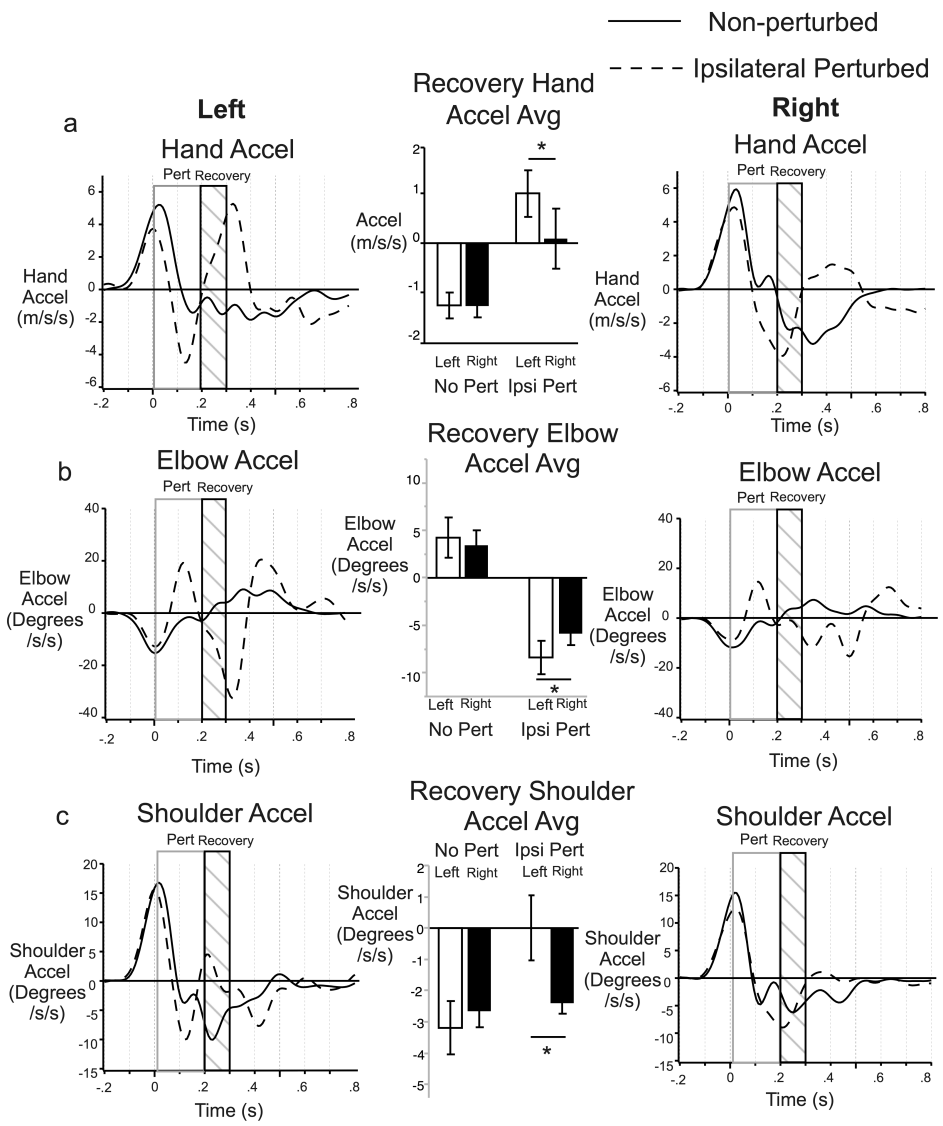

Figure 5- Ipsilateral Recovery Phase Kinematics

Contralateral Arm: Interlimb Responses

We next examined the kinematics of the unperturbed contralateral arms. Although no corrective response to the perturbation was required for the contralateral hand to complete the task, analysis of contralateral kinematics revealed bilateral responses that were asymmetric. During the recovery period, the contralateral hand decelerated in the forward direction. Figure 6a shows the peak deceleration (i.e. minimum in negative acceleration) of the hand during the 100 ms after the perturbation ended for the

contralateral hands on perturbed trials (right) and for baseline (left). The ANOVA for peak hand deceleration showed an interaction between perturbation and hand ($F(2,18)= 4.4871$, $p= .0262$), a main effect of perturbation ($F(2,18)= 9.5424$, $p= .0015$), and no main effect of hand. Post-hoc analysis showed that the contralateral non-dominant hand had a significantly lower peak hand deceleration than did the contralateral dominant hand ($p= .0471$), and the peak deceleration for the contralateral non-dominant hand was significantly lower (greater) than the baseline non-dominant hand during unperturbed trials ($p= .0252$), while the contralateral dominant hand showed no difference from baseline performance.

Immediately after the perturbation, the contralateral elbow showed positive, or flexor acceleration (Figure 6b). Our two-way ANOVA for maximum elbow acceleration showed an interaction between hand and perturbation ($F(2,18)=21.2084$, $p< .0001$), a main effect of perturbation ($F(2,18)= 72.4423$, $p<.0001$), but no main effect of hand. Post-hoc analysis showed that the contralateral non-dominant elbow showed a greater maximum acceleration than the contralateral dominant elbow ($p= .0146$).

The shoulder accelerated in the extensor direction during the recovery period. The peak shoulder extensor acceleration (negative minimum) during the 100 ms following the perturbation (Figure 6c) showed a significant interaction between perturbation and hand ($F(2,18)= 19.3707$, $p< .0001$), and a main effect of perturbation ($F(2,18)= 4.6728$, $p=.0232$), but no main effect of hand. Post-hoc analysis indicated significantly lower

peak extensor acceleration for the non-dominant, as compared to the dominant shoulder (p=.0110).

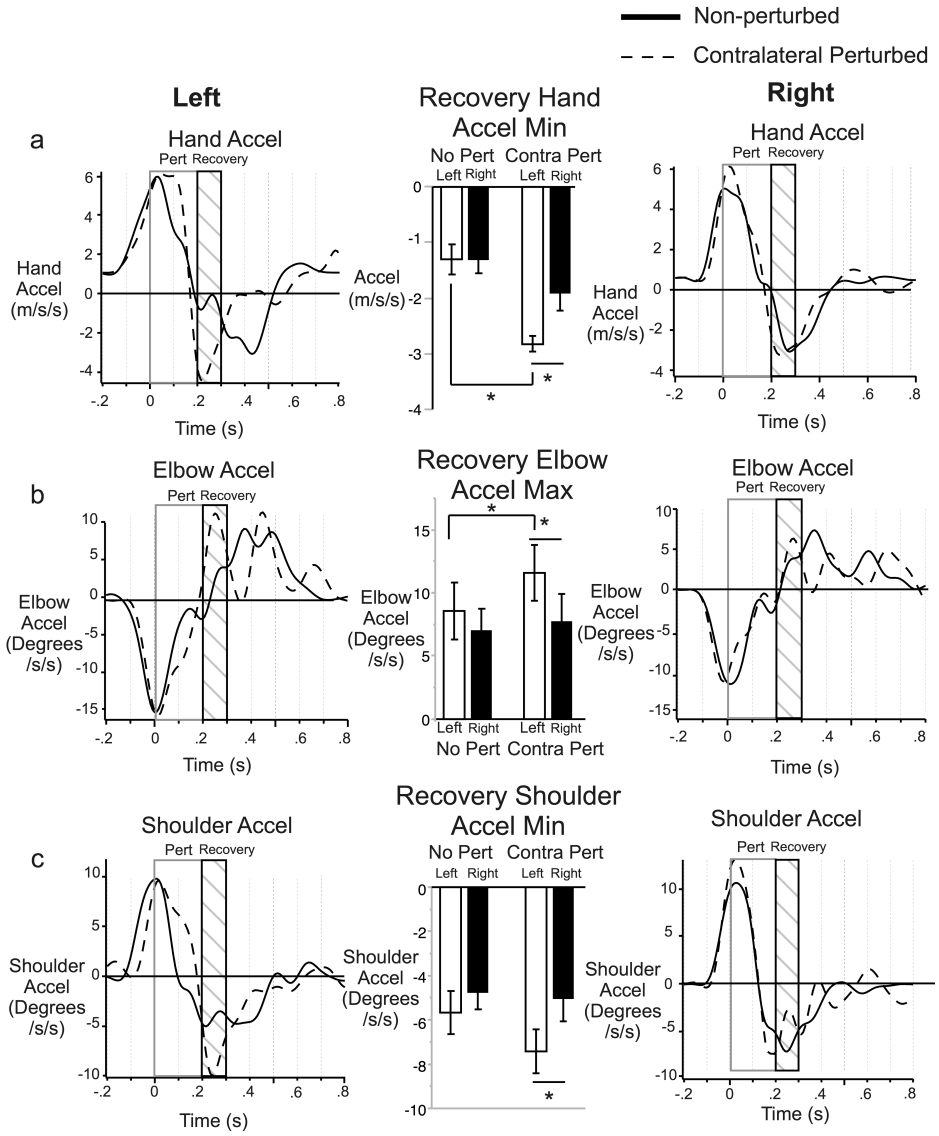

Figure 6- Contralateral Recovery Phase Kinematics

These joint kinematic data suggest that the non-dominant hand slows down significantly in response to a dominant arm perturbation. Given this finding, it would make sense that the movement duration also increases for the non-dominant hand in response to contralateral perturbation. Figure 7 shows mean movement duration for the left and right hand in baseline non-perturbed trials and in contralaterally perturbed trials.

We ran two-way (hand by perturbation condition) ANOVAs as we did with the other kinematic data, and found an interaction between perturbation condition and hand ($F(2,18)= 11.4265$, $p= .0006$), and a main effect of perturbation ($F(2,18)=18.6623$, $p< .0001$), as would be expected. Post-hoc analysis using Tukey HSD tests show that while dominant arm movement times during contralateral perturbation conditions were not significantly different from non-perturbed trials ($p= .2871$), non-dominant arm movement times during contralateral perturbations were significantly greater than non-dominant movement times during non-perturbed trials ($p= .0181$). Thus, as the joint kinematics suggest, the dominant arm movement duration is not significantly different from baseline when the non-dominant arm is perturbed, but the non-dominant arm slows down to allow the perturbed dominant arm to catch up, and to recover the horizontal orientation of the bar.

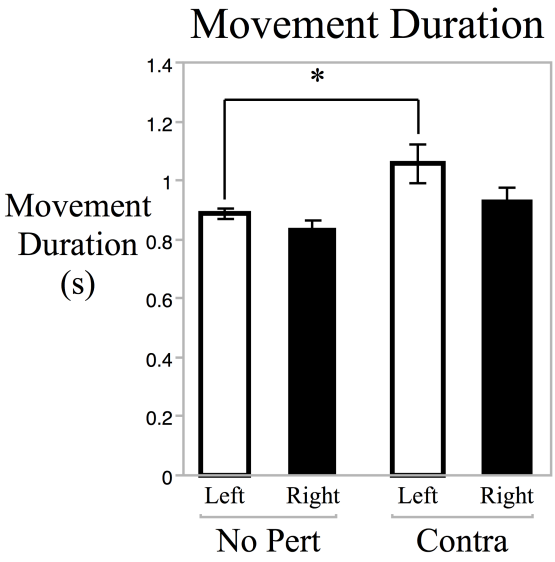

Figure 7- Non-perturbed vs Contralateral Perturbed Movement Duration

It should be noted that overall task success was similar between all perturbation conditions, showing that participants were able to recover from perturbations of either

arm to achieve accurate final positions. The two main measures of task success were the final position error of the center of the bar and the angle of the bar at the end of movement. One-way ANOVAs comparing performance of these two measures between the three perturbation conditions showed no significant difference between conditions for either measure.

Rapid EMG Responses to the Perturbation

Pre-Perturbation Muscle Activity

In order to check that the EMG activity prior to the perturbation was consistent for all conditions and ensure that automatic gain scaling (Pruszynski et al., 2009) was not a confound, we calculated the EMG impulse 100 ms prior to the perturbation onset for all muscles. As shown in Table 1, for each of the eight muscles recorded, a one-way ANOVA confirmed that there were no significant differences in the EMG impulse prior to the perturbation between perturbation conditions, assuring that any differences in the EMG activity after the perturbation were not simply a reflection of pre-perturbation muscle activity.

Muscle	Effect of Perturbation
Right Biceps	$F(2,18)= 1.0529$, $p= .3694$
Right Triceps	$F(2,18)= 3.0766$, $p= .0709$
Right Anterior Deltoid	$F(2,18)= 1.8233$, $p= .1901$
Right Posterior Deltoid	$F(2,18)= .0755$, $p= .9275$
Left Biceps	$F(2,18)= .7727$, $p= .4765$
Left Triceps	$F(2,18)= .6420$, $p= .5379$
Left Anterior Deltoid	$F(2,18)= .4360$, $p= .6532$
Left Posterior Deltoid	$F(2,18)= 1.3601$, $p= .2818$

Table 1- Pre-perturbation Muscle Activity

IPSILATERAL ARM: Intralimb Responses

Figures 8 and 9 show (Figure 8: non-dominant, Figure 9:dominant) example non-normalized EMG profiles for each muscle (low pass filtered at 10 Hz), with the baseline trial in gray and the perturbed trial in black. The bar graphs show the average normalized EMG impulse during the three intervals representing short latency, early long latency and late long latency reflexes (R1= 20-45 millisecond post-perturbation, R2= 45-75 millisecond, R3= 75-105 millisecond), with the shading of the bars corresponding to the three intervals. Statistics for the 3x3 (perturbation condition by interval) ANOVA for each muscle are shown in Table 2, with post-hoc results reported with Tukey's HSD. When post-hoc analysis showed significant difference from baseline, the corresponding shading of the bar is included in the EMG profile to illustrate the timing of the intervals. The perturbation arrested forward motion of the arm, which as expected elicited short latency, early long latency, and late long-latency reflex responses of the triceps and anterior deltoid of the dominant and non-dominant arm. We also saw significant responses in all intervals of the posterior deltoid in both arms. In the biceps, both arms showed significant R2 and R3 response, but only the non-dominant arm showed a significant R1 response.

Muscle	Effect of Perturbation	Effect of Interval	Perturbation x Interval
Right Bicep	F(2,18)= 10.1307 p= .0011*	F(2,18)= 9480.08 p< .0001*	F(4,36)= 2.5942 p= .0526
Right Tricep	F(2,18)= 4.9477 p= .0194*	F(2,18)= 29181.82 p< .0001*	F(4,36)= 1.1638 p= .3429
Right Ant. Delt.	F(2,18)= 20.8452 p< .0001*	F(2,18)= 729.4724 p< .0001*	F(4,36)= 1.2893 p= .2924
Right Post. Delt.	F(2,18)= 19.6879 P< .0001*	F(2,18)= 107.7066 p< .0001*	F(4,36)= .7277 p= .5789
Left Bicep	F(2,18)= 15.0673 p= .0001*	F(2,18)= 68.5247 p< .0001*	F(4,36)= 1.1580 p= .3455

Left Tricep	F(2,18)= 23.9688 p< .0001*	F(2,18)= 566.7890 p< .0001*	F(4,36)= 4.5686 p= .0044*
Left Ant. Delt.	F(2,18)= 14.9935 p= .0001*	F(2,18)= 10153.00 p< .0001*	F(4,36)= 2.2473 p= .0832
Left Post. Delt.	F(2,18)= 24.1431 p< .0001*	F(2,18)= 126.5930 p< .0001*	F(4,36)= 1.9801 p= .1184

Table 2- Muscle Activity in Reflex intervals

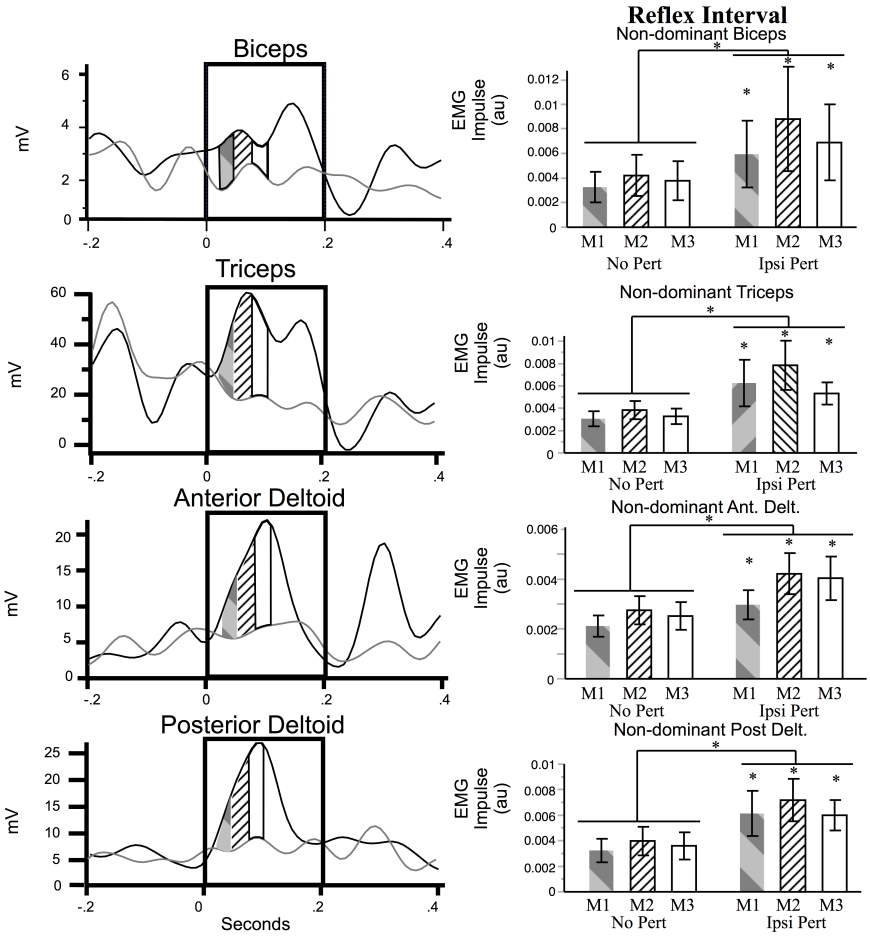

Figure 8- Non-Dominant Ipsilateral Perturbed EMG

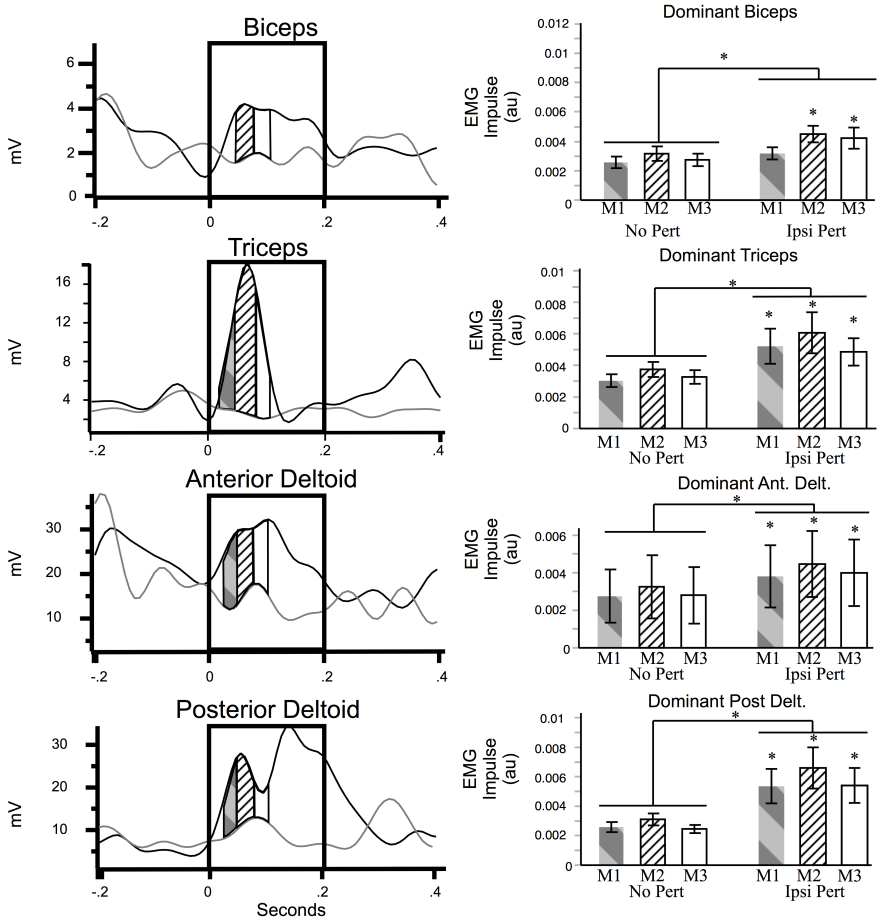

Figure 9- Dominant Ipsilateral Perturbed EMG

We also examined the EMG activity in the voluntary response interval (105-200 ms after perturbation onset) as shown in Figure 10. All muscles except for the dominant right anterior deltoid showed a significant main effect of perturbation in our one-way ANOVA. Post-hoc analysis using Tukey's HSD test show that the activity in the ipsilateral perturbed condition was significantly greater than non-perturbed trials in those muscles.

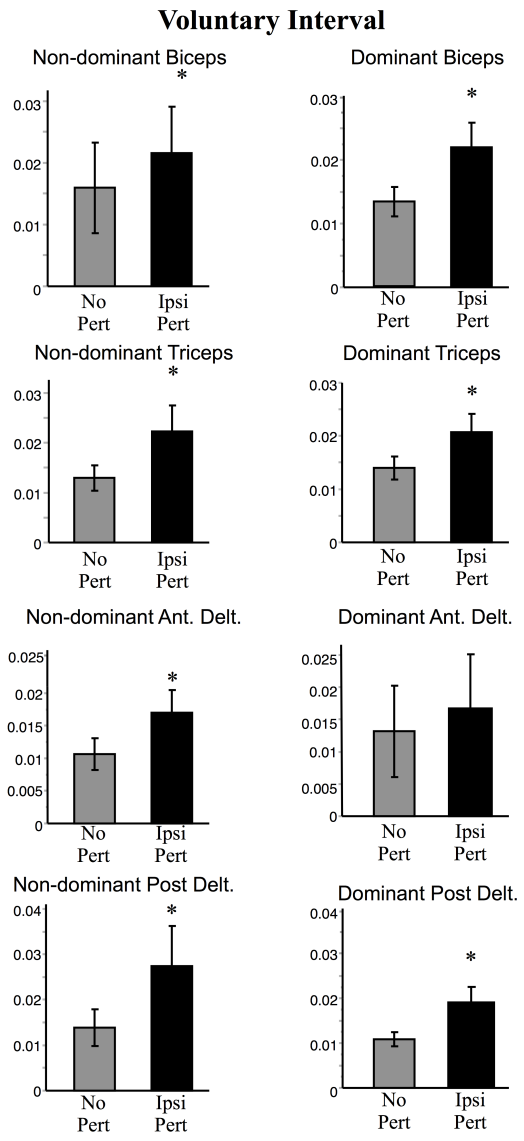

Figure 10- Ipsilateral Perturbed Voluntary EMG Activity

In summary, both arms exhibited significant short latency (R1), and early long latency (R2) responses in triceps brachii, the muscle undergoing a shortening contraction during the arrested movement. In addition, the biceps brachii showed significant R2 and R3 responses, reflecting co-activation during this long latency phase. At the shoulder, both arms showed significant responses across all intervals in the anterior and posterior

deltoid. All muscles, except for the dominant anterior deltoid also showed increased activity in the voluntary interval.

CONTRALATERAL ARM: Interlimb Responses

The contralateral arm did not experience any mechanical effect of the perturbation. However, previous research has indicated that reflex responses can be elicited in the unperturbed contralateral arm when the task is shared between both arms (Mutha and Sainburg, 2009). Figure 11 bar graphs shows average normalized EMG impulse area for the anterior deltoid under baseline conditions and contralateral conditions, along with example non-normalized EMG profiles. For the non-dominant anterior deltoid, there was a significant effect of perturbation condition ($F(2,18)= 24.1431$, $p= .0001$). Post-hoc analysis revealed that both the left and right arm perturbation conditions were significantly different from the baseline non-perturbed trials (left perturbation: $p= .0001$; right perturbation $p= .0102$). No other muscles recorded showed any significant difference from baseline in the contralateral perturbation condition. In the voluntary response interval, no muscles showed any significant difference from baseline in the contralateral perturbation condition. Interestingly, the contralateral reflex response in the non-dominant arm was consistent only with compensating the position of the bar, which was arrested by the perturbation, but not in compensating the perturbed orientation of the bar.

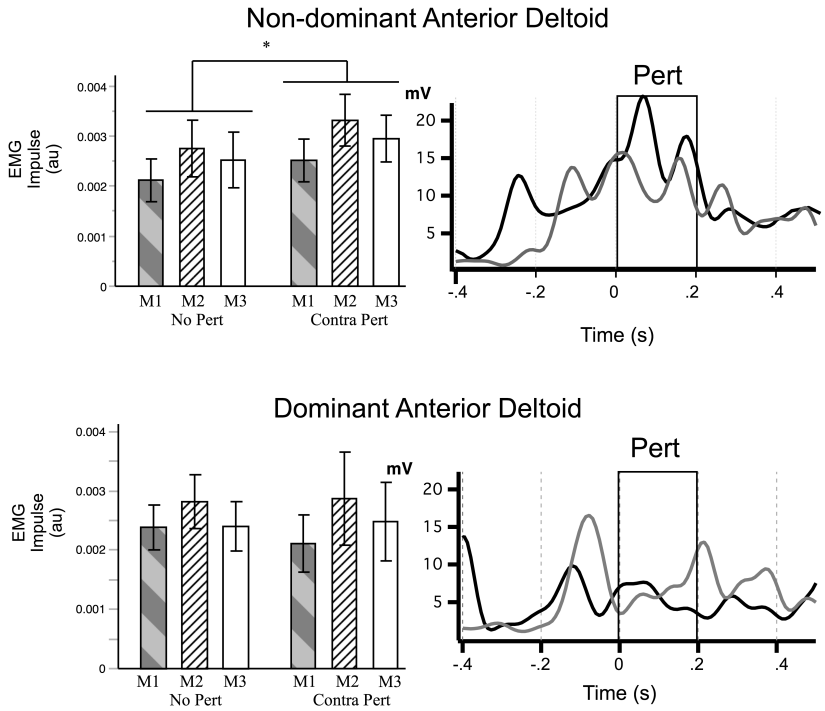

Figure 11- Contralateral Perturbed EMG

Discussion

In this study, we examined bilateral responses to unimanual perturbations during a shared bimanual task. We found apparent asymmetries in the kinematic responses between the dominant and non-dominant arms. When the dominant arm was perturbed, the contralateral non-dominant arm showed significant deceleration after the perturbation, presumably to 'wait for' the perturbed dominant arm. When the non-dominant arm was perturbed, the contralateral dominant arm showed no difference from baseline in kinematic measures. Likely due to the lack of contralateral response of the dominant arm, the perturbed non-dominant arm accelerated significantly more than the perturbed dominant arm after the perturbation. We also observed differences in muscle activity depending on which arm was perturbed. We observed a significant effect of perturbation condition of the contralateral non-dominant shoulder (anterior deltoid) but no significant responses in any muscles of the contralateral dominant arm. Overall, the non-dominant arm responded to a perturbation of the dominant arm, while the dominant arm showed little to no response to perturbation of the non-dominant arm.

The current findings suggest the non-dominant arm is highly responsive to error-related feedback during bimanual tasks, while the dominant is not. This is consistent with de Poel's hypothesis that the dominant hand takes on the role of the "prime actor" during bimanual tasks (Swinnen et al., 1996 Johansson et al., 2006; de Poel et al., 2007). In a bimanual oscillatory wrist movement, De Poel and colleagues (2007) reported that patterns of stability and bimanual coupling were higher when the dominant arm was perturbed, as compared to when the non-dominant arm was perturbed, suggesting that the

non-dominant arm compensates for the perturbation to a greater degree when the dominant is perturbed than vice versa. Similarly, in a bimanual task in which subjects had vision of one hand but not the other, visual perturbations to the dominant hand caused interference in the non-dominant hand (Kagerer, 2014).

Diedrichsen and Dowling (2009) also showed that responses to unpredictable force field exposure of one arm during reaching movements are asymmetrical, and more robust for the non-dominant arm, such that the participants relied more on their non-dominant hands to correct. These authors attributed the asymmetry to an asymmetrical error assignment process. According to this idea, when errors emerge during a bilateral task, and the origin of those errors is ambiguous, the controller tends to assign the task errors to movements in the less-reliable arm. In our current study, it is difficult to imagine how the asymmetry in responses could be attributed to error-assignment, because the nature of the perturbation is to arrest movement of one arm in the reaching direction rather than a gradual perturbation from viscous curl field, a salient cue that is not ambiguous with regard to which arm was perturbed. Thus, in our task, error assignment would appear to be dictated by the abrupt mechanical perturbation and when the dominant arm is perturbed, the response of the non-dominant arm should not be attributable to erroneous error assignment.

Our finding of substantial bilateral responses in the non-dominant but not in the dominant arm is consistent with previous studies showing that the non-dominant arm is more responsive to unexpected perturbations in unimanual movements (Bagesteiro &

Sainburg, 2003; Duff & Sainburg, 2007). This is likely due to the non-dominant hemisphere's greater reliance on impedance control mechanisms that are dependent on feedback (Schabowsky et al., 2007; Yadav & Sainburg, 2014). This study extends these findings to bimanual movements, showing that the non-dominant limb is more responsive to task-related proprioceptive feedback even when that feedback originates from the contralateral limb.

Whereas stretch reflexes are typically elicited during a postural task, the ipsilateral EMG findings here are consistent with the proposition that the rapid feedback responses reported here were mediated by stretch reflexes in our movement task. The R1 response reflects spinal circuits and has a latency of about 20-25 ms in the lower arm muscles in humans (Shemmel, 2010). Given the short latency of the R1 component, it is reasonable to conclude that a perturbation that elicits significant response during this short latency would result from activation of the same spinal circuits. As described in the results, the effect of the perturbation was to arrest forward motion of the hand, resisting ongoing extension at the elbow. The predictions for induced reflex responses at the elbow and shoulder, however, are not straightforward. This is because of two factors: 1) During voluntary movements, gamma motor neurons are activated along with alpha motor neurons (Prochazka, 1981). Thus, resisting ongoing movement should result in continued activation of gamma motor neurons, without ongoing shortening of the muscle. This should result in increased activation of the spindle afferents. 2) During multijoint movements, heteronymous pathways link the actions of muscles spanning multiple joints (Manning & Bawa, 2011), and can result in activation of muscles that are not directly

stretched by the stimulus. These heteronymous responses can occur in muscles proximal and distal to the stretched muscle, as well as in short and long-latency intervals (Manning & Bawa, 2011). We expect that our stimulus that arrests forward motion of the arm should result in stimulation of stretch reflexes in the triceps brachii and anterior deltoid, due to continued contraction of the muscle, against resistance. However, due to multi-joint effects, the posterior deltoid and biceps can be stimulated through heterogenous pathways that appear to stabilize the limb against inertial interactions produced by motion of connected segments (Shemmell et al., 2010). Stretch reflexes have also been shown to elicit short latency coactivation of muscles under conditions that warrant impedance responses in the limb (Lacquaniti et al, 1991), which is similar to our results.

Our current results from the contralateral arm are consistent with previous reports, demonstrating muscle responses within 100 ms of a perturbation in the contralateral arm. However, our study extends those findings in demonstrating that contralateral responses only occurred when the dominant arm was perturbed. In a previous study, Mutha and Sainburg (2009) reported responses of dominant arm perturbations, applied with a robotic manipulandum, during bilateral reaching movements. Long latency (50 millisecond) reflex responses occurred in the left arm in response to a perturbation applied to the dominant arm, during bilateral forward reaching movements. The current finding of significant contralateral non-dominant anterior deltoid activation is consistent with the Mutha and Sainburg finding and consistent with the asymmetric kinematic response that occurred later in movement. Dimitriou et al. (2012) did not report asymmetries in bimanual reflexes. However, this may be due to differences between postural

mechanisms and voluntary movement mechanisms (Crammond & Kalaska, 1996; Kurtzer, et al., 2005; Shadmehr, 2017) and the task-dependent nature of long-latency reflexes (Kurtzer et al., 2008; Mutha & Sainburg, 2009; Dimitriou, et al., 2012).

This finding however, is difficult to interpret, since it is unclear how anterior deltoid activation should have the opposite effect of the later response shown in the kinematics to slow down movement. It is true that these responses seem to be contradictory, however, they may reflect the dual goals of the task. The anterior deltoid response is not a functional response if the goal of the subject is to limit bar tilt, however, that is only part of the task. There are two goals for the task: 1) To move the bar forward into the target area and 2) to stabilize the bar orientation. Although an anterior deltoid response does not correct for goal #2, it is consistent with goal #1. The outcome of the perturbation is to slow the forward movement of the bar toward its target and the anterior deltoid response is consistent with correcting the position of the bar. Recent studies (Pruszynski et al., 2011; Lee and Perreault, 2019) identify distinct components of rapid motor responses; one relating to the rapid release of planned movements and the other relating to stabilization. In the Lee and Perreault study (2019), the authors construct a task in which participants must stabilize the arm against a haptic field and a force perturbation to reach a target, thus forcing a stabilizing response and a goal directed response. This is similar to what is occurring in our study, as one important component is to stabilize the orientation of the bar, and another component is to move the bar forward toward the target. In the Lee and Perreault study they found that the stabilizing response and the goal directed response worked independently from each other to form a

sophisticated response to the perturbation. It is plausible that the two distinct responses in our study of early left anterior deltoid response and later slowing down of the non-dominant hand reflect two distinct components of rapid motor responses. It is also plausible that the most rapid reflexive responses are less sophisticated than longer latency responses, and only respond to one aspect of the task goal.

Left hemisphere damage produces deficits in predictive control of bilateral coordination

Previous research has demonstrated hemisphere-specific motor deficits in ipsilesional and contralesional unimanual movements in patients with hemiparetic stroke due to MCA infarct. Due to the importance of bilateral motor actions on activities of daily living, we now examine how bilateral coordination may be differentially affected by right or left hemisphere stroke . In order to avoid the caveat of simply adding unimanual deficits in assessing bimanual coordination, we designed a unique task that requires spatiotemporal coordination features that do not exist in unimanual movements. Participants with unilateral left (LHD) or right hemisphere damage (RHD) and age-matched controls moved a virtual rectangle (bar) from a midline start position to a midline target. Movement along the long axis of the bar was redundant to the task, such that the bar remained in the center of and parallel to an imaginary line connecting each hand. Thus, in order to maintain midline position of the bar, movements of one hand closer to or further away from the bar midline required simultaneous, but oppositely directed displacements with the other hand. Our findings indicate that left (LHD), but not right (RHD) hemisphere damaged patients showed poor interlimb coordination, reflected by significantly lower correlations between displacements of each hand along the bar axis. These left-hemisphere-specific deficits were only apparent prior to peak velocity, likely reflecting predictive control of interlimb coordination. In contrast, the RHD group bilateral coordination was not significantly different than that of the control group. We conclude that predictive mechanisms that govern bilateral coordination are dependent on left hemisphere mechanisms. These findings indicate that assessment and training in

cooperative bimanual tasks should be considered as part of an intervention framework for post-stroke physical rehabilitation.

Experimental Procedures

Participants

A total of 24 subjects participated in this experiment (8 controls, 8 left-hemisphere damage, 8 right hemisphere damage), after providing informed consent, which was approved by the institutional review board of Penn State University. All groups were matched for age (Control:65.38 ± 10.16, LHD: 63.25 ± 13.47, and RHD 63.22 ± 9.82), and all stroke participants were classified as having mild impairment by the Fugl-Meyer scale (>45). Fugl-Meyer scores for the RHD group were 58.7 ± 5.9, and 62.0 ± 5.9 for LHD. All control participants self-reported being right-handed, and stroke participants reported being right-handed prior to stroke.

Out of the 16 stroke patients we were able to obtain MRI brain images for 13 participants (6 LHD, 7 RHD), which are shown in Figure 12. Three patients were unable to participate in structural MRI procedures due to medical contraindications. The origins of the brain images were reoriented to the anterior commissure using Statistical Parametric Mapping (SPR12) software (Friston, 1995). Brain lesions were then manually traced by a trained technician on T2-weighted brain images using MRIcron software (Rorden & Brett, 2000) and reviewed with a neurologist. The T2 scan was co-registered to the space of the T1 scan, then brain images and corresponding lesion maps were transformed onto a brain template based on older adults using the MR-segment-normalize algorithm of the Clinical Toolbox in SPR12 (Rorden et al., 2012). The volumes of the

resulting normalized lesion maps were then analyzed with non-parametric mapping software (MRIcron) and compared between groups using a non-parametric Wilcoxon signed-rank test. There was no significant difference between groups in lesion volume (p= .1336), although there was some variation in lesion location, as shown in Figure 12.

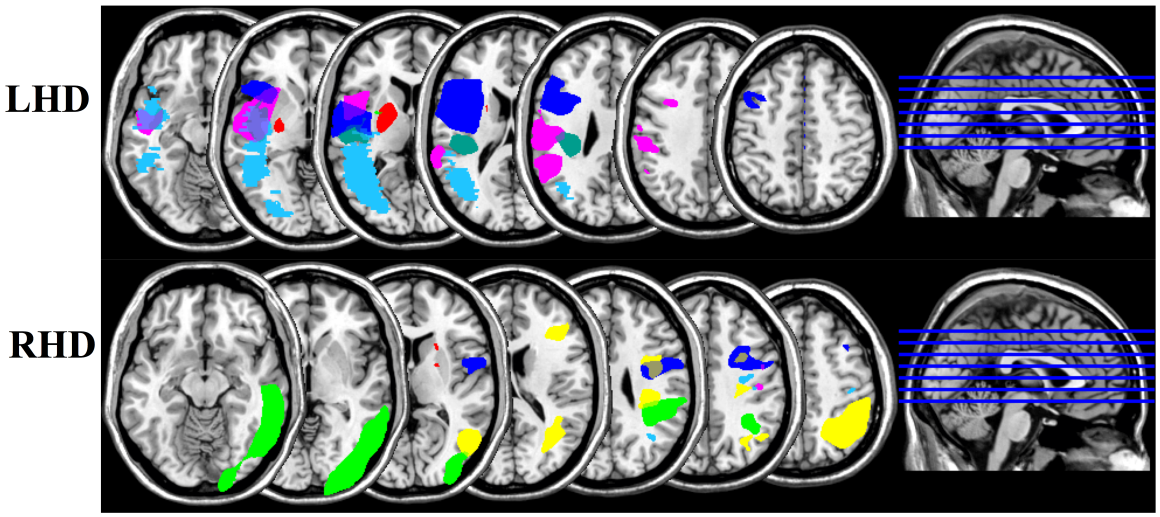

Figure 12- Lesion maps

Experimental Setup

Participants were seated at a 2-D virtual-reality workspace in which stimuli from a TV screen were reflected by a mirror, with the participants' arms under the mirror. Figure 13 shows this experimental set-up. Participants' arm movements were tracked using 6 DOF magnetic sensors (Ascension TrackStar) placed on the hand and upper arm. All joints distal to the forearm were splinted. We digitized the location of the tip of the index finger, as well as multiple locations on the hand, and upper arm, and used custom software to estimate the locations of the wrist, elbow, and shoulder joints, relative to these digitized landmarks. Vision of the participants' arms was occluded while position of the index finger was provided as a cursor on the screen. Participants' arms were supported on air sleds that reduced the effects of friction, and eliminated gravitational

torques at the joints. The experimental session consisted of 200 total bimanual movements. The task was similar to the cooperative transport task employed by Sainburg and colleagues (2013) in which the left and right hands control a shared virtual object located halfway between each hand. Instead of a single cursor, this task represented the shared virtual object as a rectangular bar on the screen, with each hand controlling one end. Participants were first required to "grab" the virtual bar (20 cm across) by moving cursors representing the position of each hand to each end of the bar. Next, participants moved the bar into the start position, with each cursor placed into small start circles. Once in the start position, after 100 ms**,** participants were given an auditory start signal and the cursors disappeared, giving participants visual feedback of only the bar. The task required participants to move the bar with both hands quickly to two targets that were 25 cm away from the start position. Accuracy required the participants to move the bar not only the correct distance, but also to stop with the bar horizontally oriented so that each end of the bar was in its respective target. As shown in Figure 13, movement along the long axis of the bar was redundant, allowing the hands to move outside of the bar once the trial began, and requiring covariation of each hand to stabilize the location of the bar along the x-axis.

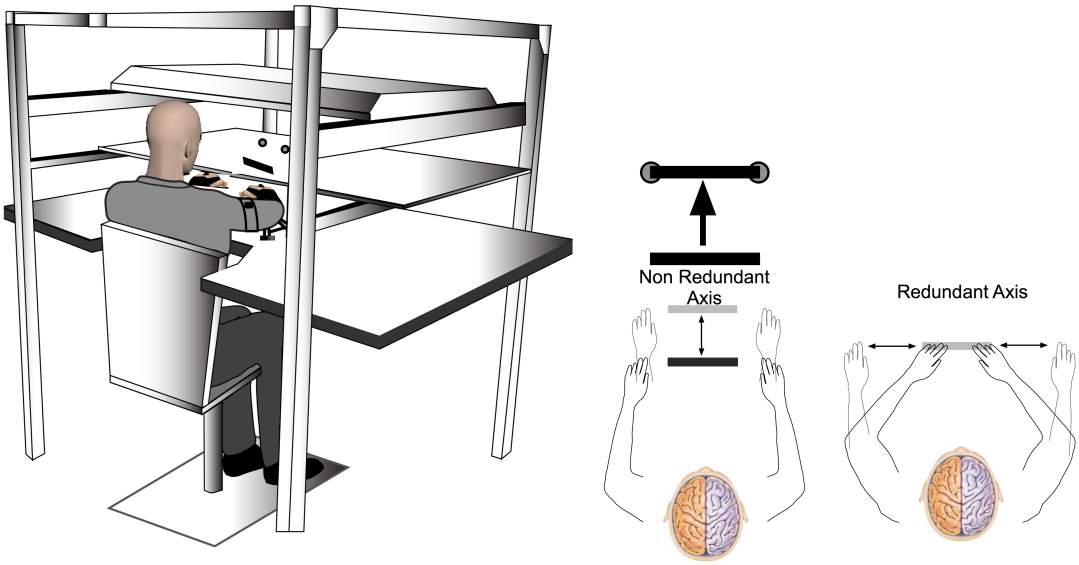

Figure 13- Experiment 2 Task Setup

Kinematic Analysis

We calculated arm segment positions and angles from digitized locations relative to the trackstar 6-DOF sensors. Data were collected from each sensor at 116 Hz. We digitized multiple positions on the hand, wrist and upper arm. Using custom software, we calculated 10 degrees of freedom per arm, however, because this task was restricted to the horizontal plane by air sled support, and all joints distal to the forearm were splinted, we analyzed only planar motion of the hand, as well as horizontal flexion/extension of the shoulder and elbow joint flexion/extension. All kinematic data were low-pass filtered at 8 Hz (3rd order, dual pass Butterworth) and differentiated to yield velocity and acceleration. Movement start was determined by identifying the time of peak velocity and searching backward in time for the first minimum below 8% of peak tangential velocity, or for zero velocity, whichever was identified first. Movement end was similarly determined by searching forward in time from peak velocity to find the first minimum

below 8% of peak tangential velocity, thereby excluding any small, corrective submovements. Data from all subjects was de-identified and analysis was done by researchers who did not participate in data collection.

Statistical Analysis

Most dependent measures were analyzed for differences between each group (LHD, RHD, Control) using a one-way ANOVA. Post-hoc analysis (Tukey HSD) was used when warranted to compare the means of every treatment to the means of every other treatment; that is, it applies simultaneously to the set of all pairwise comparisons. Our use of the Tukey HSD controls for the family-wise Type 1 error rate and allows for pairwise comparisons of multiple groups (Barnette & McLean, 2005). In order to test interlimb coordination, we calculated linear correlations of left hand vs right hand movement along the redundant x-axis of the bar within each trial. These correlations were separated into three phases to reflect different aspects of control: Phase 1, from movement start to peak velocity; Phase 2, from peak velocity to end of movement; and Phase 3, from the movement end to the end of the trial. We then performed pairwise comparisons of group mean slopes and correlation coefficients in each phase using the Steel-Dwass test, which is a non-parametric test that effectively controls for Type 1 errors associated with multiple comparisons of data that is not normally distributed (Dolgun & Demirhan, 2017). The alpha level for all statistics was set at 0.05, and only p-values less than or equal to 0.1 were reported.

Results

Stabilizing Performance Across Trials

Participants were asked to quickly move the virtual bar with both hands along the anteroposterior axis and stop the bar with the sides of the bar inside the two targets. A successful trial required the participants to reach the targets with the bar horizontally oriented. Participants were also allowed to move along the axis of the bar, although this movement must be correlated between the left and right hands to limit bar deviation in the x-direction. As shown in Figure 14, there were interesting differences in how the three groups moved along the redundant axis. Figure 14a shows a visual representation of how far the hands deviated from each end of the bar at the end of movement for each group on average, as well as how much the bar deviated from the center. Figure 14b shows the mean hand deviation along the axis of the bar at movement end. Our one-way ANOVA revealed no significant difference between the three groups ($F(2,21)= 3.1022$, $p= .066$), however there was a trend for the LHD group to move less along this redundant axis.

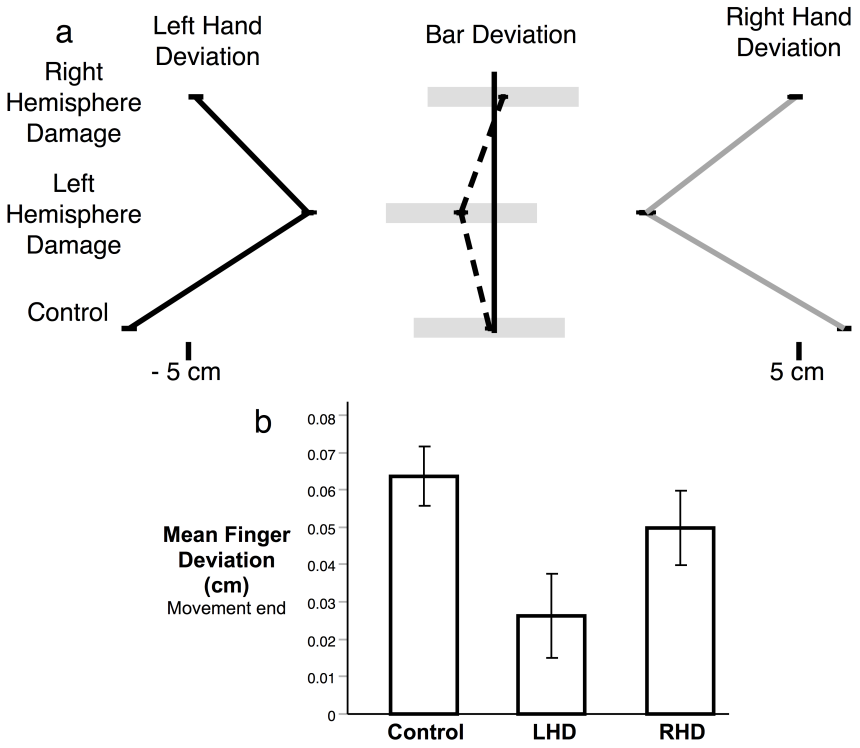

Figure 14- Movement along the bar axis

Crucial to the success of the task was the ability to coordinate the redundant movement between the hands to limit bar deviation. Figure 15 shows the correlation of left and right hand deviation along the bar axis with bar deviation across subjects for each of the three groups. For controls and RHD there was very little correlation between movement of the hand along the bar axis and deviation of the bar, showing that they could move their hands along the bar without having much effect on the x-position of the bar and task error. The LHD group, however, showed a strong correlation of left and right hand movement with bar deviation, such that subjects who moved along the redundant axis of the bar more showed more bar deviation. This indicates that control and RHD participants coordinated their hands along the bar axis, in order to reduce task error, while failure to do so led to task errors that were dependent on deviations of the hands along the bar axis in LHD patients.

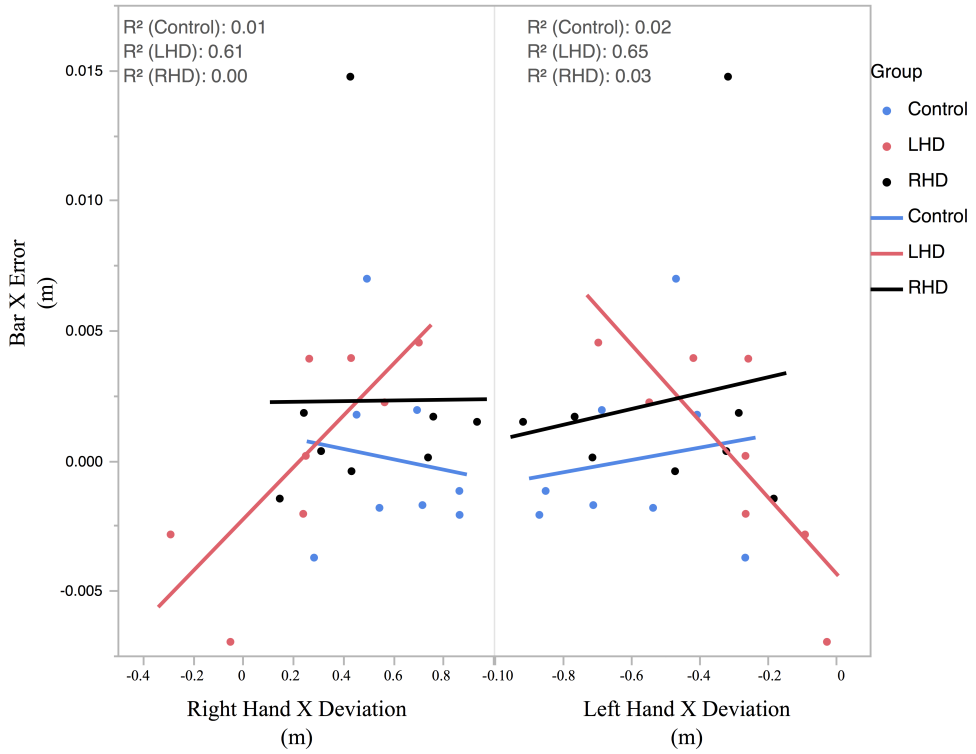

Figure 15- Correlation of bar axis deviation with bar error

Figure 16 shows the correlation between the redundant axis (bar axis) movement between the right and left hands, for all trials of all subjects, separated by group. The graphs show the overall deviation at the end of movement for the right hand vs the left hand with each point representing a single trial and a gray circle showing the 95% confidence interval. The R-squared for the linear correlations between hands for each group are also shown. Although the Control group showed the most deviation, the deviation was also the most highly correlated between the hands with an R^2= .916. The RHD group movements were slightly less correlated than those of the Control group (R^2= .846), while the LHD group showed the lowest correlation (R^2= .569). Taken together, Figures 15 and 16 show that the LHD subjects limit their deviation in the redundant axis, resulting in greater task errors.

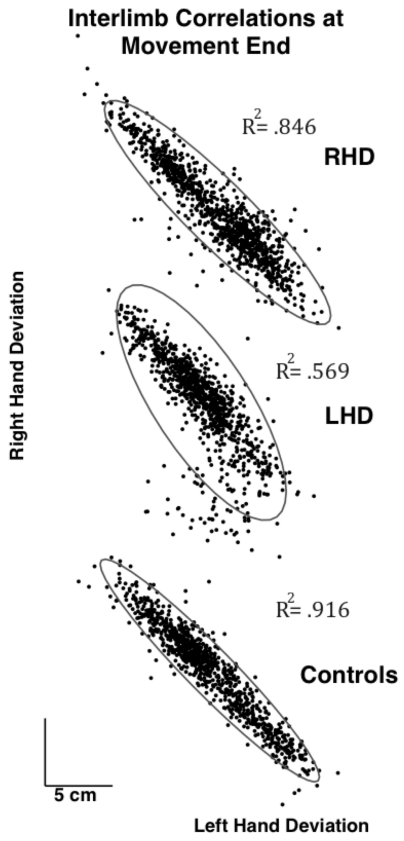

Figure 16- Interlimb correlations across trials

Stabilizing Performance Within Trials

We now examine how the redundant axis movement was correlated between the hands within each trial. Figure 17 shows example movements and velocity profiles from subjects in each of the three groups (control, RHD, LHD). The lines representing stick figures of the arm are drawn between every 2 data points (17.2 milliseconds). As shown in the examples, LHD participants moved slightly slower than controls, while RHD participants moved at a similar speed to controls. In addition, the left hand deviation in the x-axis vs the right hand deviation in the x axis are plotted in gray to the right of each example movement. The ability to correlate movements along the x-axis of the left and right hands is important for accuracy of the task and

limiting deviation of the bar. As shown by Sainburg et al. (2013) in young healthy participants, success in this cooperative task required negative covariation between the hands to limit deviation of the bar along the x-axis. To further quantify the relationship between the arms we also performed linear correlations between left and right redundant movement and broke that analysis into three phases as explained in the methods. Phase 1 of the movements (shown in black) is from movement start to peak velocity, reflecting the early predictive components of the movement, Phase 2 (shown in blue) is from peak velocity to movement end, and Phase 3 (shown in red) reflects the late corrections that occur after the initial cessation of movement. For each example movement we included the fit line of the correlation for each phase along with the correlation coefficient (Pearson's R). For the control, the left and right x-displacements in Phase 1 and Phase 2 are tightly negatively correlated, with a smaller positive correlation in the correction phase. The relationship between the hands looks similar for the RHD participant, although somewhat less tightly correlated than controls as shown by the lower R-values. The LHD participant shows very little correlation between the hands, particularly in the early phase of movement.

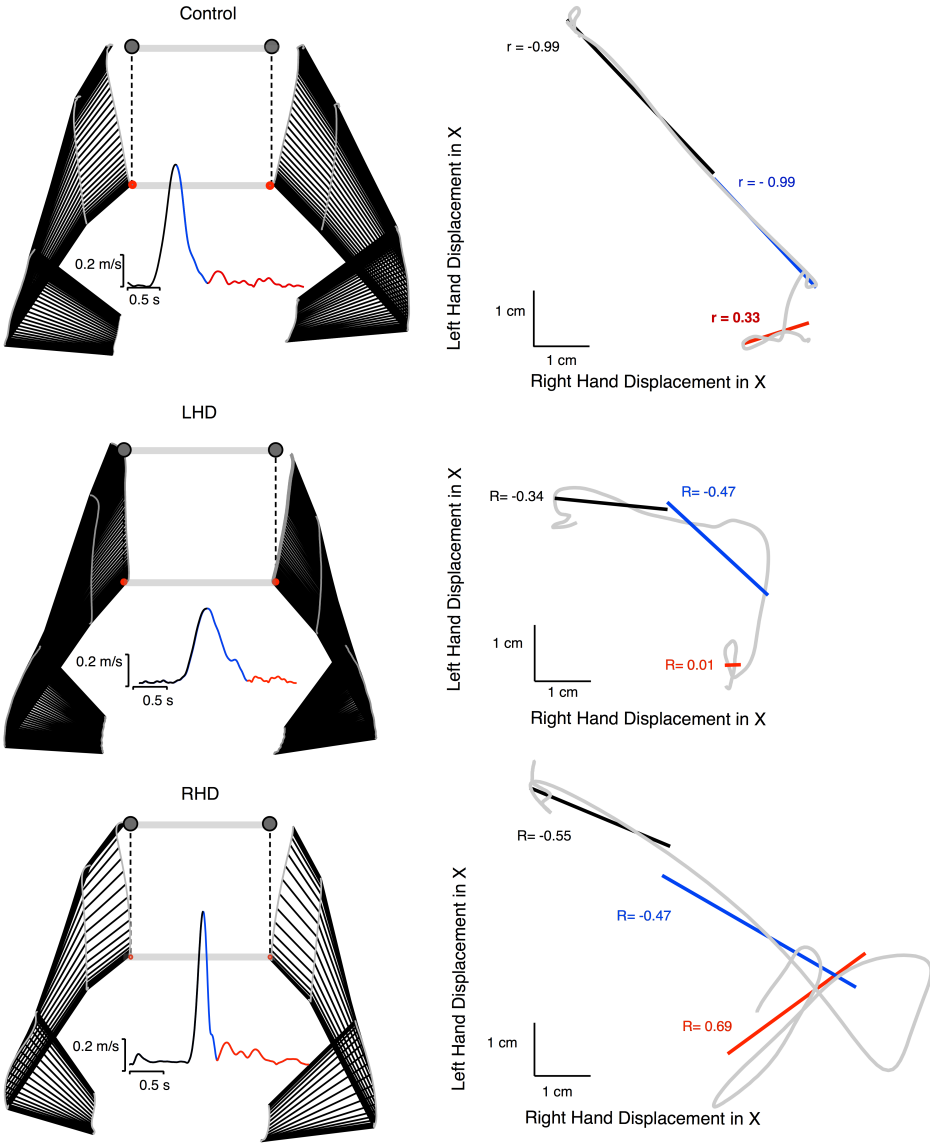

Figure 17- Interlimb correlations of example movements

Figure 18 shows the mean correlation coefficient and slope of the fit line within trials for each group in the three phases. As shown in the individual trials in Figure 17, the stroke groups show less correlation between the hands than controls, with the LHD group showing the least correlation. The lack of interlimb coordination was particularly striking for the LHD group in the early phase of movement. Comparisons between groups using Steel-Dwass Tests revealed that LHD participants had a significantly smaller negative correlation coefficient (p= .0476) than controls in the first phase of movement, which is thought to reflect predictive aspects of control.

The RHD group showed no significant difference in correlation coefficient from controls in any phase of movement. Both stroke groups show slightly lower correlations than controls in the second phase of movement, but these differences were not statistically significant. In the third corrective phase all groups showed similar positive correlations. The trends are similar when looking at the slope of the correlations, however, the difference between LHD and Controls in the first phase did not reach significance (p= .0619).

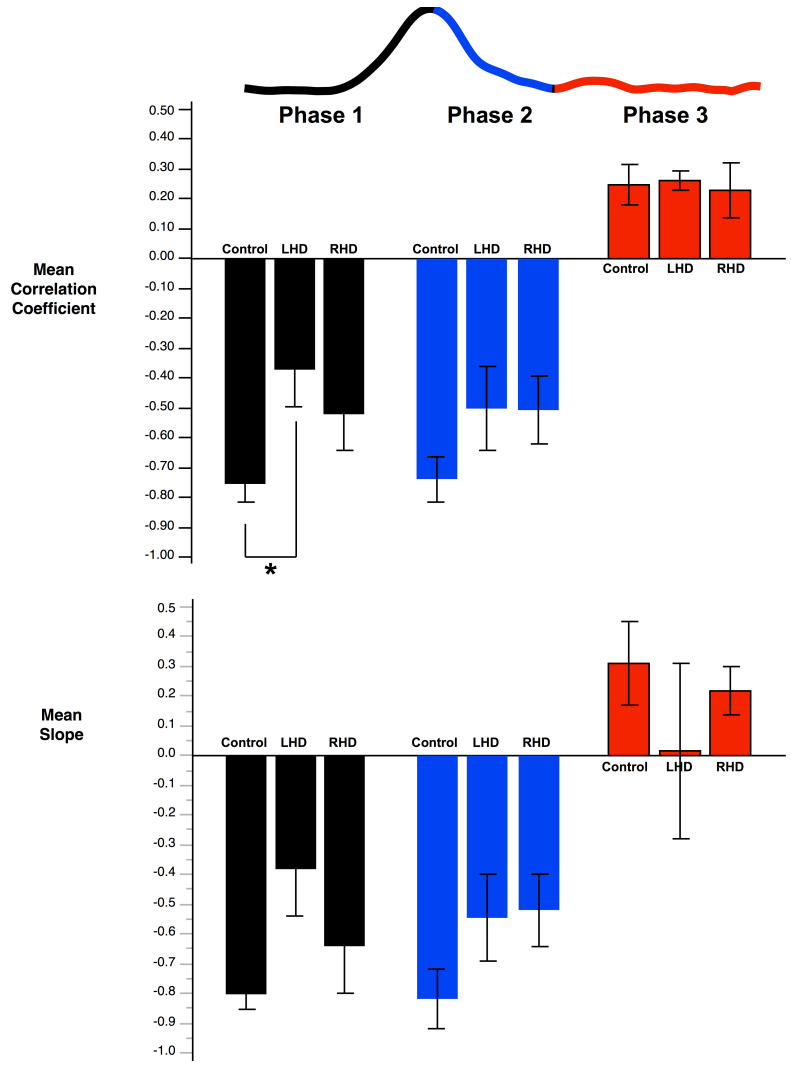

Figure 18- Three phase interlimb correlation within trials

Non-Redundant Axis Performance

As described earlier, success in this task required subjects to move the bar the proper distance and to limit tilt of the bar to keep both hands in their targets. Figure 19 shows those two measures, that describe performance in the non-redundant axis of the task. Bar tilt at movement end was measured as the angle of the bar with respect to the horizontal. Bar center distance error was the absolute distance the center of the bar was from the point halfway between the left and right target circles. All three groups were able to perform the task fairly successfully in terms of the final position errors. For bar tilt and bar center distance error, there were no significant differences between groups, although there was a large amount of variance in the stroke groups.

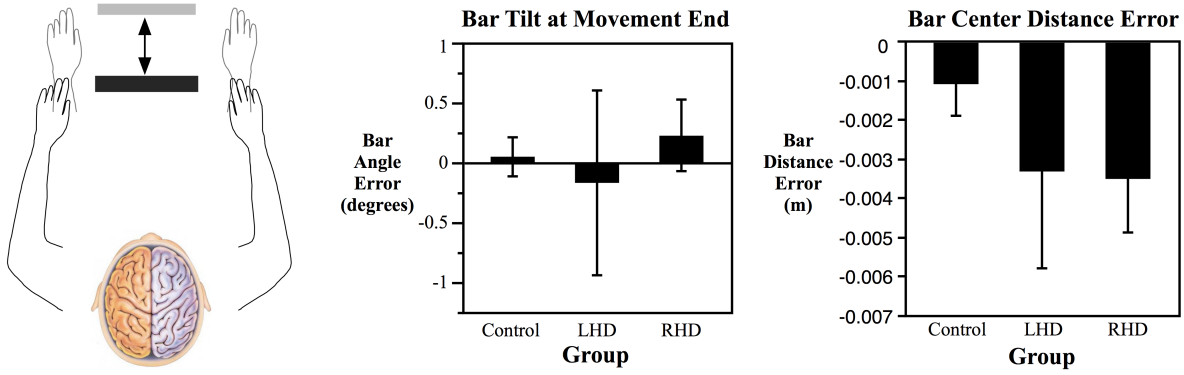

Figure 19- Task Performance

Discussion

This study examined performance in a cooperative bimanual task in RHD and LHD stroke patients compared to controls. We found significant differences in how each group moved along the axis of the bar. Specifically, the LHD group moved less along the redundant axis of the bar, and this movement was highly correlated with deviation of the bar and task error for the LHD group but not for Controls and RHD. The LHD group showed deficits in coordinating the two arms together, and this was most striking in the early predictive phase of movement, consistent with the left hemisphere's specialization for predictive control of movement.

Although deficits in bimanual coordination resulting from stroke have been previously elucidated (Kang & Cauraugh, 2014; Kantak *et al*., 2016), whether bilateral coordination deficits vary with the hemisphere of damaged has not previously been studied. One of the major differences between the LHD and RHD groups in this task was the degree to which they moved along the redundant axis of the bar. The LHD group restricted movement along this redundant axis more than controls, whereas the RHD group moved similar to controls. This movement was also not as well correlated between the right and left hands across trials for the LHD group. This suggests that the LHD participants had difficulty implementing the use of redundant degrees of freedom in a way that did not affect task performance. In a previous study examining unimanual reaching movements with both arms, Freitas and Scholz (Freitas & Scholz, 2009) found using UCM analysis that variance associated with task error (V_{ORT}) was greater for movements of the non-dominant left arm than the dominant right arm. They concluded that the right hemisphere may have more difficulty implementing the coordination needed to selectively increase motor abundance without also producing greater variability of left hand's movement path. A recent

study from our lab found a similar restriction of out-of-plane movement in the left non-dominant arm of healthy participants in a 3-D reaching task (Schaffer & Sainburg, 2017). In this study, the non-dominant arm moved less in redundant degrees of freedom, and any movement in this degree of freedom was highly correlated with task error in the non-dominant but not the dominant arm. Thus, coordination within redundant degrees of freedom that do not affect task error may require left-hemisphere mechanisms in right-handers. Our current findings are consistent with this hypothesis, but more research is necessary to examine this idea and to examine the intrahemispheric functional neuroanatomy of this control.

The LHD group also had particular deficits in coordinating the two hands together in the early phase of movement. This early phase of movement, from start to peak velocity, is thought to rely largely on open-loop aspects of control (Scheidt & Ghez, 2007). This finding is consistent with previous studies on unimanual movements showing that the dominant hemisphere seems to be specialized for predictive control of intersegmental interactions (Sainburg, 2002; Schaefer *et al.,* 2009a). In previous unimanual studies, LHD movements showed significant errors in initial trajectory, and in directional adaptation during visuomotor adaptation tasks (Schaefer *et al.*, 2009b). In this study, the redundant axis of motion along the bar reduced the importance of the accuracy of each hand's trajectory, and emphasized the role of interlimb coordination in ensuring task accuracy. Our findings that these bimanual-specific predictive processes were disrupted by LHD but not RHD suggests that the deficits seen in this study are not simply individual unimanual deficits manifesting themselves in a bimanual task, but reflect the left hemisphere's specialized contribution to bimanual coordination.

We did not find robust differences between groups in coordination near the end of movement or in final position in this task. Given the right hemisphere's specialization for positional control we expected to see some deficits for the RHD group in these later components that rely upon impedance control, but that was not the case. These findings emphasize the bimanual coordination nature of this task, and the fact that hemisphere specific deficits in unilateral movements do not directly translate to bimanual coordination deficits in right and left hemisphere damaged stroke patients. Because all stroke patients in this study were right-handed, the LHD patients' contralesional, most impaired arm, was the dominant arm, whereas RHD patients were most impaired in their non-dominant arm. It has previously been shown that individuals with the dominant arm most affected following stroke often demonstrate less impairment than those with the non-dominant arm most affected (Harris & Eng, 2006). However, other research suggests functional outcomes following stroke are equivalent for RHD and LHD patients (Fink *et al*., 2008). It is plausible that the effect of LHD on bimanual deficits might, at least in part, help explain this apparent contradiction in the literature. While LHD patients may show lower unimanual contralesional impairments, deficits in bimanual coordination might prevent transfer to functional independence and activities of daily living, which depend heavily on bilateral performance. However, it should also be emphasized that we recently provided strong evidence that ipsilesional arm deficits tend to be greater in LHD than RHD patients, when patient groups were matched for contralesional impairment level (Maenza *et al.,* 2019). We conclude that LHD induced deficits in the ipsilesional arm can combine with ipsilesional unimanual coordination deficits to contribute to functional performance deficits in this group of patients.

Clinical Implications:

While many strategies for stroke rehabilitation focus on the contralesional paretic limb, there has been an increasing focus of rehabilitation research and clinical rehabilitation on bimanual movements for stroke rehabilitation because of the functional importance of tasks that require both hands and the distinct mechanisms involved in bimanual movements (McCombe Waller & Whitall, 2008). Our current findings indicate that hemisphere of damage is an important consideration for assessing and treating bimanual movements in stroke rehabilitation. Bimanual coordination in most tasks involves not simply moving both arms at the same time, but coordinating them synergistically to compensate for one another and achieve the end goal. As most stroke rehabilitation strategies aim to improve one or both arms individually, it is important to consider that there may also be deficits in how the arms work together. We believe these findings provide evidence that assessment and training in cooperative bimanual tasks should be considered as part of a functional framework for post-stroke rehabilitation.

Somatosensory deafferentation produces deficits in predictive control of bilateral upper limb coordination and asymmetries in postural stabilization

Large fiber sensory neuropathy (LFSN) results in loss of proprioception and discriminative touch sensation, and has been shown to produce deficits in intralimb coordination and in the ability to stabilize the limb, in the absence of visual feedback. Previous studies also suggest that coordination of cooperative bimanual movements relies on proprioceptive mediated feedback responses. Given these findings, along with previous work on deafferentation showing that proprioception is essential in coordinating intersegmental dynamics (Sainburg & Ghez, 1993;Sainburg et al., 1995), we hypothesize that, in contrast to studies examining temporal coordination between the arms during repetitive bimanual motions, proprioception should be critical for spatiotemporal features of bilateral coordination during a cooperative task. We examined bimanual coordination in a participant with LFSN (GL; age 70 years; right-hand dominant) and in age-matched control participants. The task required participants to move a single virtual bar with both hands to a rectangular target with horizontal orientation. The participants received visual feedback of the virtual bar, but not of the hand positions along the bar-axis. Although the task required symmetrical movement between the arms, there were significant differences in the trajectories of the dominant and non-dominant hands in the deafferented participant. Deafferentation also produced an asymmetric deficit in stabilizing the hand at the end of motion. Specifically, the dominant arm showed significantly more drift than the non-dominant following motion. These results indicate that asymmetries in motor control persist in the absence of proprioception, and that stabilization of position at the end of motion can be achieved through feedforward mechanisms alone, better for the non-dominant than for the dominant arm. This latter finding is consistent with the proposition that the non-dominant

hemisphere may be specialized for control of positional impedance. While the findings with GL may reflect a unique adaptation to deafferentation, they suggest that end-position stability of the non-dominant arm can be specified through feedforward mechanisms that might exploit coactivation of muscles, in the absence of somatosensory feedback.

Experimental Procedures

Participants

We tested an individual, GL (female; age 70 years; right-hand dominant, LFSN), who has been living with LFSN for 40 years, following an acute post-viral onset at age 30, along with 5 healthy age-matched control participants (age 67 ± 2.9; 2 males, 3 females). Clinical tests of GL revealed a specific loss of large-diameter, myelinated Aβ afferents which resulted in a complete loss of touch, vibration, pressure, tendon reflexes, and sense of movement and position in the four limbs, the trunk being moderately affected (Cooke, Brown, Forget, & Lamarre, 1985).

Experimental Setup

Participants were seated at a 2-D virtual-reality workspace in which stimuli from a TV screen were reflected by a mirror, with the participants' arms under the mirror. Figure 20 shows this experimental set-up. Participants' arm movements were tracked using 6 DOF magnetic sensors (Ascension TrackStar) placed on the hand and upper arm. All joints distal to the forearm were splinted. We digitized the location of the tip of the index finger, as well as multiple locations on the hand, and upper arm, and used custom software to estimate the locations of the wrist, elbow, and shoulder joints, relative to these digitized landmarks. Vision of the participants' arms was occluded while position of the index finger was provided as a cursor on

the screen. Participants' arms were supported on air sleds that reduced the effects of friction, and eliminated gravitational torques at the joints. The experimental session consisted of 80 total bimanual movements. The task required participants to first "grab" a virtual bar (20 cm across) by moving cursors representing the position of each hand to each end of the bar. Next, participants moved the bar into the start position, with each cursor placed in the small green circles. Once in the start position, after 100 ms**,** participants were given an auditory start signal and the cursors disappeared, giving participants visual feedback of only the bar. The task required participants to move the bar with both hands a target trough that was 15 cm away from the start position. Points were given for accuracy, as long as participants reached the target speed of at least 0.8 m/s Accuracy required displacement of the bar the correct distance, as well as stopping with the bar parallel to the trough, requiring control of both bar displacement and bar orientation. As shown in Figure 20, movement along the long axis of the bar was redundant, allowing the hands to move outside of the bar.

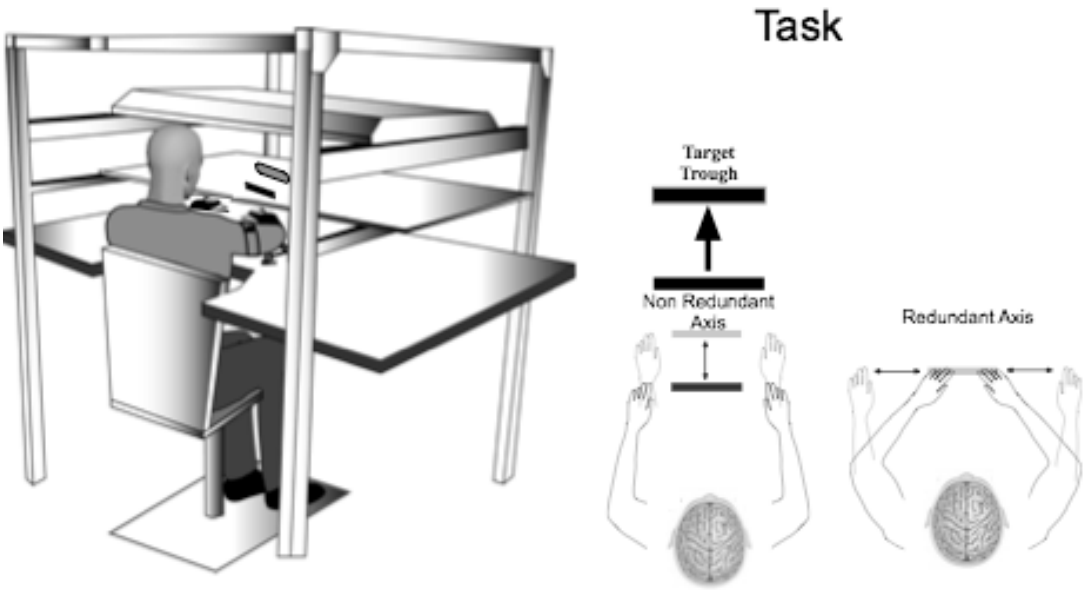

Figure 20- Experiment 3 Task Setup

Kinematic Analysis

We calculated arm segment positions and angles from digitized locations relative to the Trackstar 6-DOF sensors. Data were collected from each sensor at 116 Hz. We digitized multiple positions on the hand, wrist and upper arm. Using custom software, we calculated 10 degrees of freedom per arm, however, because this task was restricted to the horizontal plane by air sled support, and all joints distal to the forearm were splinted, we report only planar motion of the hand, as well as horizontal flexion/extension of the shoulder and elbow joint flexion/extension. All kinematic data were low-pass filtered at 8 Hz (3rd order, dual pass Butterworth) and differentiated to yield velocity and acceleration. Drift of the hand after initial movement termination to the end of the trial was also calculated. Initial movement termination was defined as the first minimum (<5% maximum tangential velocity) following peak tangential finger velocity.

Statistical Analysis

Comparisons between groups of bimanual measures of task performance such as bar distance error and bar orientation were done using the Crawford & Howell method (Crawford, Garthwaite, & Porter, 2010), for comparison of a single-case's score to scores obtained in a control, which was designed to be robust against small control sample sizes and departures from normality. This method has been employed in similar studies with single case-control study designs (Cuadra, Falaki, Sainburg, Sarlegna, & Latash, 2019; Lafargue, Paillard, Lamarre, & Sirigu, 2003)

We also analyzed differences in performance between the hands within subjects. Within-subject comparisons of single subject data using parametric tests are highly prone to Type 1 errors. Thus, single subject's difference in performance between the two conditions must be compared against the control group's performance on those two conditions. In order to assess difference between the hands within groups we used the revised standardized difference test (RSDT) (Crawford & Garthwaite, 2005). This test implements classical methods to test for a difference between a single-case's scores on two tasks, which in this task is the difference between the hands, by comparing the difference against differences observed in a control sample.

Results

Figure 21 shows example movements for deafferented and control participants with lines representing stick figures of the arm drawn between every 2 collected data points (17.2 milliseconds). Below the example movements are the hand velocities shown for each hand. In the velocity profiles, we separated the main component of movement that acted to move the bar forward (black line) from the smaller submovements that occur at the end of movement, which we call "drift" (gray line). Participants were instructed to maintain accurate final position throughout the duration of the trial. While control participants accurately moved the bar into the target trough and held the position with little drift, the deafferented movements were somewhat less accurate and the movements of the right and left arm appeared much less symmetric. In addition, more drift was seen in the deafferented movement, particularly in the right hand.

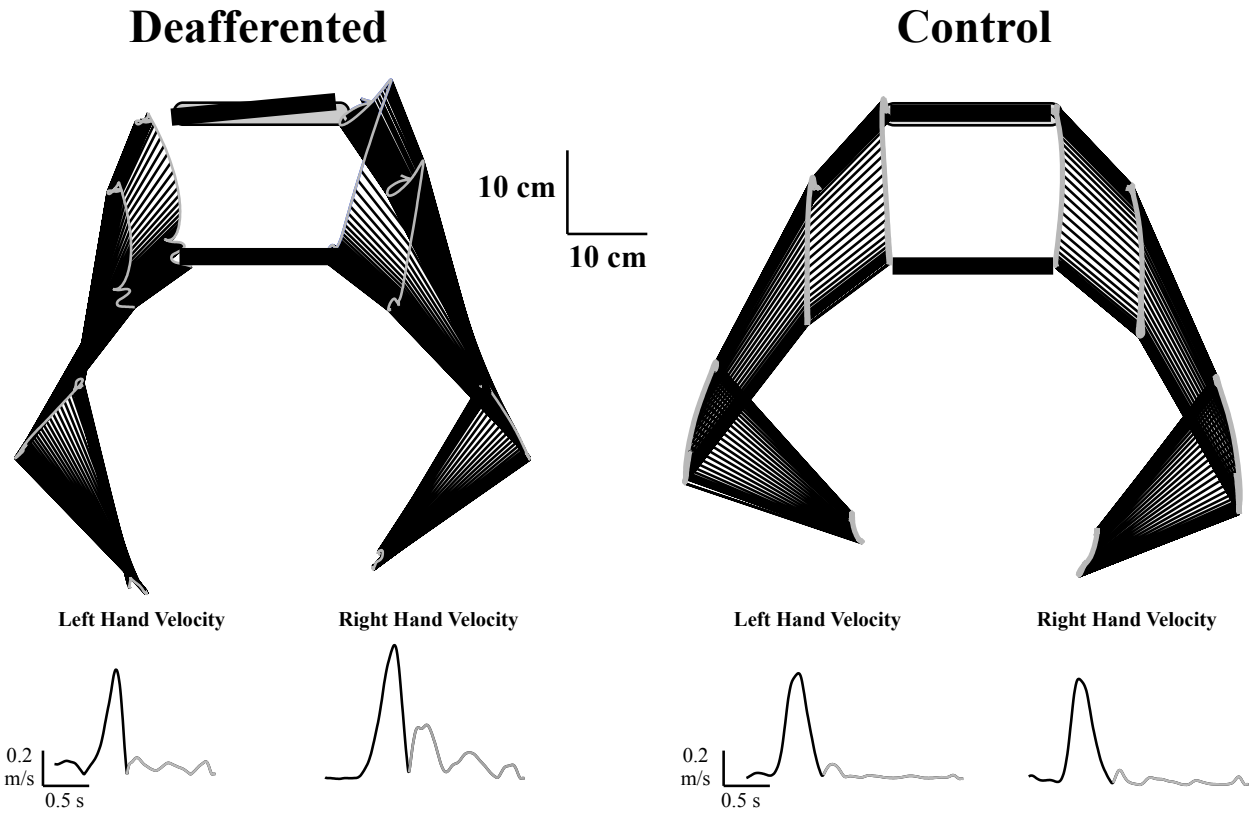

Figure 21- Deafferented and control example movements

Figure 22 shows the main task performance measures including the final position error of the bar and the orientation of the bar throughout the movement. Both measures were important for task success, as the goal was to move the bar the correct distance while also keeping it horizontally oriented to align with the target trough. The deafferented participant showed significantly larger errors in final position of the bar at movement end (p=.02898). The deafferented participant also showed significantly increased angle of the bar at peak velocity (p= .00071) however the orientation of the bar at movement end was not significantly different from controls (p= .3147). Control participants were able to maintain a consistent, small bar orientation angle, while the deafferented participant showed large changes in bar angle throughout movement.

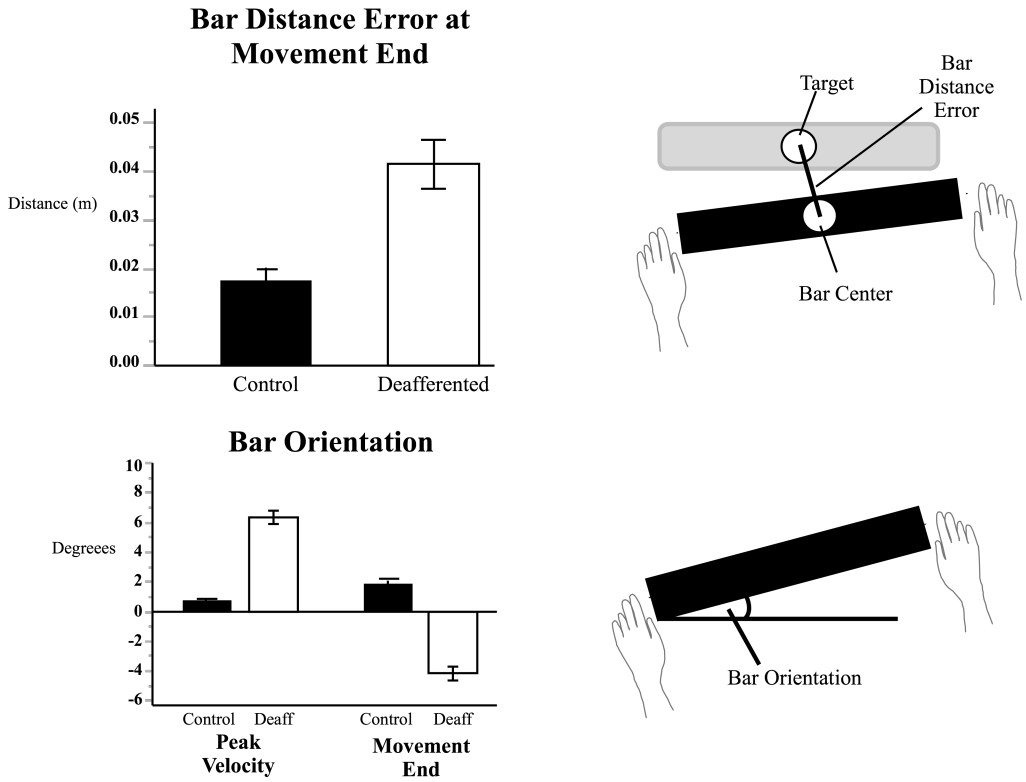

Figure 22- Task Performance

Figure 23 shows our spatial measures for the movement of both hands. The control group showed significantly lower deviation from linearity in both hands than the deafferented

participant. A large asymmetry in this measure was also seen in the deafferented participant but not in the control group. We analyzed whether the difference between the hands (asymmetry) for the deafferented participant was significantly different than for our control group , using the RSDT. We found this asymmetry in linearity was significantly larger in the deafferented participant than in our control group (p= .01945). While a similar trend was seen in the absolute direction deviation at peak velocity, this asymmetry did not reach significance (p= .07307). This asymmetry in trajectory was likely related to the increased bar angle of the deafferented participant throughout the movement as shown in Figure 22.

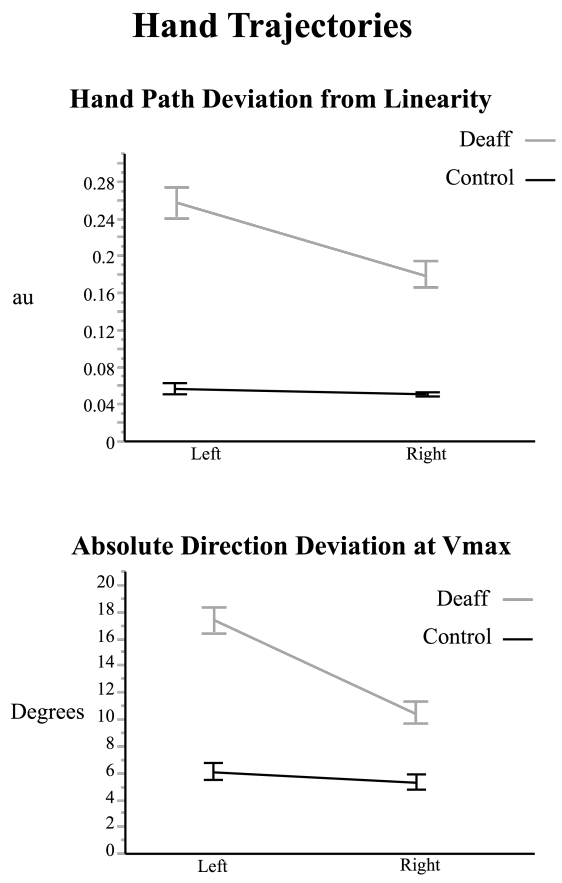

Figure 23- Hand Trajectories

Deafferentation was associated with a pronounced asymmetry in stabilizing the hand at the end of motion. The velocity profiles of Figure 21 show substantial submovements at the end of the initial motion, during which the deafferented participant's right hand tended to drift away from the initial stop position significantly more than the deafferented left hand. Figure 24 shows example movements that illustrate the typical pattern of movement for controls and deafferented participants after the initial stop of movement. The black part of the hand paths in the example movements show the main component of the movement from start to the initial stop, and the drift that occurred until the end of the trial is shown in gray. We calculated drift as total distance travelled by the hands after initial movement end and also as the displacement from the position of the hand at movement end to the position of the hand at the end of the trial in order to characterize whether the hands drifted away from the endpoint or oscillated around the endpoint. Figure 24 shows both of these measures. For total distance of drift RSDT revealed that the differences between the hands for the deafferented participant were significantly different from the control group ($p = .01786$). Drift measured as displacement showed a similar trend as the asymmetry in the deafferented participant was significantly greater than that of the control group ($p = .00232$).

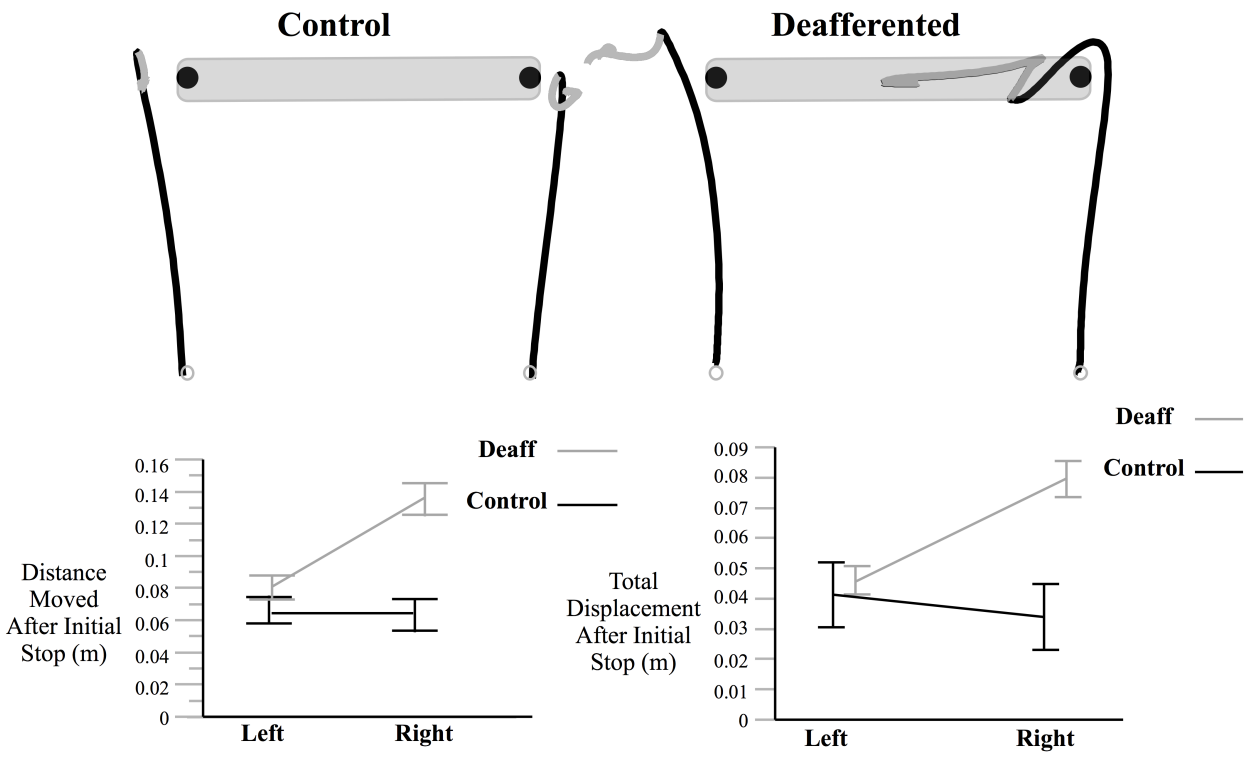

Figure 24- Final Position Drift

The characteristics of the movement that occurred after the initial stop were also different between the deafferented participant and the control group. In the control group, late movement was typically corrective to move the hands closer to the target, whereas the late movement for the deafferented participant was typically associated with a drift further away from the target. Figure 25 shows our measure of drift for each hand of the control group and for the deafferented participant. Drift was calculated by taking the distance of each end of the bar to its target location at the end of the trial and subtracting the distance from the target at initial movement stop. If this late movement moved the bar closer to the target, that corresponds to negative drift, and if it moved farther away from the target the drift is positive. As shown in Figure 25, on average, the hands of the deafferented participant drifted away from the targets, while the control group

corrected to move slightly closer to the target. In addition, there was a significant asymmetry between the hands for the deafferented participant on this measure. Statistical analysis using the RSDT showed that the asymmetry in the deafferented participant was significantly greater than that of the control group (p= .00454).

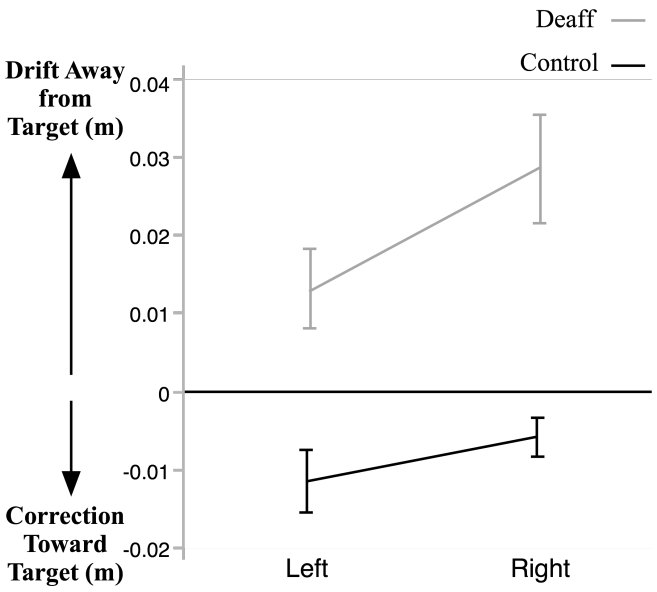

Figure 25- Direction of Drift

Discussion

In this study, we examined how somatosensory deafferentation affects bimanual coordination by comparing performance in a shared bimanual task in a person with large fiber sensory neuropathy with a typical age-matched control group. We found significant asymmetry in control of hand trajectory in the deafferented participant, which resulted in movements that were poorly coordinated between the two limbs. In addition, we found significant asymmetries in the drift of each hand after initial cessation of movement, such that the dominant right hand drifted significantly more than the left hand of the deafferented participant. In contrast, no drift occurred for the control participants, who tended to either remain stable, or make small corrections toward the target.

Both hands of the deafferented participant showed significant deficits in trajectory control, which is consistent with previous studies on deafferented movements (Messier, Adamovich, Berkinblit, Tunik, & Poizner, 2003; Sainburg & Ghez, 1993; Sainburg et al., 1995). However, during this bimanual task, the non-dominant arm of the deafferented participant showed significantly larger trajectory errors than the dominant arm. This asymmetry reflects findings from studies on healthy participants in which the dominant hand exhibits significantly straighter, and efficient movements (Sainburg, 2002). We have previously hypothesized that this difference reflects a dominant hemisphere specialization for predictive control of intersegmental coordination, whereas the non-dominant hemisphere is more reliant on impedance control through feedback mechanisms (Sainburg, 2014). The fact that deafferentation has previously been shown to interfere with predictive control of intersegmental dynamics (Messier, et al.,

2003; Sainburg & Ghez, 1993; Sainburg et al., 1995) is consistent with this interpretation. Thus, asymmetry in trajectory control during reaching movements persists, following deafferentation, supporting a feedforward role in this process.

It is interesting that this asymmetry in trajectory persists in this shared bimanual task in which symmetry between the limbs at the beginning and end of motion is required. It is a widely reported phenomenon that during simultaneous bimanual tasks the two arms tend to perform similarly to each other whether the movements of each arm are instructed to be the same or different (Kelso, Southard, & Goodman, 1979a; Swinnen, 2002). In symmetrical bimanual movements, healthy participants tend to show very tight coordination, particularly in temporal components, between the limbs. For studies in which two different movements are to be performed simultaneously by each arm, there is a tendency for the two movements to become similar, a phenomenon referred to as bimanual interference. This has led some to believe that during bimanual movements, a shared control signal might "couple" the movements of the arms (Kelso et al., 1979a; Marteniuk, MacKenzie, & Baba, 1984). The lack of trajectory and position "coupling" found in the deafferented participant in this study suggests that somatosensory signals from the two moving arms might be critical for such spatiotemporal coupling. This provides support for the findings of Kazennikov and Wiesendanger (Kazennikov & Wiesendanger, 2005), who found that synchronization of the two hands during a bimanual reach and grab task was disrupted by altering proprioception via tendon vibration applied to one of the arms. The current results extend these findings by showing that complete loss of proprioception results in even greater disruption of synchronization between the arms.

The most novel finding of this study is the dramatic asymmetry in final position drift demonstrated by the deafferented participant. Large postural drifts, when required to hold the limb still without visual monitoring has consistently been reported for deafferented individuals (Nougier et al., 1996; Rothwell et al., 1982; Sanes, Mauritz, Dalakas, & Evarts, 1985). In addition, large drifts at the end of planar reaching movements have been reported (Gordon, Ghilardi, & Ghez, 1995). However, those studies examined dominant arm movement, and thus, asymmetry in drift was not reported. Some authors have hypothesized independent neural mechanisms for controlling trajectory and stable final positions during reaching (Kurtzer, Herter, & Scott, 2005; Scheidt & Ghez, 2007). These mechanisms may be lateralized, as suggested by Yadav and Sainburg (Yadav & Sainburg, 2014) utilizing a serial model to explain lateralization of simple reaching movements, in which movements are initiated with predictive trajectory control (dominant hemisphere) and terminated using an impedance controller (non-dominant hemisphere). They predicted that the difference in performance between the arms would be based on the difference in the timing of the switch of control mechanisms between each arm, such that the non-dominant arms reaches would switch to impedance control earlier than the dominant. It has been proposed that the mechanism of switching between controllers relies on proprioceptive information (Cordo, Carlton, Bevan, Carlton, & Kerr, 1994; Scheidt & Ghez, 2007). In the absence of proprioception, this hypothetical switch, from movement to postural control, may not occur or may occur too late for the right hand, leading to less effective impedance control, and greater postural drift.

Whatever mechanisms might be responsible for specifying and controlling movement trajectories, and achieving stable and accurate final positions, our current results indicate that

deafferentation had differential effects on each aspect of control in the two limbs. The non-dominant left hand of the deafferented participant showed substantial deficits in trajectory coordination, but was better able to stabilize position at the end of motion, whereas, the dominant right hand showed better trajectory control, but demonstrated greater drift at the end of movement.

Isometric force generation in one hand facilitates long latency, but not short latency reflexes in the opposite wrist

Although interhemispheric inhibition via transcallosal pathways is a well-known phenomenon, recent studies have found that when forces exceed approximately 70% of MVC, these interhemispheric interactions can result in increased cortical excitability in the opposite hemisphere (Perez and Cohen, 2008; Long et al., 2016). Facilitation, or increased excitability via contralateral force production has been well documented, but the neural pathways that mediate it are not known. A number of pathways, both at the cortical and subcortical level, have been suggested as candidates for being involved in this phenomenon. We now ask if the mechanisms mediating this increase in movement vigor are reflected in spinal and supraspinal reflexes. We examined this question using a perturbation task, in which participants were instructed to hold the position of their left wrists against a background flexor load, and on random trials a perturbation was applied to the wrist, eliciting a stretch reflex of the wrist flexors. Similar to the previous experiment, the contralateral force condition required participants to exert isometric force with their right index finger for the entirety of the trial. In a baseline condition required, the right arm did not exert force. EMG activity of the flexor and extensor carpi muscles of the left forearm was recorded and separated into three intervals (M1: 20-45 ms post-perturbation, M2: 45-75 ms, and M3: 75-105 ms). We compared activity in these intervals to see if the contralateral force of the right arm altered the reflex response of the left arm. Our results suggest an interaction between contralateral force condition and reflex interval for the flexors, such that the M2 interval showed increased activity in the contralateral force condition compared to baseline, but M1 did not. This indicates a

cortical, but not a spinal facilitation from contralateral isometric force generation, and may be related to inhibition of intercortical inhibition reported previously by Perez and Cohen (2008), and Long et al. (2016).

Experimental Procedures

Participants

Participants were 8 healthy right-handed adults aged 18-35 years old. All participants were screened for handedness using the Edinburgh Inventory (Oldfield, 1971) and provided informed consent before participation in this study, which was approved by the institutional review board of Penn State University.

Experimental Setup

Participants were seated at a 2-D virtual-reality workspace in which stimuli from a TV screen were reflected by a mirror, with the participants' arms under the mirror. Figure 1 shows this experimental set-up. Participants' arm movements were tracked using 6 DOF magnetic sensors (Ascension TrackStar) placed on the hand and upper arm. All joints distal to the forearm were splinted. We digitized the location of the tip of the index finger, as well as multiple locations on the hand, and upper arm, and used custom software to estimate the locations of the wrist, elbow, and shoulder joints, relative to these digitized landmarks. Vision of the participants' arms was occluded while position of the index finger was provided as a cursor on the screen. The task required the participants to stabilize the position of the cursor within the start circle for the duration of the four-second trial. EMG activity was recorded from the flexor carpi ulnaris, flexor

carpi radialis, extensor carpi ulnaris, and extensor carpi radialis of the left arm with active electrodes (35 mm electrode distance, 500 Hz low pass filter, Biopac Systems Inc.).

Figure 26 shows a diagram of the setup. Both forearms were stabilized in sleds with the wrists free to move. The left forearm was strapped in the sled in a neutral position with the thumb pointed up holding on to a handle, which was attached to a spring, providing a background flexor load. Another spring attached to the handle was locked in place providing no resistance. On random trials the second spring was released, moving the wrist into extension and eliciting a stretch reflex of the wrist flexors. Participants were instructed to keep the hand stable if possible, and to move the hand (cursor) back to the original position as quickly as possible if position was changed by the perturbation. EMG activity of the flexor and extensor carpi muscles of the left forearm was separated into three intervals: R1 (20-45 ms post-perturbation), R2 (45-75 ms), and R3 (75-105 ms). For the left arm there were two conditions: one in which the perturbation was triggered three seconds into the four second trial, and a sham condition in which the spring initiating the perturbations is detached from the hand without the participant's knowledge and no perturbation occurred. This condition was done to assure that the perturbations were unpredictable and thus that the responses were not anticipatory in nature. For the right arm there were two conditions: 1) a contralateral resistance condition, in which participants pulled down on a spring with their index finger, exerting isometric finger and radial wrist flexor force against a constant spring force of 40 N for the entirety of the trial and 2) a no resistance condition, in which the right arm was at rest. The forearm was supported up to the wrist and the wrist was left unconstrained.

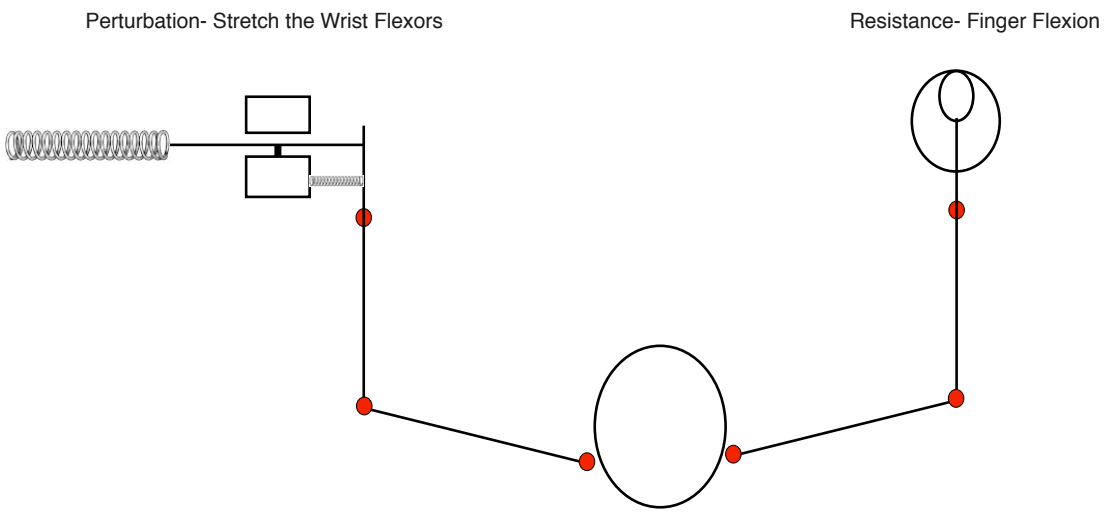

Figure 26- Diagram of Perturbation and Contralateral Resistance Setup

EMG Analysis

EMG data were collected at 1 KHz for the flexor carpi ulnaris, flexor carpi radialis, extensor carpi ulnaris, and extensor carpi radialis of the left arm. Collection began one second prior to the start of the trial and ended at the end of the three-second trial. EMG signal was then full-wave rectified, low-pass filtered at 400 Hz using a third-order dual-pass Butterworth filter, and normalized to the maximum EMG recorded during the experiment for that muscle for each subject. Trials in which there was no discernable response in perturbed arm electrodes were eliminated from analysis. Similar to previous studies (Kurtzer et al., 2008; Omrani et al., 2013) we binned muscle activity into three intervals, relative to the initiation of the perturbation: 1) R1 (20-45 ms), 2) R2 (45-75 ms), and 3) R3 (75-105 ms) to reflect the latencies of the previously reported components of the stretch reflex. In order to examine the effect of the perturbation on muscle activity, for each muscle we calculated the integral of the EMG in each of these intervals. We

compared muscle activity in these intervals in the contralateral resistance condition to the activity in the no resistance condition.

Statistical Analysis

For statistical analysis of the EMG, we compared muscle activity for each muscle and each interval with a 2 by 2 mixed-factor ANOVA with resistance condition (contralateral resistance, no resistance) and perturbation condition (perturbation, sham) as the within subject variables. When indicated, post- hoc analysis was done using the Tukey HSD test, which adjusts for family-wise multiple comparisons (JMP Statistical Software, SAS Software).

Results

Figure 27 shows the left wrist flexion angle during a representative perturbation trial (gray) and a sham trial (black). The wrist angle starts at close to a neutral angle and then is pulled into extension by the perturbation three seconds into the trial. Participants then quickly respond to the perturbation by bringing the wrist back close to the neutral starting position with a slight overshoot into flexion.

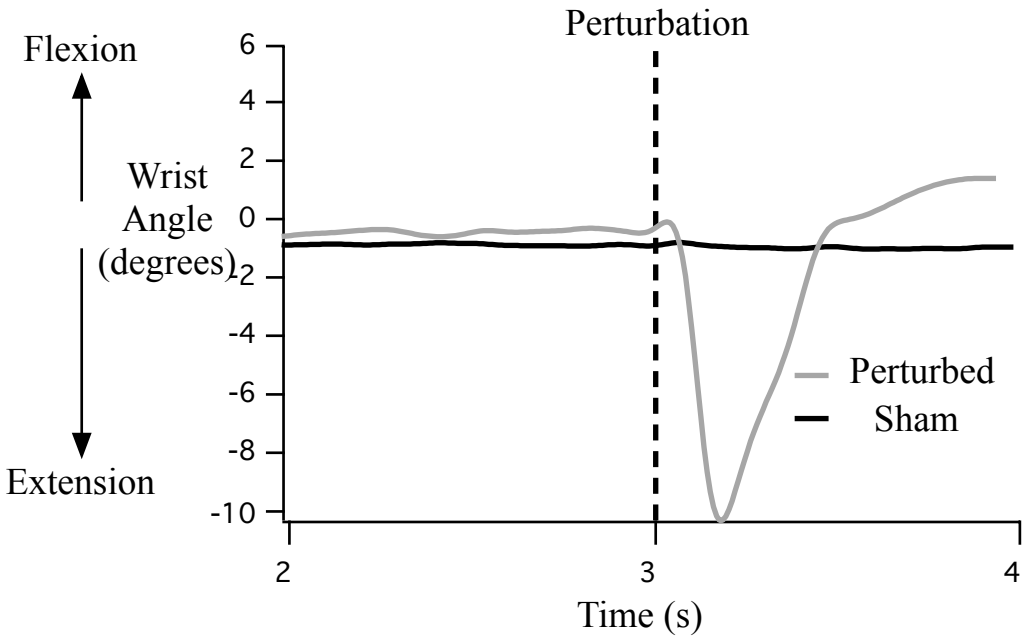

Figure 27- Example Wrist Kinematics

We first analyzed flexor muscle activity 100 milliseconds prior to the perturbation in order to check that the EMG activity prior to the perturbation was consistent for all conditions and ensure that automatic gain scaling (Pruszynski et al., 2009) was not a confound. We found no significant differences in flexor muscle activity pre-perturbation between perturbation conditions (flexor carpi radialis: $F(1,7)= .0503$, $p= .829$; flexor carpi ulnaris: $F(1,7)= .0004$, $p= .9839$), or contralateral resistance conditions (flexor carpi radialis: $F(1,7)= 1.058$, $p= .3379$; flexor carpi ulnaris: $F(1,7)= 1.7946$, $p= .2222$), nor was

there any interaction (flexor carpi radialis: $F(1,7)= .1351$, $p= .724$; flexor carpi ulnaris: $F(1,7)= .1458$, $p= .7139$). There was also no significant difference in extensor muscle activity pre-perturbation between perturbation conditions (extensor carpi radialis: $F(1,7)= 2.9044$, $p= .1321$; extensor carpi ulnaris: $F(1,7)= .4814$, $p= .5101$), contralateral resistance conditions (extensor carpi radialis: $F(1,7)= 3.6982$, $p= .0959$; extensor carpi ulnaris: $F(1,7)= 4.1856$, $p= .0800$), nor any interaction (extensor carpi radialis: $F(1,7)= 1.2676$, $p= .2973$; extensor carpi ulnaris: $F(1,7)= 3.7612$, $p= .0936$) showing that activity in all muscles recorded was consistent prior to the perturbation.

We then compared activity in the R1, R2, and R3 intervals using a two-way (perturbation by resistance condition) mixed factor ANOVA in each interval to see if the contralateral force of the right arm altered the reflex response of the left arm. Figure 28 shows the bar graphs of the integrated EMG average over the three intervals for both conditions in the flexor carpi radialis as well as example EMG profiles. Figure 29 shows the results for the flexor carpi ulnaris. We found reflexes in all three intervals in both flexor muscles. Neither extensor muscle showed a significant reflex response to the perturbation in the R1 or R2 interval, however, the extensor carpi radialis did show a significant response to the perturbation in the R3 interval ($F(1,7)= 6.8771$, $p= .0343$). No effect of contralateral resistance was seen in any interval for the extensor muscles, nor were there any interactions. There was, however, a specific effect of contralateral resistance on the R2 interval of the flexor carpi radialis. Our ANOVA for the flexor carpi radialis R1 interval showed that there was an effect of perturbation ($F(1,7)= 40.0014$, $p= .0004$) but neither an effect of resistance condition nor any interaction. The flexor carpi ulnaris R1 also showed an effect of perturbation ($F(1,7)= 48.6634$, $p= .0002$) but no

effect of resistance or interaction. For the flexor carpi radialis R2 there was an effect of perturbation ($F(1,7)= 26.6281$, $p= .0013$), effect of resistance ($F(1,7)= 11.2484$, $p= .0122$), and an interaction of perturbation and resistance ($F(1,7)= 12.9486$, $p= .0088$). Post-hoc analysis revealed that the activity of the perturbed flexor carpi radialis R2 was significantly greater with contralateral resistance ($p= .0084$). Although there is a trend for increased muscle activity in the R2 interval with contralateral resistance this result does not reach significance. There is an effect of perturbation ($F(1,7)= 102.0166$, $p< .0001$) but no effect of resistance or interaction. There was also a significant R3 response to the perturbation in both the flexor carpi radialis ($F(1,7)= 17.7672$, $p= .004$) and flexor carpi ulnaris ($F(1,7)= 28.2999$, $p=.0011$), but there was no effect of contralateral resistance or an interaction in either muscle.

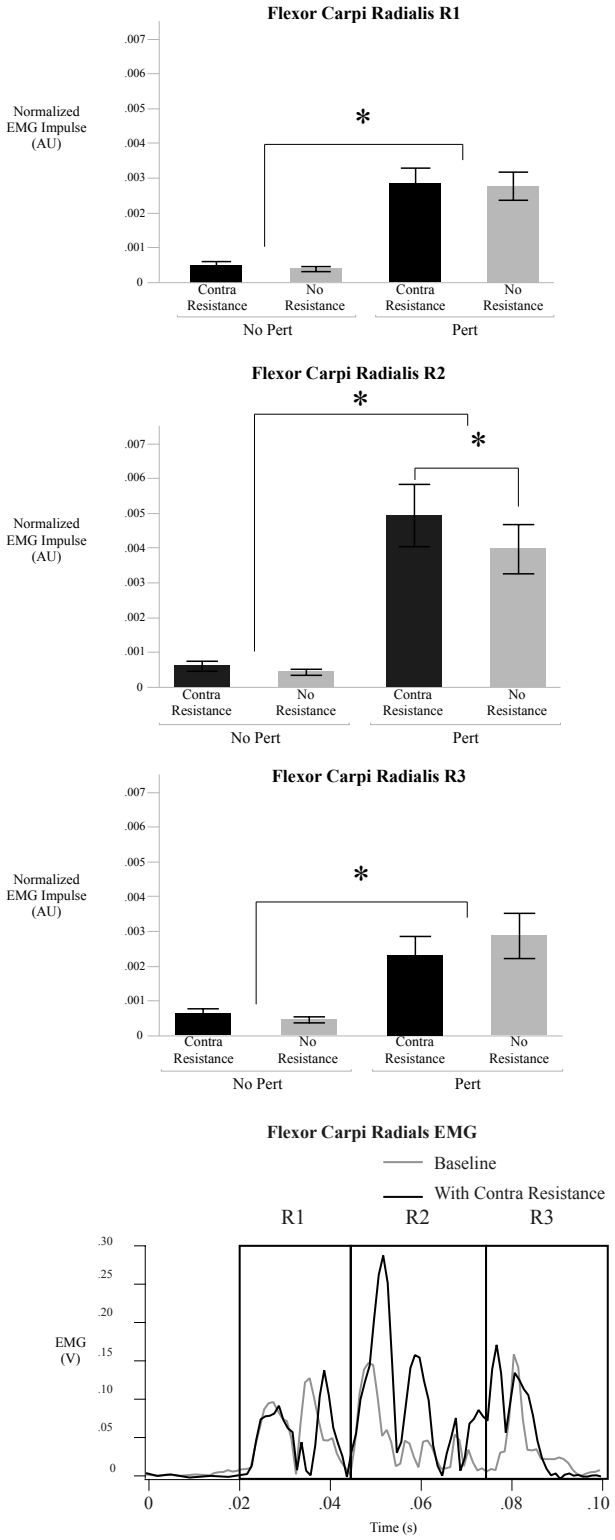

Figure 28- EMG Response of Flexor Carpi Radialis

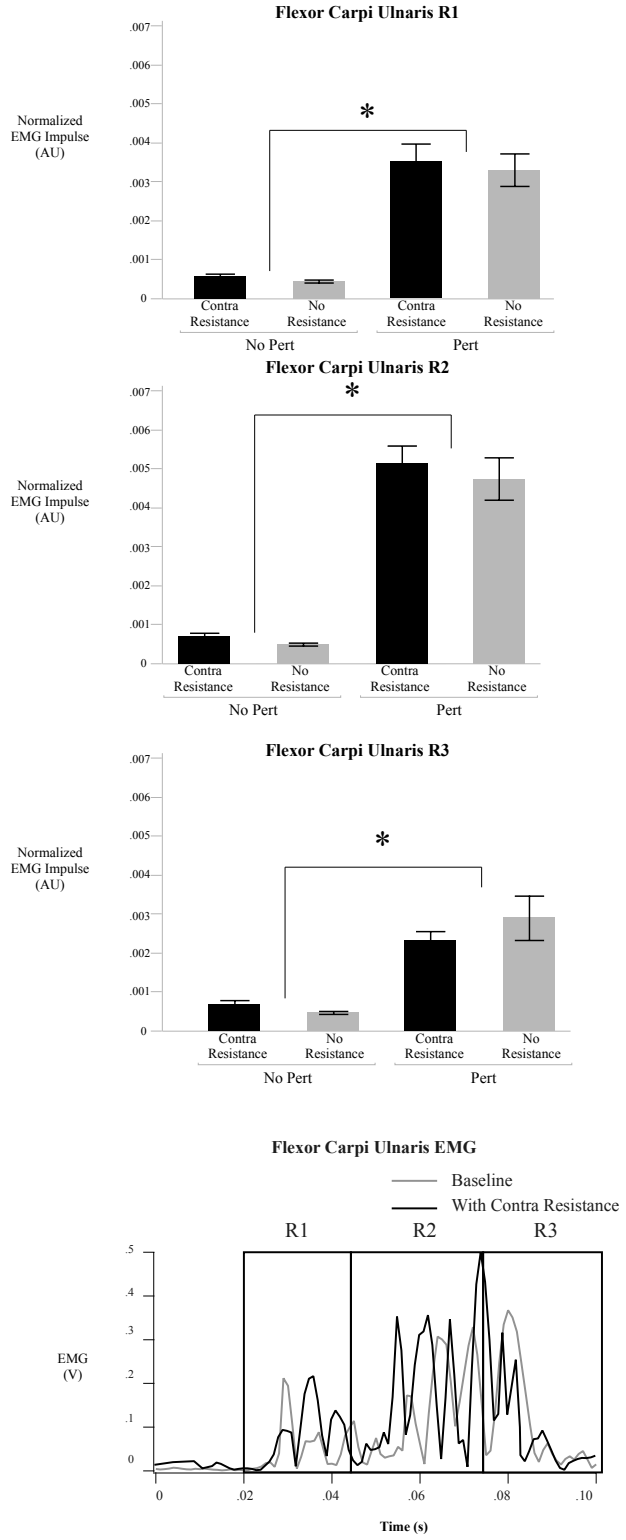

Figure 29- EMG Response of Flexor Carpi Ulnaris

Discussion

This study showed that reflexes can be modulated by forceful contraction of muscles of the contralateral limb. The perturbation, which caused stretching of the left wrist flexor muscles, elicited a significant increase in muscle activity in all reflex intervals for both flexor muscles. This included a significant muscle response in the R1 reflex interval, occurring 20-45 milliseconds after the perturbation. Given the unique short latency component of the R1 response, it is reasonable to conclude that any perturbation that elicits contraction at this short latency is mediated by spinal loops of 1a afferents from muscle spindles synapsing with alpha motorneurons (Shemmell et al., 2010). Thus, we were able to reliably elicit a stretch reflex response in the wrist flexors with this perturbation setup. We then analyzed the effect that forceful isometric contraction of the contralateral limb had on these reflex responses. We found that contralateral resistance resulted in a specific facilitation of the reflex response of the flexor carpi radialis in the R2 latency (45-75 ms post-perturbation). Previous studies have shown that responses evoked in hand muscles, by transcranial magnetic stimulation of the motor cortex, are facilitated by tonic contraction of homologous muscles of the opposite limb (Hess, et al., 1986; Muellbacher, et al., 2000; Perez & Cohen, 2008; Long, et al., 2016). Our results extend those findings by showing that a similar facilitation of reflex responses also occurs via strong contraction of homologous muscles. Due to the spinal pathways mediating short-latency reflexes, we hypothesized that any modulation in the short-latency component of the reflex that occurred with contralateral force would be due to increased excitation of these spinal pathways. Given that we saw no change in the R1

response with contralateral force, this suggests that any reflex modulation was not occurring strictly at the spinal level.

One of the first studies documenting facilitation caused by strong contraction of homologous muscles on the opposite side by Hess et al. (1986) attributed this facilitation to increased excitability of motor pathways projecting to the resting contralateral hand muscle, most likely at the level of the spinal cord rather than the cerebral hemisphere. However, more recent studies have provided evidence that the facilitation occurs at the cortical level (Stedman et al., 1998; Tinazzi & Zanette, 1998). We saw an increase in muscle activity in the R2 interval of the flexor carpi radialis in the contralateral force condition. EEG potentials have been recorded preceding long-latency reflexes (Mackinnon et al., 2000), and TMS over cortical areas has been shown to influence long-latency reflexes (Palmer & Ashby, 1992), suggesting that transcortical pathways are involved in long-latency reflexes. Given that the modulation of the reflex seen in this task was specific to the R2 interval and did not act on short-latency R1, this supports previous findings that the facilitation is likely involving supraspinal mechanisms. Although the specific pathways are unclear, it is likely that the facilitation seen in this study occurred via cortical loops (Mathews, 1991).

It is possible that interhemispheric interactions via transcallosal pathways are involved in altering the response of the perturbed limb. Interhemispheric interactions have been well-documented, although typically activity in one hemisphere tends to inhibit activity in the opposite hemisphere, a phenomenon known as interhemispheric

inhibition (IHI), which is thought to be mediated by transcallosal pathways (Cracco, et al., 1989; Ferbert et al. 1992; Meyer, et al., 1995). However, more recent studies on interhemispheric interactions have shown that as the forces increase on one side, the effect on the contralateral side becomes facilitatory (Hess, et al., 1986; Muellbacher, et al., 2000; Perez & Cohen, 2008; Long, et al., 2016). These interhemispheric pathways have been shown to significantly influence local inhibitory interneurons within each hemisphere, and can have a disinhibitory effect on the opposite hemisphere as force increase (Perez & Cohen, 2008). However, the inhibitory and facilitatory interhemispheric interactions may occur through different mechanisms, as Meyer et al. (1995) has shown that although IHI is delayed or absent in patients with callosal agenesis, the facilitatory effect persisted. This suggests that mechanisms beside transcollosal interactions may be involved in this effect. It is also possible that the increased reflex response was caused by an increase in excitation of ipsilateral pathways projecting to the perturbed arm. Ipsilateral corticospinal pathways have been shown to play a role in bimanual movements, as they have been implicated in causing instability in asymmetric bimanual movements (Cattaert et al., 1999; Kagerer et al., 2003). In addition, ipsilateral pathways are recruited more in complex (Swinnen et al., 2010) or high force movements (Muellbacher, et al., 2000), such as the finger flexion forces necessary for this task.

The fact that the R2 interval was specifically modulated by contralateral force but not the R1 interval suggests an effect that is different from generalized effects that have been seen such as those associated with the Jendrassic maneuver. The Jendrassic

maneuver facilitated reflex response via remote muscle contraction; however, this effect has been shown to act on spinal reflexes, as changes in H-reflex have been documented associated with the Jendrassic maneuver (Dowman & Wolpaw, 1988). Thus, the differential effect on R1 and R2 reflex intervals seen in the current study suggest that a different, more specific mechanism is involved. The finding that this effect did not reach significance in the flexor carpi ulnaris may also point to the specificity of the effect of contralateral force. Participants pressed on the spring with their contralateral index finger, meaning that more radial muscles of the contralateral arm were activated in order to press down the spring. This may be why the homologous muscles on the other limb showed more modulation of the reflex compared to the ulnaris muscle; however, this has not been specifically tested.

Scientists and clinicians have been studying whether bilateral mechanisms may affect the functional recovery of the paretic limb after stroke. For example, interhemispheric inhibition coming from the contralesional hemisphere to the ipsilesional hemisphere has been implicated in reducing the excitability of the ipsilesional hemisphere and contributing to functional deficits of the paretic arm (Boroojerdi, Diefenbach, & Ferbert, 1996; Liepert, Hamzei, & Weiller, 2000; Murase et al., 2004). This idea has informed strategies for stroke rehabilitation protocols such as constraint induced movement therapy (Wolf et al., 2006; Kwakkel et al., 2015). However, as our results as well as others show, it may be possible to engage these interhemispheric pathways for facilitatory effects. It is important to understand the mechanisms of such bilateral interactions in order to determine the efficacy of such approaches and to tailor

strategies to patient populations who may benefit. However, more work needs to be done examining whether the facilitation extends to aspects of functional movements. For example, can contralateral force improve movement characteristics such as speed of reaching movements, and how do factors such as lesion size and location change this effect? The current results may provide a basis upon which to evaluate such questions and to develop task and deficit-specific programs of movement rehabilitation and therapy.

Summary and Concluding Remarks

The goal of this dissertation was to examine the neural mechanisms involved in bimanual control, in particular, how a lateralized brain allows for interaction and cooperation between the two hemispheres. In the first study, we asked whether the bilateral feedback responses seen in previous studies reflected lateralized control mechanisms. The second study examined the role of each hemisphere in bimanual movements, and whether certain aspects of control were driven by one hemisphere or the other in a way similar to unimanual control. Then we studied the role of somatosensory feedback on cooperative control of bimanual movements. Finally, we assessed possible mechanisms of how the hemispheres interact with each other.

The first and second studies show that even in cooperative bimanual tasks, in which movement of the limbs appears similar, each hemisphere plays a specialized role. The first study showed that responses to perturbations during bilateral movements are expressed asymmetrically, such that non-dominant arm responses to perturbations to the dominant arm are stronger than dominant arm responses to non-dominant arm perturbations. The differences in performance between the arms reflect differences previously seen in unimanual movements, showing that asymmetry persists in cooperative bimanual tasks. However, the second study showed that aspects of control that are specific to bimanual movements are also lateralized. In this study left hemisphere damage impaired the ability to coordinate each arm together, particularly early in movement.

The third study shows that in the absence of somatosensory feedback during cooperative bimanual movements, the specialized role of each hemisphere becomes even more apparent. Movement of the dominant and non-dominant limbs was significantly different, such that the non-dominant arm had large errors in trajectory and the dominant arm was unable to stabilize the arm in its final position. These errors correspond to the specializations of each hemisphere that have been elucidated based on unimanual movements of healthy people. This asymmetry was apparent even in a cooperative task in which both arms were required to move symmetrically. In such tasks, synchronization is usually observed in the movements of the dominant and no-dominant limbs, but without somatosensory feedback this synchronization did not exist. This suggests the somatosensory feedback is crucial in synchronizing movement of each limb for cooperative control of a lateralized system, opposing the view that such synchronization was due to a shared motor command. This finding, in combination with the hemispheric asymmetry found in the first two studies provide important insight into possible training strategies for improving bimanual coordination in clinical populations.

This dissertation provides some evidence and methodological considerations that may inform research on identifying and treating bimanual deficits in clinical populations. For example, the cooperative task with a virtual bar used throughout these studies provides a way of examining parameters of movement that are specific to bimanual coordination, in contrast to analyzing each arm individually. Many studies have focused on training of rhythmic bimanual movements, or activities in which both arms move simultaneously but independently as a way to improve performance of bimanual and

unimanual movements after stroke (McCombe Waller & Whitall, 2008). These studies typically attempt to use bimanual training as a way to make the limbs move more similarly to each other by exploiting any shared or facilitative effects. Yet in many functional tasks, matching movements are not required and instead cooperation between the hands is necessary, such as in opening a jar. As our results suggest, there are significant deficits associated specifically with left hemisphere damage that may limit the ability of both hands to covary with each other in a cooperative way. This aspect of bimanual control should be addressed. In addition, although interhemispheric interactions do occur, somatosensory feedback appears crucial in mediating these interactions. Thus, adequate somatosensory function may be necessary for targeting any interhemispheric interactions in bilateral training. These studies provide evidence that identifying patient characteristics, such as hemisphere of damage and somatosensory function will allow for more targeted interventions and improved function.

The fourth study specifically examines one such interhemispheric interaction that has been well-documented in the literature. In this study we show that feedback responses can be facilitated by strong contralateral force of homologous muscles, and that this facilitation is likely mediated at a level above the spinal cord. The aim of this study was to examine the mechanisms mediating this interaction so that the functional consequences of it could be greater understood. Similar interhemispheric interactions, such as interhemispheric inhibition have informed stroke rehabilitation protocols for many years, however, little is known about the mechanisms involved in facilitatory effects such as those seen in this study. Although more work needs to be done evaluating whether this

phenomenon may have an effect on more functional movements and the specific mechanisms involved, this study provides insight to inform more targeted approaches to manipulating corticospinal output.

Taken together, these studies show clear asymmetries in control between the dominant and non-dominant movements during bimanual tasks. This provides further evidence of lateralized motor control mechanisms that result in the dominant hemisphere being proficient for processes that predict the effects of body and environmental dynamics, while the non-dominant hemisphere is proficient at impedance control processes that are robust to unexpected mechanical conditions, and can achieve accurate steady-state positions. Such lateralization, although apparent in unimanual movements (reviewed by Sainburg, 2014), has not been clearly elucidated before in bimanual movements. In fact, many aspects of movements appear more similar between the limbs during shared bimanual movements. However, the findings from this dissertation suggest that coordination between the limbs resulting in synchronized movements is reliant on left hemisphere (in right-handers) processes as well as bilateral interactions that are mediated by somatosensory information coming from each limb, and are not likely to be the result of a shared motor command.

Funding: This work was supported by the National Institutes of Health # R01HD059783 from NIH, NICHD to RLS. The findings and conclusions do not necessarily reflect the view of the funding agency.

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CONFERENCE PRESENTATIONS

- Schaffer, J. E., Jayasinghe, S, Maenza, C, Sarlegna, F, Sainburg, R. L. Somatosensory deafferentation produces deficits in predictive control of bilateral upper limb coordination and asymmetries in postural stabilization. Poster presented at Society for Neuroscience Conference; 2019 Oct. 19-23; Chicago, IL.
- Schaffer, J. E. & Sainburg, R. L. Isometric force generation in one hand facilitates long latency but not short latency reflexes in the opposite wrist. Poster presented at Society for Neuroscience Conference; 2018 Nov 3-7; San Diego, CA.
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