

**DIFFERENTIAL CONTRIBUTIONS OF TRANSCALLOSAL
SENSORIMOTOR FIBER TRACT STRUCTURE AND NEUROPHYSIOLOGIC
FUNCTION TO MANUAL MOTOR CONTROL IN YOUNG AND OLDER
ADULTS**

by

Brett W. Fling

A dissertation submitted in partial fulfillment
of the requirements for the degree of
Doctor of Philosophy
(Kinesiology)
in The University of Michigan
2011

Doctoral Committee:

Associate Professor Rachael D. Seidler, Chair
Professor Patricia A. Reuter-Lorenz
Associate Professor Susan H. Brown
Associate Professor Stephan F. Taylor
Research Assistant Professor Robert Cary Welsh

© Brett W. Fling 2011
All Rights Reserved

ACKNOWLEDGEMENTS

Throughout my career as a graduate student I have been blessed to be around wonderful individuals who helped me in various aspects of my development.

Clearly my acknowledgements must start with my dissertation advisor and mentor, Dr. Rachael Seidler. Rachael was brave enough to take a chance on me four years ago, and the rest of my career will be forever influenced by her excellent guidance. Rachael has shown me how to be a successful and compassionate mentor while maintaining a top-flight research laboratory. She is, and will continue to be, my role model as I progress in my academic career.

I'd also like to thank my dissertation committee: Drs. Patti Reuter-Lorenz, Susan Brown, Steve Taylor and Robert Welsh. They have always been friendly and responsive, and were helpful in a variety of ways from the day I set foot on campus. A special thank you to Patti for her help in developing my scientific writing. Her editing skills, and ability to clarify the most complex aspects of a manuscript will remain with me for years to come. Additionally, I'd like to thank Susan for her constant support and mentoring, particularly with regards to teaching at the University level. Through her work ethic and passion, Susan has inspired me to continually strive to improve my performance in the classroom (and to enjoy a nice Scotch every now and then!).

Thanks are certainly due to all of the great people at the University's Functional MRI laboratory. Specifically Drs. Luis Hernandez and Scott Peltier for their assistance

and camaraderie on a daily basis. An extra thanks is due to Keith Newnham for all of the work he does at the fMRI lab, and for training me during my time as an employee there. I would also like to thank Scott Carr from Kinesiology for his help in equipment fabrication and experimental paradigm design. Finally, numerous research assistants helped with data collection including Nick Rademacher, Melanie Chapekis, Nicole Chapman, Kathleen Olson, Eleni Papalekas, Zack Wisti, and Yanin Vongkancom. Without their help I never would have finished!

The individuals who participated in my study deserve their own thank you as well. These individuals were willing to lie in a claustrophobia-inducing tube and let me “zap” their brains, all in the name of science. It was because of their active cooperation throughout the experimental procedure and their appreciation for my research that I have been able to accomplish anything.

I’d like to thank the School of Kinesiology for all the training they’ve provided, both in and out of the classroom/laboratory. Particularly I’d like to thank Pat Van Volkinburg for her dedication to improving the undergraduate experience for all Kinesiology students and, consequently, improving the experience of all the Graduate Student Instructors who are lucky enough to work with her.

My friends and colleagues here in Ann Arbor have been my greatest source of emotional support. I’d like to thank current and past members of the NBL, Joaquin Anguera, Jin Bo, Jessica Bernard, Youngbin Kwak, and Jeanne Langan who have all been instrumental for a variety of reasons during my graduate career. I owe a special thanks to Bryan Benson for his analytical prowess and the wonderful scientific

conversations he provided. Additionally I owe Nate Boyden an extra thank you for reminding me that there is a world of wonder going on outside of the CCRB basement, and for always supplementing my futbol knowledge. One final thanks to my great friends Phil Esposito and Megan MacDonald for their help and friendship during my time at Michigan.

There are not enough words to express my appreciation to my amazing wife and partner Suzanne. She is a constant sounding board for my joys and frustrations and has always guided me in the right direction with her unending support. She is my closest friend and will remain my compass in life as long as she'll have me.

Lastly, I'd like to thank my parents and my brother for all the support they've provided throughout my lifetime. I am truly lucky to have them in my life and will always appreciate their constant love and encouragement.

TABLE OF CONTENTS

ACKNOWLEDGMENTS	ii
LIST OF FIGURES	vii
LIST OF TABLES	ix
LIST OF ABBREVIATIONS	x
ABSTRACT	xii
CHAPTER I. General Introduction	1
Motivation	1
Bimanual Control.....	2
Age Effects on Motor Control.....	8
Age-Related Structural Brain Differences.....	9
Age Differences in Corpus Callosum Macro- & Microstructure.....	12
Age Differences in Interhemispheric Neurophysiological Function.....	15
The Current Investigation.....	18
References	20
CHAPTER II. Transcallosal sensorimotor fiber tract structure-function relationships...	28
Abstract	28
Introduction	30
Materials and Methods	34
Results	44
Discussion	50
References	59
CHAPTER III. Task-dependent effects of interhemispheric inhibition on motor control	64
Abstract	64
Introduction	66
Materials and Methods	70

Results	79
Discussion	84
References	90
CHAPTER IV. Fundamental differences in callosal structure, neurophysiologic function, and bimanual control in young and older adults.....	93
Abstract	93
Introduction	95
Materials and Methods	97
Results	107
Discussion	117
References	124
CHAPTER V. General discussion and conclusions	127
Overview	127
General discussion.....	128
Caveats & Limitations.....	132
Implications and future directions.....	136
Conclusions	138
References	140
APPENDIX.....	143

LIST OF FIGURES

Figure 1.1. Representative cortical structures involved in bimanual motor control.....	4
Figure 1.2. Transcallosal white matter connections.....	5
Figure 2.1. Interhemispheric fiber tracts connecting homologous sensorimotor cortical regions.....	37
Figure 2.2. Depiction of the force production set-up used in the current experiments.....	38
Figure 2.3. An example force trace during the unimanual force production task.....	41
Figure 2.4. Representative example of an ipsilateral silent period.....	43
Figure 2.5. Individual participants' average y- and z- coordinates of transcallosal fiber pathways ($X = 0$).....	47
Figure 2.6. Positive linear relationship between strength of interhemispheric inhibition and microstructure of fiber tracts connecting bilateral primary motor cortices.....	49
Figure 2.7. No relationship was observed between strength of interhemispheric inhibition and microstructure of fiber tracts connecting bilateral supplementary or pre-supplementary motor areas.....	49
Figure 2.8. Individual participants' average y- and z- coordinates of transcallosal fiber pathways with the geometric segmentation of Hofer and Frahm overlaid.....	55
Figure 3.1. Representative force traces for the: A) dominant hand unimanual force condition, B) non-dominant (upper panel) and dominant hand (lower panel) during a bimanual synchronous force production trial and, C) non-dominant (upper panel) and dominant hand (lower panel) during the bimanual independent force production task.....	73
Figure 3.2. Scatterplot of interhemispheric inhibition and non-dominant hand EMG (motor overflow) during unimanual dominant hand contraction.....	82
Figure 3.3. Scatterplot of interhemispheric inhibition, as assessed by diSP, and dominant hand variability during all conditions.....	83
Figure 3.4. Scatterplot of dominant hand force variability during the bimanual simultaneous force production task and between-hand force coupling.....	84
Figure 4.1. Bimanual independent force production task for a representative young (A) and older adult (B).....	102
Figure 4.2. Dominant hand variability during the two bimanual conditions.....	109
Figure 4.3. Age-related differences in interhemispheric inhibition (A) and facilitation (B).....	112

Figure 4.4. Rectified EMG activity during a unimanual force production trial from one representative young (top two panels) and older adult (bottom two panels) demonstrating motor overflow in older adults (A).....	113
Figure 4.5. Age differences in the relationship between microstructure of fiber tracts connecting primary motor cortices and interhemispheric inhibitory capacity (A) Examples of young and older adult fiber tracts connecting M1 (B).....	114
Figure 4.6. Age differences in the relationship between microstructure of interhemispheric fiber tracts connecting primary motor cortices and dominant hand force variability during the bimanual independent force task.....	116
Figure 5.1. Graphical representation of my hypothesis that performance on bimanual tasks falls along a continuum which demonstrates a shared optimal region of callosal microstructure and interhemispheric inhibition for young and older adults.....	132

LIST OF TABLES

Table 2.1. Interhemispheric sensorimotor fiber tract metrics.	45
Table 2.2. Average interhemispheric fiber location on a mid-sagittal slice of the corpus callosum ($X = 0$)..	47
Table 2.3. Resting motor threshold and ipsilateral silent period metrics.	48
Table 3.1. Constant isometric force production variables describing dominant hand performance across the three force conditions.....	80
Table 3.2. Characteristics of dominant hand ipsilateral silent periods across the three force production conditions.	81
Table 4.1. Group performance on tasks assessing general cognitive performance, manual dexterity, and manual performance of daily functional tasks	108
Table 4.2. Measures evoked using transcranial magnetic stimulation.	111

LIST OF ABBREVIATIONS

Ag/AgCl: Silver / Silver chloride

ANOVA: Analysis of variance

ApEn: Approximate entropy

CC: Corpus callosum

diSP: Depth of ipsilateral silent period

DTI: Diffusion tensor imaging

DW: Diffusion weighted

EMG: Electromyography

FA: Fractional anisotropy

FDI: First dorsal interosseous

fMRI: Functional magnetic resonance imaging

GABA: Gamma-aminobutyric acid

HMAT: Human motor area template

Hz: Hertz

IHI: Interhemispheric inhibition

iSP: Ipsilateral silent period

LIHI: Long interstimulus interval interhemispheric inhibition

ms: Millisecond

mV: Millivolt

M1: Primary motor cortex

MCD: Mean consecutive difference

MEP: Motor evoked potential

MNI: Montreal Neurological Institute

MOCA: Montreal Cognitive Assessment

MRI: Magnetic resonance imaging

MVC: Maximal voluntary contraction

PMd: Dorsal premotor cortex

PMv: Ventral premotor cortex

pSMA: Pre-supplementary motor area

RMSE: Root mean squared area

RMT: Resting motor threshold

S1: Primary somatosensory cortex

SIHI: Short interstimulus interval interhemispheric inhibition

SMA: Supplementary motor area

TMS: Transcranial magnetic stimulation

μV: Microvolt

ABSTRACT

With advanced age comes a decline in fine motor control affecting the ability of older adults to perform activities of daily living and limiting their independence. Specifically, older adults show pronounced deficits in the ability to perform bimanual tasks. Consider tying your shoes, one of the most automatic daily acts. Each hand works independently during this task to accomplish a unified goal. In my dissertation, I investigated whether age-related declines in corpus callosum microstructural integrity (assessed with diffusion weighted imaging) and interhemispheric inhibition (assessed with the transcranial magnetic stimulation induced ipsilateral silent period) contribute to age differences in the ability to perform such tasks.

In the first study I determined the relationship between corpus callosum microstructural integrity and interhemispheric inhibition in young adults. I found that individuals with greater microstructural integrity of interhemispheric fiber tracts connecting the primary motor cortices had greater capacity for interhemispheric inhibition. My second study revealed that young adults with greater interhemispheric inhibition had reduced motor overflow during a unimanual force production task; however these same individuals had the poorest performance during a bimanual task in which the two hands produced different force trajectories. I suggest that a high capacity for interhemispheric inhibition from one motor cortex to another can effectively prevent motor overflow during unimanual tasks. However, it also limits the ability for optimal control during independent bimanual tasks, possibly due to a reduced capability for

interhemispheric cooperation. In my third study I determined whether age reductions in callosal structure and inhibitory function underlie impairments in independent bimanual control. I found that better microstructure of callosal tracts connecting the two primary motor cortices was positively related to bimanual task performance in older adults, but negatively related to performance in young adults. Further, increased interhemispheric inhibition was related to poorer bimanual task performance in older adults across all tasks, whereas this relationship was only observed in young adults for the independent bimanual task.

Collectively, the results of my dissertation have identified age reductions in callosal structure and their resultant impact on neurophysiological function and manual motor control. These studies provide a mechanistic understanding that can be leveraged for the design of targeted training interventions that will allow individuals with dysfunction of interhemispheric inhibition, such as those living with a stroke or multiple sclerosis, to maintain independence and improve their quality of life.

CHAPTER I

General Introduction

Motivation

In 2030, nearly one in five U.S. residents is expected to be 65 or older (henceforth referred to as older adults). This age group is projected to increase to 88.5 million in 2050, more than doubling the current number (38.7 million, US Census data). The Congressional Budget Office estimates that expenditures on long-term care for older adults totaled more than \$120 billion in 2000 (Congressional Budget Office 1999). Conservative estimates suggest total long-term care expenditures for older adults will increase at a rate of 2.6 percent per year above inflation over the next twenty years, to a staggering \$270 billion in 2030 (Knickman and Snell, 2002).

With advanced age comes a decline in sensorimotor control and functioning (Seidler et al., 2010). These declines in fine motor control, gait and balance affect the ability of older adults to perform activities of daily living and maintain their independence. The causes of these motor deficits are multi-factorial, with central nervous system declines and changes in sensory receptors, muscles and peripheral nerves playing a role (Seidler et al., 2010). Emerging evidence indicates that both the structure and neurophysiologic function of the corpus callosum decline with advancing age and have significant behavioral implications (cf. Fling et al., 2011; Raz et al., 2010; Sullivan

et al., 2010). In my dissertation, I investigate the effects that age decreases in callosal microstructural integrity and inhibitory capacity have on uni- and bimanual control. This chapter will address the background and rationale for the current investigations.

Bimanual Control

Coordinated bimanual actions are ubiquitous in everyday life. Consider tying your shoes in the morning, one of the most automatic movements an adult performs. Each hand works independently during this task to achieve a unified goal. How the nervous system accomplishes this goal is not always as simple as it appears; the action of each hand must be independently controlled, yet the two hands must also be temporally and spatially linked. Bimanual movements involve coordinated motion in time and space, but also rely on the ability of movements performed with each hand to be different without interfering with the other (Franz 1997; Perrig et al., 1999). The neurophysiological mechanisms underlying the production of such orchestrated behaviors remain unclear.

Since the seminal work of Kelso and colleagues (1979a; 1979b), bimanual movement control has gained increasing research attention for several reasons. First, complex bimanual skills provide accessible examples for the study of cognitive motor control. Second, they represent a special case of multitasking, informing us about how the central nervous system orchestrates the organization of multiple command streams. Third, bimanual tasks can be used as tools to reveal motor dysfunctions and features of lateralization and asymmetry of brain function (Swinnen, 2002).

Neuroimaging studies in humans have provided information about brain areas active during bilateral hand movements including the inferior parietal lobule, dorsal lateral premotor cortex, medial prefrontal area, pre-cuneus, primary motor (M1) cortex,

somatosensory cortices, and the superior temporal gyrus, with particular involvement of the left (dominant) hemisphere (Andres et al., 1999; de Jong et al., 1999; Disbrow et al., 2001; Goerres et al., 1998; Immisch et al., 2001; Jancke et al., 1998; Nair et al., 2003; Sadato et al., 1997; Toyokura et al., 2002; Ullen et al., 2003; Urbano et al., 1998). Lesion studies have shown that although damage to the basal ganglia, cerebellum, corpus callosum, superior parietal lobule, supplementary motor area (SMA), and cingulate motor area negatively affects different aspects of bimanual movements, they do not abolish them completely (Brown et al., 1993; Cardoso de Oliveira et al., 2001; Doody and Jankovic, 1992; Eliassen et al., 2000; Franz et al., 1996; Geffen et al., 1994; Jackson et al., 2000; Leonard et al., 1988; Obhi et al., 2002; Serrien et al., 2001a; Serrien et al., 2001b; Stancak et al., 2003; Stephan et al., 1999; Tanaka et al., 1996). In sum, numerous electrophysiologic and functional imaging studies reinforce the notion that multiple brain regions are involved in the production of bimanual movements, and that activation of these regions during bimanual actions does not differ greatly from activation during unimanual movements (Kazennikov et al., 1999; Kermadi et al., 1997; 1998; 2000). Consequently, it appears that the same brain regions (and, indeed, the same neuronal populations) are active during unimanual and bimanual movements. The current dissertation will focus on primary and secondary sensorimotor cortical regions including the primary motor (M1) and somatosensory cortices (S1), the premotor cortices, and the supplementary (SMA) and pre-supplementary motor areas (pSMA) (**Figure 1.1**). A large body of work indicates that both unimanual and bimanual movements rely heavily on transcallosal communication between these regions for movement control.

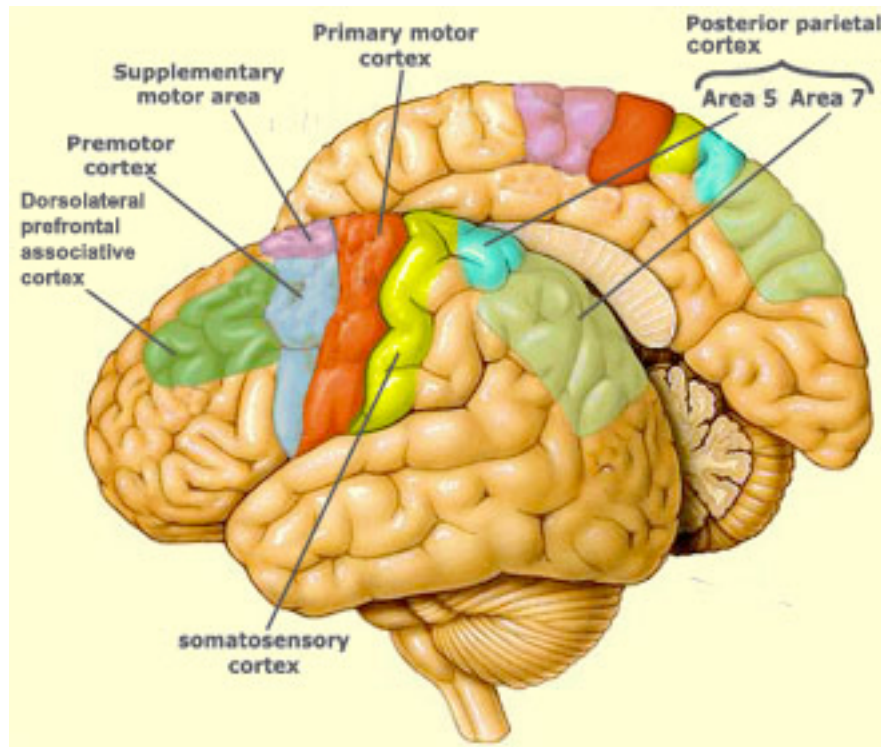


Figure 1.1 – Representative cortical structures involved in bimanual motor control. The primary motor cortex (red) is located in the frontal lobe along the central sulcus, and outputs commands for motor execution. Adjacent to it are higher order motor areas (SMA: purple, and premotor cortices: blue) involved in movement planning. In the parietal lobe along the central sulcus is the primary somatosensory cortex (yellow) (thebrain.mcgill.ca).

Interhemispheric communication is primarily mediated via the corpus callosum, the principal white matter fiber bundle connecting the two hemispheres of the brain (cf. Wahl & Ziemann, 2008; **Figure 1.2**). The majority of commissural cerebral fibers, which interconnect predominantly homologous cortical areas in the two cerebral hemispheres, traverse the callosum bidirectionally. The density of axons within the human CC ranges from approximately 300,000 to 400,000 axons per mm^2 , organized with thin, largely unmyelinated and densely packed fibers predominately in the genu and splenium (anterior and posterior CC), while larger diameter, highly myelinated and less densely packed fibers are concentrated in the posterior midbody of the CC (i.e. the transcallosal motor fibers) (Aboitiz et al., 1992a; 1992b; 1992c). The total number of

axons traversing the human CC is estimated as 200-260 million (assuming a midsagittal area of $\sim 650\text{mm}^2$). Since the human cerebral cortex contains somewhere between 20-30 billion neurons, it can be assumed that less than 1% of these neurons contribute axons to form the callosal structure (Aboitiz et al., 1992a; 1992b; 1992c).

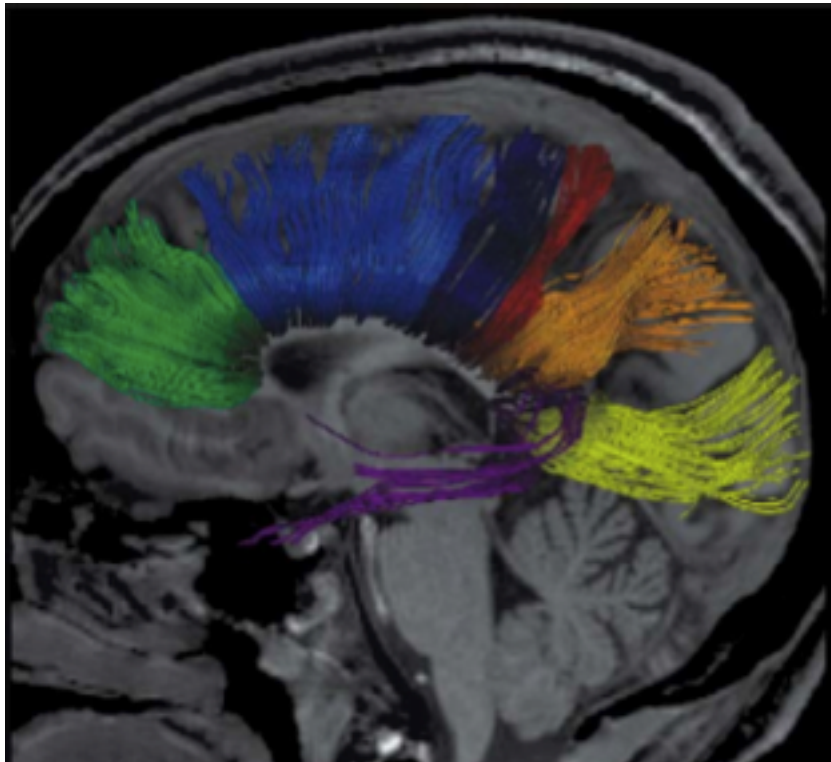


Figure 1.2 – Transcallosal white matter connections. These connections comprise bundles projecting into the prefrontal lobe (coded in green), premotor and supplementary motor areas (light blue), primary motor cortex (dark blue), primary sensory cortex (red), parietal lobe (orange), occipital lobe (yellow), and temporal lobe (violet). Hofer and Frahm, *Neuroimage* 2006.

Interhemispheric *inhibition* (IHI), the ability to stop the spread of neuronal excitability in the brain from one hemisphere to the other, is particularly important for performance of individuated unimanual actions and bimanual actions where each hand has its own independent goal (e.g. shoe tying). Inhibition within the nervous system is a complex, multifaceted phenomenon that relies on multiple inhibitory circuits mediated by

different neurotransmitters. Neurons mediating IHI arise in one hemisphere and send axons to the opposite hemisphere. Considering that gamma-amino butyric acid (GABA)-ergic neurons mainly serve local neuronal circuits (Somogyi et al., 1998), it appears that IHI is the result of excitatory axons crossing the corpus callosum and acting on local inhibitory neurons in the contralateral cortex mediated by GABA receptors (cf. Chen 2003). The fiber tracts that comprise the corpus callosum are integral for inhibiting the ipsilateral motor cortex during both unimanual movement (Giovannelli et al., 2009; Netz, 1999; Sohn et al., 2003) and unimanual force production (Vercauteren et al., 2008). In addition, IHI plays an important role during bimanual coordination (cf. Carson, 2005). Geffen et al. (1994) suggest that the CC may be involved in the smooth, feed-forward execution of bimanual control through the inhibitory or excitatory transfer of motor commands, in transmission of efferent information from one hemisphere to the other as part of an updating process, and in the transference of corollary output information when sensory feedback is necessary. Thus, interhemispheric collaboration via the CC is necessary in regulating coordinated bimanual actions.

The magnitude of IHI is modulated dependent upon task conditions in young adults. For example, the amount of IHI relative to rest is significantly increased when the limbs (or hands) are moving asynchronously, whereas inhibition is minimal when the limbs move in synchrony (Stinear & Byblow, 2002). Furthermore, repetitive bimanual finger tapping is stable and accurate when movements are performed with the hands moving either in-phase or anti-phase across a range of frequencies (Kelso, 1984; cf. Swinnen, 2002). However, during asynchronous conditions split-brain patients make more pronounced errors reflecting stronger attraction to in-phase and anti-phase patterns

as compared to healthy controls. These findings, along with those mentioned earlier (e.g. Sohn et al., 2003) indicate that transcallosal inhibitory control is important during unimanual and bimanual asynchronous movements presumably to prevent interference from the opposite hemisphere, or “motor overflow” (cf. Hoy et al., 2004).

Motor overflow is a blanket term used to describe involuntary movement of the contralateral side, which sometimes accompanies the production of voluntary movement (Liederman & Foley, 1987). The most prominent theory put forward to explain the occurrence of motor overflow is known as the bilateral activation theory (Hoy et al., 2004). This hypothesis states that activation of a cortical region (e.g. left primary motor cortex) resulting in voluntary movement facilitates activation of the same area in the opposite hemisphere (right primary motor cortex), via interhemispheric connections (Cernacek, 1961). Such facilitation leads to motor overflow unless the contralateral hemisphere inhibits it via IHI (cf. Hoy et al., 2004). Therefore, motor overflow involves a series of excitatory and inhibitory cortical processes leading to bilateral activation. These transcallosal processes, believed to occur during unilateral voluntary movements, are central to the bilateral activation theory of motor overflow. When either the degree or spread of the cortical activation increases, facilitation is replaced by inhibition (Ferber et al., 1992; Meyer, 1998). Thus IHI ensures unilateral movements in these situations. According to the bilateral activation theory of motor overflow, lack of IHI would prevent suppression of the initial facilitation, which may then lead to unintended movements of the opposite hand (Liepert et al., 1998; Stinear & Byblow, 2003). Such motor overflow can be readily observed when neurological damage is present (Cohen et al., 1991; Schott & Wyke, 1977), although motor overflow has also been documented in neurologically

normal adults (Armatas et al., 1996).

It remains unknown whether motor overflow is reflective of cortical activity related to motor planning, motor execution, or both. Furthermore it is unclear whether motor overflow occurs during bimanual actions that require independent manual control of temporal, spatial, or force production parameters. For example, following callosotomy for relief from excessive seizures, significant spatial uncoupling of the hands is possible, allowing an individual to draw a circle with one hand while simultaneously drawing a square with the other (Franz et al., 1997). However, this spatial uncoupling is offset by a loss of temporal coordination between the two sides of the body (Kennerley et al., 2002), suggesting that IHI may contribute to independent bimanual control in a task specific fashion.

Age Effects on Motor Control

With advanced age comes a decline in sensorimotor control and functioning. These declines in fine motor control, gait and balance affect the ability of older adults to perform activities of daily living and maintain their independence (cf. Seidler et al. 2010). Age differences in motor performance include reduced coordination (Seidler et al., 2002), increased variability of movement (Contreras-Vidal et al., 1998; Darling et al., 1989), slowing of movement (Diggles-Buckles, 1993), and difficulties with balance and gait (Woollacott & Tang, 1997) for older adults.

Pertinent to this dissertation, older adults show pronounced deficits in bimanual coordination. As previously discussed, temporal bimanual coordination is most stable when movements are performed either in-phase or anti-phase (Kelso, 1984; cf. Swinnen, 2002). Young and older adults perform almost identically during in-phase bimanual

movements across a range of frequencies; however, older adults exhibit greater movement variability than their younger counterparts during anti-phase movements at increasing frequencies (Wishart et al., 2000). Furthermore, older adults demonstrate differentially poorer performance than young adults on temporally asynchronous bimanual tasks (Bangert et al., 2010). Motor performance impairments in older adults may arise from changes to peripheral structures in the neuromuscular system such as sensory receptors, muscles, peripheral nerves, and/or motor unit reorganization (Fling et al., 2009; Kaplan et al., 1985; Wright et al., 2011). In the past, the literature has focused primarily on peripheral mechanisms; in recent years, however, the focus has shifted to the investigation of more central mechanisms (for a recent review see Seidler et al., 2010).

Age-Related Structural Brain Differences

Structural brain changes with age may be causally related to motor deficits. Several studies have demonstrated decreases in gray matter volume with age (Courchesne et al., 2000; Good et al., 2001; Jernigan et al., 2001; Raz et al., 1997; Resnick et al., 2003), with some studies reporting linear declines (cf. Ge et al., 2002) and others reporting nonlinear patterns (Sowell et al., 2003). These declines in gray matter volume often occur concomitantly with significant increases in ventricular (Good et al., 2001) and cerebrospinal fluid volume (Courchesne et al., 2000). Though it is clear that there are global declines in gray matter with age, the prefrontal cortex is particularly susceptible to gray matter atrophy (Good et al., 2001; Jernigan et al. 2001; Raz et al., 1997; Resnick et al., 2003). Additionally, several studies have shown that parietal cortex exhibits more gray matter decreases than either temporal or occipital regions (Good et al. 2001; Resnick et al., 2003). This differential loss in prefrontal and parietal cortices is likely relevant to

motor performance declines in old age because motor control is more dependent on these brain regions in older versus young adults (Heuninckx et al., 2005; 2008).

Given the previously described patterns of decreases in gray matter, with the prefrontal cortex seemingly the most affected region, a question of particular interest is whether or not the sensorimotor cortex shows the same differential volume loss as the rest of the frontal cortex. The overall pattern of neural tissue decline is consistent with a “last in, first out” hypothesis of atrophy. According to this hypothesis, brain regions that are last to develop are the first to atrophy (Bartzokis et al., 2004; Salat et al., 2004). This suggests that the sensorimotor regions of the brain would be relatively spared given that they are early to develop, both on a lifespan and evolutionary time scale (Jerison, 1976; Webb et al., 2001). Conflicting evidence currently exists in the literature as Raz et al. (1997) found that the primary motor and somatosensory cortices were both minimally affected with age. Conversely, other studies have shown that the sensorimotor regions of the brain indeed show age-related atrophy. Using voxel-based morphometry Good et al. (2001) found that there was gray matter loss in both the pre- and post-central gyri with age. Furthermore, in their study of cortical thinning, Salat et al. (2004) found significant thinning in both the primary motor cortex and the somatosensory cortex. In fact, the greatest overall rate of thinning of cortical regions was in the primary motor cortex. These studies indicate the vulnerability of the motor and somatosensory regions of the brain to age-related atrophy. Many of the studies described thus far did not test for relationships between brain structural declines and motor performance measures, but it is certainly plausible that primary motor cortex atrophy contributes to the movement slowing seen with age. Additionally, proprioceptive feedback is important for both

balance and motor coordination (reviewed in Goble et al., 2009). Thus, atrophy in the somatosensory cortex may be related to increased falls, poorer balance, and increased reliance on visual feedback for motor performance in older adults. For example, Rosano et al. (2009) recently reported that atrophy in the sensorimotor cortex, as well as regions associated with both visuospatial and cognitive processing, was associated with individual differences in gait in older adults.

Declines in white matter volume with age begin later and continue at a more accelerated rate than declines in gray matter volume (Courchesne et al., 2000; Ge et al., 2002; Jernigan et al., 2001). Similar to the pattern for gray matter, the “last in first out” hypothesis may be applicable to white matter changes. Prefrontal areas undergo myelination last during development (Webb et al., 2001). Multiple studies have found regional effects on white matter microstructure occurring along an anterior to posterior gradient, such that white matter microstructure is poorest in anterior relative to posterior fiber bundles for older adults (Davis et al., 2009; O’Sullivan et al., 2001; Salat et al., 2004; Sullivan et al., 2001; 2010; Zahr et al., 2009). Sullivan et al. (2010) reported that scores on a fine finger movement task were positively correlated with white matter microstructure in both the internal and external capsules and cerebellar white matter bundles, indicating the importance of these white matter tracts for maintaining motor task performance in old age. Pertinent to the studies in this dissertation, the relative contributions of white matter morphology to age-related changes in cortical recruitment are substantially more robust than those that result from gray matter decline (Colcombe et al., 2005). Colcombe and colleagues (2005) therefore suggest that impaired

interhemispheric communication may play a more significant role than the structure of local gray matter.

Age Differences in Corpus Callosum Macro- & Microstructure

Sullivan et al. (2001) noted that age-related changes in the corpus callosum were associated with declines in interhemispheric communication efficiency. This may be important for bimanual coordination and may result in difficulty with day-to-day activities requiring the coordinated use of both hands such as dressing and driving. In this dissertation I investigate whether declines in bimanual coordination with age are related to microstructure of the corpus callosum, particularly given the role that this structure plays in bimanual movements for young adults (Kennerley et al., 2002; Stancak et al., 2003). In addition, it is known that older adults have slower interhemispheric transit times (Reuter-Lorenz and Stanczak, 2000; Jeeves and Moes, 1996). However, older adults show an advantage for bilateral transfer conditions for attentional (Reuter-Lorenz and Stanczak, 2000; Reuter-Lorenz et al., 1999) and cognitive tasks (Fling et al., 2011), suggesting that callosal declines with age have differential behavioral effects.

Age differences in brain activation patterns are often posited to be the result of changes in brain structure. Transcallosal fibers connect largely homologous cortical regions of the right and left hemispheres; thus, the corpus callosum mediates the transfer and integration of lateralized cognitive, motor, and sensory information between cortices (Aboitiz, 1992). Structural magnetic resonance imaging (MRI) has demonstrated that there is substantial interindividual variability in callosal size and morphology for both young and older adults (Fling et al., in press; Raz et al., 2010; Sullivan et al., 2010; Stanczak et al., 2003). Interestingly, less lateralized task processing during both

cognitive (Muller-Oehring et al., 2007) and motor (Langan et al., 2010) tasks has been shown to be associated with reductions in callosal cross-sectional area in older adults. Therefore, structural differences of the corpus callosum appear to impact cortical activity both at rest and during task performance, with significant implications for behavior.

An emerging body of literature indicates that not only is the quantity of white matter reduced in older adults, but the quality of remaining white matter is compromised as well (reviewed in Seidler et al., 2010). The use of conventional MRI allows for measurements of regional brain volume, while diffusion tensor imaging (DTI) allows assessment of white matter microstructure. Thus, DTI may be more sensitive to more subtle age-related white matter changes than conventional volumetric MRI. For example, some MRI investigations suggest that the corpus callosum does not undergo extensive volumetric declines with age (Raz et al., 2001), whereas several studies have shown declining callosal microstructure and volume with age (Fling et al., 2011; Langan et al., 2010; Sullivan et al., 2010). Numerous studies have identified associations between callosal macrostructure or microstructure and behavior (Fling et al., in press; Stancak et al., 2003; Sullivan et al., 2010). Furthermore, recent studies utilizing fiber tractography have demonstrated relationships between interhemispheric motor fiber tract microstructure and task performance in both healthy participants (Johansen-Berg, et al. 2007) and in those with white matter dysfunction (Bartels et al., 2008; Bonzano et al., 2008; Kern et al., 2010). While individual differences in callosal quantity and quality have shown to be behaviorally relevant in both young and older adults, it appears there may be a fundamental shift with age in these relationships.

Interhemispheric communication can have either net facilitatory or inhibitory

effects on the cortex (Chen, et al. 2003). Multiple lines of research indicate that interhemispheric connections between the sensorimotor cortical regions have primarily inhibitory effects (De Gennaro et al., 2004; Lenzi et al., 2007; Netz, 1999). This IHI is presumably to prevent interference from the opposite hemisphere, or motor overflow (cf. Hoy et al., 2004). This is thought to allow for simultaneous but independent control of the two hands, such as required for shoe tying. Intriguingly, I have recently reported that young adults with *increased* microstructural quality of callosal regions connecting sensorimotor cortical areas perform with *more* variability on unimanual and asynchronous bimanual motor tasks (Fling et al., In press). Conversely, larger size and *better* microstructure of these same callosal regions was associated with *better* performance in older adults. Moreover, we recently reported that older adults exhibit greater recruitment of ipsilateral primary motor cortex during unimanual motor task performance, which was associated with *longer* reaction times (Langan et al., 2010). Additionally, greater recruitment of ipsilateral primary motor cortex in older adults was correlated with reduced resting state interhemispheric connectivity and a larger corpus callosum. I posit that reduced interhemispheric motor connectivity may be associated with a loss of the ability to inhibit the ipsilateral hemisphere during unimanual motor task performance for older adults, which has a negative impact on response time. These data provide evidence for a link between callosal structural and physiological changes with age, lending credence to the de-differentiation hypothesis. Specifically, interhemispheric interactions require a balance between excitatory and inhibitory processes; taken together the aforementioned studies suggest that this overall balance is likely shifted in the aging brain, with reductions in IHI in particular.

Age Differences in Interhemispheric Neurophysiological Function

Experiments conducted with individuals with callosal pathology (e.g. partial callosotomy or multiple sclerosis) demonstrate that while the total number of callosal fibers connecting the two primary motor cortices is relatively few in number, communication between these homologous areas has the capability to strongly influence motor behavior (Bonzano et al., 2008; Eliassen et al., 1999; Eliassen et al., 2000; Kennerley et al., 2002; Lenzi et al., 2007). The fiber tracts that comprise the corpus callosum are integral for inhibiting the ipsilateral motor cortex during both uni- and bi-manual control (Netz, 1999; Perez and Cohen, 2008; Vercauteren et al., 2008). Monosynaptic connections between primary motor cortices (Porter & Lemon, 1993), along with densely transcallosally-connected secondary motor areas, have been shown to significantly influence IHI and neuromotor control. Although full characterization of the transcallosal inhibitory sensorimotor network is still lacking, neuroimaging data suggest that it includes the supplementary and pre-supplementary motor areas (Grefkes et al., 2008; Serrien et al., 2002), the dorsal premotor cortices (Giovannelli et al., 2006; van den Berg et al., 2010) and the somatosensory cortices (Ni et al. 2009).

Callosally-mediated IHI is a complex process that has traditionally been measured in humans using paired-pulse transcranial magnetic stimulation (TMS) to each primary motor cortex at an interstimulus interval of i) 8-12 ms (short-interval IHI [SIHI]) or ii) ~40 ms (long-interval IHI [LIHI]) (cf. Chen, 2004). Paired-pulse TMS utilizes two magnetic stimulation coils to investigate the effect of a supra-threshold conditioning stimulus over one primary motor cortex (M1) on the size of a test motor evoked potential elicited by stimulation of the opposite M1. Although both SIHI and LIHI are reflective

of transcallosal inhibition, they do not appear to rely on the same physiological mechanisms, nor are the two values correlated with each other across individuals (Chen, et al., 2003). Although both measures reflect inhibition of synchronized activation of the corticospinal system induced by the conditioning stimulus (the first stimulus applied), a pharmacological experiment suggests that LIHI is likely mediated by postsynaptic gamma-aminobutyric acid type B (GABA)_B receptors, whereas SIHI is potentially mediated by GABA_A receptors, although this remains to be fully elucidated (Irlbacher et al., 2007).

In line with my hypothesis of reductions in interhemispheric inhibitory interactions with age, accumulating evidence demonstrates reduced inhibition within the nervous system of older adults, both at the cortical (Talelli et al., 2008a, 2008b) and spinal levels (Kido et al., 2004). A discussion of age-related changes in inhibition at the spinal level is beyond the scope of the current review, and thus I will focus on cortical inhibition. Paired-pulse TMS studies have shown that healthy older adults display decreased excitability of intracortical inhibitory circuits within the motor cortex while at rest (Peinemann et al., 2001). Task-related increases in LIHI also diminish with advancing age and are correlated with the degree of ipsilateral primary motor cortex recruitment during unimanual motor tasks (Talelli et al., 2008a, 2008b). In agreement with Talelli and colleagues, Fujiyama et al. (2009) found that older adults have a reduced ability to modulate inhibitory function in a task-dependent manner in comparison to young adults. Specifically, older adults exhibited a reduced ability to increase inhibition during coordination of the arm and leg on the same side of the body. These age-related declines in IHI and in the ability to modulate inhibitory function to meet task demands

may be associated with bimanual movement deficits observed in older adults.

It is interesting that cortical inhibition is less effective in musicians, individuals with extraordinary control of independent finger movements. Surprisingly, both inter- and intra-hemispheric inhibition are *reduced* in musicians (Nordstrom & Butler, 2002; Ridding et al., 2000) relative to nonmusicians. However, it is unclear whether these effects represent an adaptive change related to exceptional control of finger movements or a maladaptive change brought about by overuse of the hand from extensive training (Nordstrom & Butler, 2002). Training experiments may shed some light on the counterintuitive finding that musicians with superior bimanual control and larger callosal size have reduced IHI. Shim and colleagues (2005) were the first to investigate the effects of practice on callosal physiology; following just two days of practice of a novel bimanual force production task, participants demonstrated task-selective reductions in IHI. In accord with this finding, Hortobagyi et al. (*in press*) reported a significant decrease in IHI and a concomitant increase in ipsilateral primary motor cortex excitability following 20 sessions of unimanual submaximal force production. These studies, taken together with those in trained musicians, suggest that interhemispheric inhibitory projections can show plastic changes that favor the execution of a practiced task, likely through a cooperative action of the two hemispheres (Shim et al., 2005). In other words, although IHI is integral for the performance of coordinated bimanual tasks, it appears that high levels of inhibition may have a negative impact on performance.

Declines in callosal size and integrity, coupled with decreases in the interconnectedness of the two hemispheres of the brain suggest that age-related cognitive and

motor impairments may be due, at least in part, to reductions in IHI. I will critically evaluate this hypothesis in the current dissertation.

The Current Investigation

The overarching goal of my dissertation is to determine whether age-related declines in callosal structure and interhemispheric inhibition contribute to previously described age deficits in uni- and bimanual control. To gain a thorough understanding of the contributions of fiber tract structure to motor control, I collected diffusion tensor imaging to identify interhemispheric connections between homologous primary and secondary sensorimotor areas. Paralleling my previous work, I hypothesized that fiber tract structure would be related to motor control differently in young and older adults. In the same individuals, transcranial magnetic stimulation was used to assess interhemispheric inhibitory capacity while participants performed uni- and bimanual force production tasks. I hypothesized that there would be a shift with age in the relationship between interhemispheric fiber tract microstructure and inhibitory function. That is, I predicted that increased interhemispheric inhibition would be associated with greater fiber tract microstructural integrity in young adults, whereas the inverse relationship would be true in older adults. The dissertation is comprised of three studies addressing the following questions:

Question 1 (Chapter 2). How do individual differences in microstructure of sensorimotor callosal fiber tracts relate to IHI in young adults?

I hypothesized that there would be a relationship between interhemispheric inhibition and fiber tract microstructure. I expected this relationship to be specific to

fiber tracts connecting the bilateral primary motor cortices. I evaluated this hypothesis by analyzing callosal fiber tract microstructure and inhibitory function in neurologically intact young adults (18-30 years old). Using DTI I mapped mutually exclusive transcallosal connections between homologous somatosensory, motor, and premotor regions and provide a comprehensive callosal spatial atlas of these fiber tracts. In addition I utilized TMS to elicit the ipsilateral silent period, a technique used to measure IHI of volitional cortical activity.

Question 2 (Chapter 3). Do individual differences in IHI have task-dependent effects on motor control in young adults?

I hypothesized that IHI would be inversely related to motor performance on both unimanual and bimanual independent tasks, but not for bimanual simultaneous tasks. I tested this hypothesis on a subset of participants from Chapter 2. Participants performed three force production tasks: 1) unimanual (right hand) constant force, 2) bimanual constant force, (bimanual simultaneous) and 3) bimanual with right hand constant force and left hand sine wave tracking (bimanual independent).

Question 3 (Chapter 4). Do age differences in IHI and callosal fiber tract microstructure underlie declines in manual motor control?

I evaluated the hypothesis that age-related degradation of callosal structure and inhibitory function contribute to the selective difficulty older adults have with performing asynchronous actions. I evaluated this hypothesis by having a cohort of older adults (65-76 years old) perform the tasks previously described in Chapters 2 and 3.

References

- Aboitiz, F. (1992a). Brain connections: interhemispheric fiber systems and anatomical brain asymmetries in humans. *Biol Res*, 25(2), 51-61.
- Aboitiz, F., Scheibel, A. B., Fisher, R. S., & Zaidel, E. (1992b). Fiber composition of the human corpus callosum. *Brain Res*, 598(1-2), 143-153.
- Aboitiz, F., Scheibel, A. B., Fisher, R. S., & Zaidel, E. (1992c). Individual differences in brain asymmetries and fiber composition in the human corpus callosum. *Brain Res*, 598(1-2), 154-161.
- Andres, F. G., Mima, T., Schulman, A. E., Dichgans, J., Hallett, M., & Gerloff, C. (1999). Functional coupling of human cortical sensorimotor areas during bimanual skill acquisition. *Brain*, 122 (Pt 5), 855-870.
- Armataz, C. A., Summers, J. J., & Bradshaw, J. L. (1996). Handedness and performance variability as factors influencing mirror movement occurrence. *J Clin Exp Neuropsychol*, 18(6), 823-835.
- Bangert, A. S., Reuter-Lorenz, P. A., Walsh, C. M., Schachter, A. B., & Seidler, R. D. (2010). Bimanual coordination and aging: neurobehavioral implications. *Neuropsychologia*, 48(4), 1165-1170.
- Bartels, C., Mertens, N., Hofer, S., Merboldt, K. D., Dietrich, J., Frahm, J., et al. (2008). Callosal dysfunction in amyotrophic lateral sclerosis correlates with diffusion tensor imaging of the central motor system. *Neuromuscul Disord*, 18(5), 398-407.
- Bartzokis, G., Sultzer, D., Lu, P. H., Nuechterlein, K. H., Mintz, J., & Cummings, J. L. (2004). Heterogeneous age-related breakdown of white matter structural integrity: implications for cortical "disconnection" in aging and Alzheimer's disease. *Neurobiol Aging*, 25(7), 843-851.
- Bastian, A. J., Martin, T. A., Keating, J. G., & Thach, W. T. (1996). Cerebellar ataxia: abnormal control of interaction torques across multiple joints. *J Neurophysiol*, 76(1), 492-509.
- Bonzano, L., Tacchino, A., Roccatagliata, L., Abbruzzese, G., Mancardi, G. L., & Bove, M. (2008). Callosal contributions to simultaneous bimanual finger movements. *J Neurosci*, 28(12), 3227-3233.
- Brown, R. G., Jahanshahi, M., & Marsden, C. D. (1993). The execution of bimanual movements in patients with Parkinson's, Huntington's and cerebellar disease. *J Neurol Neurosurg Psychiatry*, 56(3), 295-297.
- Cardoso de Oliveira, S., Gribova, A., Donchin, O., Bergman, H., & Vaadia, E. (2001). Neural interactions between motor cortical hemispheres during bimanual and unimanual arm movements. *Eur J Neurosci*, 14(11), 1881-1896.
- Carson, R. G. (2005). Neural pathways mediating bilateral interactions between the upper limbs. *Brain Res Brain Res Rev*, 49(3), 641-662.
- Cernacek, J. (1961). Contralateral motor irradiation—cerebral dominance. *Arch. Neurol.* 4 61– 68.
- Chen, R. (2004). Interactions between inhibitory and excitatory circuits in the human motor cortex. *Exp Brain Res*, 154(1), 1-10.
- Chen, R., Yung, D., & Li, J. Y. (2003). Organization of ipsilateral excitatory and inhibitory pathways in the human motor cortex. *J Neurophysiol*, 89(3), 1256-1264.

- Cohen, L. G., Meer, J., Tarkka, I., Bierner, S., Leiderman, D. B., Dubinsky, R. M., et al. (1991). Congenital mirror movements. Abnormal organization of motor pathways in two patients. *Brain*, 114 (Pt 1B), 381-403.
- Colcombe, S. J., Kramer, A. F., Erickson, K. I., & Scalf, P. (2005). The implications of cortical recruitment and brain morphology for individual differences in inhibitory function in aging humans. *Psychol Aging*, 20(3), 363-375.
- Contreras-Vidal, J. L., Teulings, H. L., & Stelmach, G. E. (1998). Elderly subjects are impaired in spatial coordination in fine motor control. *Acta Psychol (Amst)*, 100(1-2), 25-35.
- Cooke, J. D., Brown, S. H., & Cunningham, D. A. (1989). Kinematics of arm movements in elderly humans. *Neurobiol Aging*, 10(2), 159-165.
- Courchesne, E., Chisum, H. J., Townsend, J., Cowles, A., Covington, J., Egaas, B., et al. (2000). Normal brain development and aging: quantitative analysis at in vivo MR imaging in healthy volunteers. *Radiology*, 216(3), 672-682.
- Darling, W. G., Cooke, J. D., & Brown, S. H. (1989). Control of simple arm movements in elderly humans. *Neurobiol Aging*, 10(2), 149-157.
- Davis, S. W., Dennis, N. A., Buchler, N. G., White, L. E., Madden, D. J., & Cabeza, R. (2009). Assessing the effects of age on long white matter tracts using diffusion tensor tractography. *Neuroimage*, 46(2), 530-541.
- De Gennaro, L., Cristiani, R., Bertini, M., Curcio, G., Ferrara, M., Fratello, F., et al. (2004). Handedness is mainly associated with an asymmetry of corticospinal excitability and not of transcallosal inhibition. *Clin Neurophysiol*, 115(6), 1305-1312.
- de Jong, B. M., Willemsen, A. T., & Paans, A. M. (1999). Brain activation related to the change between bimanual motor programs. *Neuroimage*, 9(3), 290-297.
- Diggles-Buckles, V., 1993. Age-related slowing. In: Stelmach, G.E., Homberg, V. (Eds.), *Sensorimotor Impairment in the Elderly*. Kluwer Academic, Norwell, MA.
- Disbrow, E., Roberts, T., Poeppel, D., & Krubitzer, L. (2001). Evidence for interhemispheric processing of inputs from the hands in human S2 and PV. *J Neurophysiol*, 85(5), 2236-2244.
- Doody, R. S., & Jankovic, J. (1992). The alien hand and related signs. *J Neurol Neurosurg Psychiatry*, 55(9), 806-810.
- Eliassen, J. C., Baynes, K., & Gazzaniga, M. S. (1999). Direction information coordinated via the posterior third of the corpus callosum during bimanual movements. *Exp Brain Res*, 128(4), 573-577.
- Eliassen, J. C., Baynes, K., & Gazzaniga, M. S. (2000). Anterior and posterior callosal contributions to simultaneous bimanual movements of the hands and fingers. *Brain*, 123 Pt 12, 2501-2511.
- Ferbert, A., Priori, A., Rothwell, J.C., Day, B.L., Colebatch J., Marsden, C.D. (1992). Interhemispheric inhibition of the human motor cortex, *J. Physiol.* 453 525– 546.
- Fling BW, Chapekis M, Reuter-Lorenz PA, Anguera, J, Bo J, Langan J, Welsh RC, Seidler RD (2011). Age differences in callosal contributions to cognitive processes. *Neuropsychologia* [Epub ahead of print; 2011 May 12].
- Fling, B. W., Knight, C. A., & Kamen, G. (2009). Relationships between motor unit size and recruitment threshold in older adults: implications for size principle. *Exp Brain Res*, 197(2), 125-133.

- Fling, B.W., Peltier, S.J., Bo, J., Welsh, R.C., & Seidler, R.D. (2011). Age differences in interhemispheric interactions: callosal structure, physiological function, and behavior. *Frontiers in Neuroscience* 5:38. PMID: 21519384
- Fling, B. W., Walsh, C. M., Bangert, A. S., Reuter-Lorenz, P. A., Welsh, R. C., & Seidler, R. D. (In press). Differential Callosal Contributions to Bimanual Control in Young and Older Adults. *J Cogn Neurosci*. Oct 18, 2010 [Epub ahead of print].
- Franz, E.A., Ivry, R.B., Helmuth, L.L., (1996). Reduced timing variability in patients with unilateral cerebellar lesions during bimanual movements. *J. Cogn. Neurosci*. 8 (2), 107–118.
- Franz, E. A. (1997). Spatial coupling in the coordination of complex actions. *Q J Exp Psychol A*, 50(3), 684-704.
- Fujiyama, H., Garry, M. I., Levin, O., Swinnen, S. P., & Summers, J. J. (2009). Age-related differences in inhibitory processes during interlimb coordination. *Brain Res*, 1262, 38-47.
- Ge, Y., Grossman, R. I., Babb, J. S., Rabin, M. L., Mannon, L. J., & Kolson, D. L. (2002). Age-related total gray matter and white matter changes in normal adult brain. Part I: volumetric MR imaging analysis. *AJNR Am J Neuroradiol*, 23(8), 1327-1333.
- Geffen, G. M., Jones, D. L., & Geffen, L. B. (1994). Interhemispheric control of manual motor activity. *Behav Brain Res*, 64(1-2), 131-140.
- Giovannelli, F., Borgheresi, A., Balestrieri, F., Ragazzoni, A., Zaccara, G., Cincotta, M., and Ziemann, U. (2006). Role of the right dorsal premotor cortex in "physiological" mirror EMG activity. *Exp Brain Res*, 175(4), 633-640.
- Giovannelli, F., Borgheresi, A., Balestrieri, F., Zaccara, G., Viggiano, M. P., Cincotta, M., et al. (2009). Modulation of interhemispheric inhibition by volitional motor activity: an ipsilateral silent period study. *J Physiol*, 587(Pt 22), 5393-5410.
- Goble, D. J., Coxon, J. P., Wenderoth, N., Van Impe, A., & Swinnen, S. P. (2009). Proprioceptive sensibility in the elderly: degeneration, functional consequences and plastic-adaptive processes. *Neurosci Biobehav Rev*, 33(3), 271-278.
- Goerres, G. W., Samuel, M., Jenkins, I. H., & Brooks, D. J. (1998). Cerebral control of unimanual and bimanual movements: an H2(15)O PET study. *Neuroreport*, 9(16), 3631-3638.
- Good, C. D., Johnsrude, I. S., Ashburner, J., Henson, R. N., Friston, K. J., & Frackowiak, R. S. (2001). A voxel-based morphometric study of ageing in 465 normal adult human brains. *Neuroimage*, 14(1 Pt 1), 21-36.
- Grefkes, C., Eickhoff, S. B., Nowak, D. A., Dafotakis, M., & Fink, G. R. (2008). Dynamic intra- and interhemispheric interactions during unilateral and bilateral hand movements assessed with fMRI and DCM. *Neuroimage*, 41(4), 1382-1394.
- Heuninckx, S., Wenderoth, N., Debaere, F., Peeters, R., & Swinnen, S. P. (2005). Neural basis of aging: the penetration of cognition into action control. *J Neurosci*, 25(29), 6787-6796.
- Heuninckx, S., Wenderoth, N., & Swinnen, S. P. (2008). Systems neuroplasticity in the aging brain: recruiting additional neural resources for successful motor performance in elderly persons. *J Neurosci*, 28(1), 91-99.

- Hofer S, Frahm J. (2006): Topography of the human corpus callosum revisited--comprehensive fiber tractography using diffusion tensor magnetic resonance imaging. *Neuroimage* 32(3):989-94.
- Hortobagyi T, Richardson SP, Lomarev M, Shamim E, Meunier S, Russman H, Dang N, and Hallett M. Interhemispheric Plasticity in Humans. *Med Sci Sports Exerc* 2010.
- Hoy, K. E., Fitzgerald, P. B., Bradshaw, J. L., Armatas, C. A., & Georgiou-Karistianis, N. (2004). Investigating the cortical origins of motor overflow. *Brain Res Brain Res Rev*, 46(3), 315-327.
- Immisch, I., Waldvogel, D., van Gelderen, P., & Hallett, M. (2001). The role of the medial wall and its anatomical variations for bimanual antiphase and in-phase movements. *Neuroimage*, 14(3), 674-684.
- Jackson, G. M., Jackson, S. R., & Hindle, J. V. (2000). The control of bimanual reach-to-grasp movements in hemiparkinsonian patients. *Exp Brain Res*, 132(3), 390-398.
- Jancke, L., Peters, M., Schlaug, G., Posse, S., Steinmetz, H., & Muller-Gartner, H. (1998). Differential magnetic resonance signal change in human sensorimotor cortex to finger movements of different rate of the dominant and subdominant hand. *Brain Res Cogn Brain Res*, 6(4), 279-284.
- Jeeves, M. A., & Moes, P. (1996). Interhemispheric transfer time differences related to aging and gender. *Neuropsychologia*, 34(7), 627-636.
- Jerison, H.J., (1976). Principles of the evolution of the brain and behavior. In: *Evolution, Brain and Behavior: Persistent Problems*. Masterson, R.B., Hodos, W., Jerison, H.J. (Eds.). Lawrence Earlbaum Associates, Inc., Hillsdale, NJ. 573.
- Jernigan, T. L., Archibald, S. L., Fennema-Notestine, C., Gamst, A. C., Stout, J. C., Bonner, J., et al. (2001). Effects of age on tissues and regions of the cerebrum and cerebellum. *Neurobiol Aging*, 22(4), 581-594.
- Johansen-Berg, H., Della-Maggiore, V., Behrens, T. E., Smith, S. M., & Paus, T. (2007). Integrity of white matter in the corpus callosum correlates with bimanual co-ordination skills. *Neuroimage*, 36 Suppl 2, T16-21.
- Kaplan, F.S., Nixon, J.E., Reitz, M., Rindfleish, L., & Tucker, J. (195). Age-related changes in proprioception and sensation of joint position. *Acta Orthop Scand*, 56(1), 72-4.
- Kazennikov, O., Hyland, B., Corboz, M., Babalian, A., Rouiller, E. M., & Wiesendanger, M. (1999). Neural activity of supplementary and primary motor areas in monkeys and its relation to bimanual and unimanual movement sequences. *Neuroscience*, 89(3), 661-674.
- Kelso, J. A. (1984). Phase transitions and critical behavior in human bimanual coordination. *Am J Physiol*, 246(6 Pt 2), R1000-1004.
- Kelso, J. A., Southard, D. L., & Goodman, D. (1979a). On the coordination of two-handed movements. *J Exp Psychol Hum Percept Perform*, 5(2), 229-238.
- Kelso, J. A., Southard, D. L., & Goodman, D. (1979b). On the nature of human interlimb coordination. *Science*, 203(4384), 1029-1031.
- Kennerley, S. W., Diedrichsen, J., Hazeltine, E., Semjen, A., & Ivry, R. B. (2002). Callosotomy patients exhibit temporal uncoupling during continuous bimanual movements. *Nat Neurosci*, 5(4), 376-381.
- Kermadi, I., Liu, Y., & Rouiller, E. M. (2000). Do bimanual motor actions involve the

- dorsal premotor (PMd), cingulate (CMA) and posterior parietal (PPC) cortices? Comparison with primary and supplementary motor cortical areas. *Somatosens Mot Res*, 17(3), 255-271.
- Kermadi, I., Liu, Y., Tempini, A., Calciati, E., & Rouiller, E. M. (1998). Neuronal activity in the primate supplementary motor area and the primary motor cortex in relation to spatio-temporal bimanual coordination. *Somatosens Mot Res*, 15(4), 287-308.
- Kermadi, I., Liu, Y., Tempini, A., & Rouiller, E. M. (1997). Effects of reversible inactivation of the supplementary motor area (SMA) on unimanual grasp and bimanual pull and grasp performance in monkeys. *Somatosens Mot Res*, 14(4), 268-280.
- Knickman, J.R., and Snell, E.K. (2002). The 2030 problem: caring for aging baby boomers. *Health Services Research*, 37(4), 849-884.
- Langan, J., Peltier, S. J., Bo, J., Fling, B. W., Welsh, R. C., & Seidler, R. D. (2010). Functional implications of age differences in motor system connectivity. *Front Syst Neurosci*, 4, 17.
- Larson, E. B., Burnison, D. S., & Brown, W. S. (2002). Callosal function in multiple sclerosis: bimanual motor coordination. *Cortex*, 38(2), 201-214.
- Lazarus, J. A., & Whittall, J. (1999). Motor overflow and children's tracking performance: is there a link? *Dev Psychobiol*, 35(3), 178-187.
- Lenzi, D., Conte, A., Mainiero, C., Frasca, V., Fubelli, F., Totaro, P., et al. (2007). Effect of corpus callosum damage on ipsilateral motor activation in patients with multiple sclerosis: a functional and anatomical study. *Hum Brain Mapp*, 28(7), 636-644.
- Leonard, G., Milner, B., & Jones, L. (1988). Performance on unimanual and bimanual tapping tasks by patients with lesions of the frontal or temporal lobe. *Neuropsychologia*, 26(1), 79-91.
- Liederman, J., & Foley, L. M. (1987). A modified finger lift test reveals an asymmetry of motor overflow in adults. *J Clin Exp Neuropsychol*, 9(5), 498-510.
- Liepert, J., Classen, J., Cohen, L. G., & Hallett, M. (1998). Task-dependent changes of intracortical inhibition. *Exp Brain Res*, 118(3), 421-426.
- Meyer, B.U., Roricht, S., Woiciechowsky, C. (1998). Topography of Fibers in the Human corpus callosum mediating interhemispheric inhibition between the motor cortices, *Ann. Neurol.* 43 360–369.
- Muller-Oehring, E. M., Schulte, T., Raassi, C., Pfefferbaum, A., & Sullivan, E. V. (2007). Local-global interference is modulated by age, sex and anterior corpus callosum size. *Brain Res*, 1142, 189-205.
- Nair, D. G., Purcott, K. L., Fuchs, A., Steinberg, F., & Kelso, J. A. (2003). Cortical and cerebellar activity of the human brain during imagined and executed unimanual and bimanual action sequences: a functional MRI study. *Brain Res Cogn Brain Res*, 15(3), 250-260.
- Netz, J. (1999). Asymmetry in transcallosal inhibition. *Electroencephalogr Clin Neurophysiol Suppl*, 51, 137-144.
- Nordstrom MA, and Butler SL. Reduced intracortical inhibition and facilitation of corticospinal neurons in musicians. *Exp Brain Res* 144: 336-342, 2002.
- Obhi, S. S., Haggard, P., Taylor, J., & Pascual-Leone, A. (2002). rTMS to the

- supplementary motor area disrupts bimanual coordination. *Motor Control*, 6(4), 319-332.
- Oldfield, R. C. (1971). The assessment and analysis of handedness: the Edinburgh inventory. *Neuropsychologia*, 9(1), 97-113.
- O'Sullivan, M., Jones, D. K., Summers, P. E., Morris, R. G., Williams, S. C., & Markus, H. S. (2001). Evidence for cortical "disconnection" as a mechanism of age-related cognitive decline. *Neurology*, 57(4), 632-638.
- Peinemann, A., Lehner, C., Conrad, B., & Siebner, H. R. (2001). Age-related decrease in paired-pulse intracortical inhibition in the human primary motor cortex. *Neurosci Lett*, 313(1-2), 33-36.
- Perrig, S., Kazennikov, O., & Wiesendanger, M. (1999). Time structure of a goal-directed bimanual skill and its dependence on task constraints. *Behav Brain Res*, 103(1), 95-104.
- Porter R., and Lemon R. (1993). *Corticospinal Function and Voluntary Movement*. Oxford; Clarendon Press.
- Raz, N., Gunning, F. M., Head, D., Dupuis, J. H., McQuain, J., Briggs, S. D., et al. (1997). Selective aging of the human cerebral cortex observed in vivo: differential vulnerability of the prefrontal gray matter. *Cereb Cortex*, 7(3), 268-282.
- Raz, N., Gunning-Dixon, F., Head, D., Williamson, A., & Acker, J. D. (2001). Age and sex differences in the cerebellum and the ventral pons: a prospective MR study of healthy adults. *AJNR Am J Neuroradiol*, 22(6), 1161-1167.
- Resnick, S. M., Pham, D. L., Kraut, M. A., Zonderman, A. B., & Davatzikos, C. (2003). Longitudinal magnetic resonance imaging studies of older adults: a shrinking brain. *J Neurosci*, 23(8), 3295-3301.
- Reuter-Lorenz, P. A., & Stanczak, L. (2000). Differential effects of aging on the functions of the corpus callosum. *Dev Neuropsychol*, 18(1), 113-137.
- Reuter-Lorenz, P.A., Stanczak, L., Miller, A. (1999). Neural recruitment and cognitive aging: Two hemispheres are better than one especially as you age. *Psychological Science* 10, 494-500.
- Ridding MC, Brouwer B, and Nordstrom MA. Reduced interhemispheric inhibition in musicians. *Exp Brain Res* 133: 249-253, 2000.
- Rosano, C., Aizenstein, H., Brach, J., Longenberger, A., Studenski, S., & Newman, A. B. (2008). Special article: gait measures indicate underlying focal gray matter atrophy in the brain of older adults. *J Gerontol A Biol Sci Med Sci*, 63(12), 1380-1388.
- Sadato, N., Yonekura, Y., Waki, A., Yamada, H., & Ishii, Y. (1997). Role of the supplementary motor area and the right premotor cortex in the coordination of bimanual finger movements. *J Neurosci*, 17(24), 9667-9674.
- Sainburg, R. L., Ghilardi, M. F., Poizner, H., & Ghez, C. (1995). Control of limb dynamics in normal subjects and patients without proprioception. *J Neurophysiol*, 73(2), 820-835.
- Salat, D. H., Buckner, R. L., Snyder, A. Z., Greve, D. N., Desikan, R. S., Busa, E., et al. (2004). Thinning of the cerebral cortex in aging. *Cereb Cortex*, 14(7), 721-730.
- Salat, D. H., Tuch, D. S., Greve, D. N., van der Kouwe, A. J., Hevelone, N. D., Zaleta, A. K., et al. (2005). Age-related alterations in white matter microstructure measured by diffusion tensor imaging. *Neurobiol Aging*, 26(8), 1215-1227.

- Sale, M. V., & Semmler, J. G. (2005). Age-related differences in corticospinal control during functional isometric contractions in left and right hands. *J Appl Physiol*, 99(4), 1483-1493.
- Schott, G. D., & Wyke, M. A. (1977). Obligatory bimanual associated movements. Report of a non-familial case in an otherwise normal left-handed boy. *J Neurol Sci*, 33(3), 301-312.
- Seidler, R. D., Alberts, J. L., & Stelmach, G. E. (2002). Changes in multi-joint performance with age. *Motor Control*, 6(1), 19-31.
- Seidler, R. D., Bernard, J. A., Burutolu, T. B., Fling, B. W., Gordon, M. T., Gwin, J. T., et al. (2010). Motor control and aging: Links to age-related brain structural, functional, and biochemical effects. *Neurosci Biobehav Rev*.
- Serrien, D. J., Nirkko, A. C., Lovblad, K. O., & Wiesendanger, M. (2001a). Damage to the parietal lobe impairs bimanual coordination. *Neuroreport*, 12(12), 2721-2724.
- Serrien, D. J., Nirkko, A. C., & Wiesendanger, M. (2001b). Role of the corpus callosum in bimanual coordination: a comparison of patients with congenital and acquired callosal damage. *Eur J Neurosci*, 14(11), 1897-1905.
- Shim JK, Kim SW, Oh SJ, Kang N, Zatsiorsky VM, and Latash ML. Plastic changes in interhemispheric inhibition with practice of a two-hand force production task: a transcranial magnetic stimulation study. *Neurosci Lett* 374: 104-108, 2005.
- Sohn, Y. H., Jung, H. Y., Kaelin-Lang, A., & Hallett, M. (2003). Excitability of the ipsilateral motor cortex during phasic voluntary hand movement. *Exp Brain Res*, 148(2), 176-185.
- Somogyi, P., Tamas, G., Lujan, R., & Buhl, E. H. (1998). Salient features of synaptic organisation in the cerebral cortex. *Brain Res Brain Res Rev*, 26(2-3), 113-135.
- Sowell, E. R., Peterson, B. S., Thompson, P. M., Welcome, S. E., Henkenius, A. L., & Toga, A. W. (2003). Mapping cortical change across the human life span. *Nat Neurosci*, 6(3), 309-315.
- Stancak, A., Cohen, E. R., Seidler, R. D., Duong, T. Q., & Kim, S. G. (2003). The size of corpus callosum correlates with functional activation of medial motor cortical areas in bimanual and unimanual movements. *Cereb Cortex*, 13(5), 475-485.
- Stephan, K. M., Binkofski, F., Halsband, U., Dohle, C., Wunderlich, G., Schnitzler, A., et al. (1999). The role of ventral medial wall motor areas in bimanual co-ordination. A combined lesion and activation study. *Brain*, 122 (Pt 2), 351-368.
- Stinear, C. M., & Byblow, W. D. (2003). Role of intracortical inhibition in selective hand muscle activation. *J Neurophysiol*, 89(4), 2014-2020.
- Stinear, J. W., & Byblow, W. D. (2002). Disinhibition in the human motor cortex is enhanced by synchronous upper limb movements. *J Physiol*, 543(Pt 1), 307-316.
- Sullivan, E. V., Adalsteinsson, E., Hedehus, M., Ju, C., Moseley, M., Lim, K. O., et al. (2001). Equivalent disruption of regional white matter microstructure in ageing healthy men and women. *Neuroreport*, 12(1), 99-104.
- Sullivan, E. V., Rohlfing, T., & Pfefferbaum, A. (2010). Quantitative fiber tracking of lateral and interhemispheric white matter systems in normal aging: relations to timed performance. *Neurobiol Aging*, 31(3), 464-481.
- Swinnen, S. P. (2002). Intermanual coordination: from behavioural principles to neural-network interactions. *Nat Rev Neurosci*, 3(5), 348-359.
- Talelli, P., Ewas, A., Waddingham, W., Rothwell, J. C., & Ward, N. S. (2008a). Neural

- correlates of age-related changes in cortical neurophysiology. *Neuroimage*, 40(4), 1772-1781.
- Talelli, P., Waddingham, W., Ewas, A., Rothwell, J. C., & Ward, N. S. (2008b). The effect of age on task-related modulation of interhemispheric balance. *Exp Brain Res*, 186(1), 59-66.
- Tanaka, Y., Yoshida, A., Kawahata, N., Hashimoto, R., & Obayashi, T. (1996). Diagnostic dyspraxia. Clinical characteristics, responsible lesion and possible underlying mechanism. *Brain*, 119 (Pt 3), 859-873.
- Toyokura, M., Muro, I., Komiya, T., & Obara, M. (2002). Activation of pre-supplementary motor area (SMA) and SMA proper during unimanual and bimanual complex sequences: an analysis using functional magnetic resonance imaging. *J Neuroimaging*, 12(2), 172-178.
- Tuller, B., & Kelso, J. A. (1989). Environmentally-specified patterns of movement coordination in normal and split-brain subjects. *Exp Brain Res*, 75(2), 306-316.
- Ullen, F., Forssberg, H., & Ehrsson, H. H. (2003). Neural networks for the coordination of the hands in time. *J Neurophysiol*, 89(2), 1126-1135.
- Urbano, A., Babiloni, C., Onorati, P., Carducci, F., Ambrosini, A., Fattorini, L., et al. (1998). Responses of human primary sensorimotor and supplementary motor areas to internally triggered unilateral and simultaneous bilateral one-digit movements. A high-resolution EEG study. *Eur J Neurosci*, 10(2), 765-770.
- Vercauteren, K., Pleysier, T., Van Belle, L., Swinnen, S. P., & Wenderoth, N. (2008). Unimanual muscle activation increases interhemispheric inhibition from the active to the resting hemisphere. *Neurosci Lett*, 445(3), 209-213.
- Wahl, M., & Ziemann, U. (2008). The human motor corpus callosum. *Rev Neurosci*, 19(6), 451-466.
- Webb, S. J., Monk, C. S., & Nelson, C. A. (2001). Mechanisms of postnatal neurobiological development: implications for human development. *Dev Neuropsychol*, 19(2), 147-171.
- Woollacott, M. H., & Tang, P. F. (1997). Balance control during walking in the older adult: research and its implications. *Phys Ther*, 77(6), 646-660.
- Wright, M.L., Adamo, D.E., & Brown, S.H. (2011). Age-related declines in the detection of passive wrist movement. *Neurosci Lett*, 500(2), 108-12.
- Zahr, N. M., Rohlfing, T., Pfefferbaum, A., & Sullivan, E. V. (2009). Problem solving, working memory, and motor correlates of association and commissural fiber bundles in normal aging: a quantitative fiber tracking study. *Neuroimage*, 44(3), 1050-1062.

CHAPTER II

Transcallosal sensorimotor fiber tract structure-function relationships

Published with stylistic modifications as - Fling BW, Benson BL, Seidler RD (In press). Transcallosal sensorimotor fiber tract structure-function relationships. *Human Brain Mapping*.

Abstract

Recent studies have demonstrated neuroanatomically selective relationships between white matter tract microstructure, physiological function and task performance. Such findings suggest that the microstructure of transcallosal motor fibers may reflect the capacity for interhemispheric inhibition between the primary motor cortices, although full characterization of the transcallosal inhibitory sensorimotor network is lacking. Thus, the goal of the current study was to provide a comprehensive description of transcallosal fibers connecting homologous sensorimotor cortical regions and to identify the relationship(s) between fiber tract microstructure and interhemispheric inhibition during voluntary cortical activity. To this end, I assessed microstructure of fiber tracts connecting homologous sensorimotor regions of the cortex with diffusion tensor imaging. I also quantified interhemispheric inhibition by eliciting the ipsilateral silent period (iSP) within the same participants. I mapped mutually exclusive transcallosal connections between homologous sensorimotor regions and computed quantitative metrics of each fiber tract. Paralleling work in non-human primates I found the greatest interhemispheric

sensorimotor connections to be between the medial motor areas. Additionally, I provide a mid-sagittal callosal atlas in normalized MNI space for future studies to use when investigating callosal fiber tracts connecting primary and secondary sensorimotor cortices. Finally, I report a strong, positive relationship ($r = 0.76$) between strength of interhemispheric inhibition (iSP) and microstructure of interhemispheric fibers that is specific to tracts connecting the primary motor cortices. Thus, increased fiber microstructure in young adults predicts interhemispheric inhibitory capacity.

Introduction

Execution of unimanual or asymmetric bimanual movement relies on cortical activity that is independently localized within each hemisphere (Carson 2005). Multiple lines of research indicate that the corpus callosum (CC) plays an integral role in this lateralization of control (Kennerley, et al., 2002; Kobayashi et al., 2003; Tuller and Kelso, 1989). One standard approach to studying callosal function involves parsing the callosum into seven segments using a geometric scheme (Witelson 1989). These seven sub-regions approximately correspond to distinct anatomical connections of the caudal/orbital prefrontal cortices (rostrum; region 1), prefrontal cortices (genu; 2), premotor cortices (rostral truncus; 3), cingulate motor, pre-supplementary and supplementary motor areas (anterior intermediate truncus; 4), primary motor cortices (posterior intermediate truncus; 5), primary sensory cortices (isthmus; 6), superior temporal and posterior parietal cortices and occipital and inferior temporal cortices (splenium; 7) (Hofer & Frahm, 2006). Numerous studies relying on this approach have identified associations between CC macrostructure (i.e. volume or cross-sectional area), microstructure and behavior (Fling et al., In press; Fling et al., 2011; Luders et al., 2010; Stancak et al., 2003; Sullivan et al., 2010b). Tractography analyses of diffusion tensor imaging (DTI) data may allow for a more fine-grained approach to investigate regional specificity of callosal function. Recent studies utilizing fiber tractography have demonstrated relationships between specific interhemispheric fiber tract microstructure and task performance in both healthy participants (Johansen-Berg, et al. 2007) and in those with white matter dysfunction (Bartels et al., 2008; Bonzano et al., 2008; Kern et al., 2010).

Interhemispheric communication can have either net facilitatory or inhibitory effects (Chen, et al. 2003); however multiple lines of research indicate that callosal connections between the two motor cortices have primarily inhibitory effects (De Gennaro et al., 2004; Lenzi et al., 2007; Netz, 1999). Callosally-mediated interhemispheric inhibition is a complex process that has traditionally been measured in humans using one of the following methods: i) the transcranial magnetic stimulation (TMS)-induced ipsilateral silent period and ii) paired-pulse TMS to each primary motor cortex at an interstimulus interval of 8-12 ms (cf. Chen, 2004; short interhemispheric inhibition, or SIHI). Although both the ipsilateral silent period (iSP) and SIHI are reflective of transcallosal inhibition, they do not appear to represent the same phenomenon, nor are the two values correlated with each other across individuals (Chen, et al. 2003). The iSP is elicited by focal TMS of the primary motor cortex ipsilateral to the hand making a voluntary contraction, leading to a brief suppression of voluntary activity in the electromyogram (EMG) signal of this muscle (Ferber et al., 1992; Meyer et al., 1995). Therefore, the iSP represents interruption of voluntary cortical activity and likely relies upon γ -aminobutyric acid (GABA)_B receptors (Werhahn et al., 1999). Also relying upon GABA-ergic neurotransmitters, SIHI is mediated by GABA_A receptors (Hanajima, et al. 1998) and reflects inhibition of synchronized activation of the corticospinal system induced by the conditioning stimulus (the first stimulus applied). Due to the fact that the iSP reflects inhibition of volitional motor activity, it appears to be particularly well-suited to investigate interhemispheric control of voluntary cortical motor output (Giovannelli et al., 2009). The relationship between iSP and interhemispheric microstructure has yet to be well-defined.

Experiments conducted with individuals with callosal pathology (e.g. partial callosotomy or multiple sclerosis) demonstrate that while the total number of callosal fibers connecting the two primary motor cortices is relatively few in number, communication between these homologous areas has the capability to strongly influence motor behavior (Bonzano, et al. 2011; Eliassen, et al. 1999; Eliassen, et al. 2000; Kennerley, et al. 2002; Lenzi, et al. 2007). It is important to note that, in addition to the primary motor cortex (M1), multiple secondary motor regions also appear to be involved in this interhemispheric inhibitory network (Grefkes, et al. 2008). For example, although full characterization of the transcallosal inhibitory sensorimotor network is still lacking, neuroimaging data suggest that it includes the supplementary and pre-supplementary motor areas (Grefkes, et al. 2008; Serrien, et al. 2002), the dorsal premotor cortices (Giovannelli et al., 2006; van den Berg et al., 2010) and the somatosensory cortices (Ni, et al. 2009). While several studies have suggested that callosal fiber tracts connecting these cortical regions play a role in interhemispheric inhibition, there has not been a comprehensive study examining the relationship between microstructure of fiber tracts connecting the sensorimotor cortical regions and interhemispheric inhibition during voluntary cortical activation.

Recent work suggests that the microstructure of transcallosal motor fibers, assessed with diffusion tensor imaging, reflects the capacity for interhemispheric inhibition between the primary motor cortices. Wahl and colleagues (2007) report a positive relationship between microstructural integrity of transcallosal motor fibers and strength of inhibition as measured with SIHI in adults. Similarly, a positive relationship between interhemispheric inhibition (assessed by iSP area and duration) and callosal

microstructure across development (range: ~7-26 yrs.; Koerte et al., 2009) has been shown. However, further analysis of Koerte and colleagues' dataset is warranted; it is clear that the observed relationship is strongly driven by the child group in their study (mean age: 8.4 yrs). In fact, it appears that the relationship between iSP and fiber microstructure may well be in the opposite direction in their adult group (mean age: 25.9 yrs). Thus, as opposed to the relationship described by Wahl and colleagues (2007) when participants were at rest, it is possible that adults with better white matter microstructure (as assessed by fractional anisotropy) have reduced interhemispheric inhibition during volitional cortical activity. This hypothesis is supported by recent work from our laboratory demonstrating that higher CC microstructural integrity is associated with *poorer* performance on bimanual tasks requiring a large degree of interhemispheric inhibition (Fling et al., In press). Furthermore, it has previously been shown that musicians (experts in bimanual control) have reduced interhemispheric inhibition compared to non-musicians (Ridding, et al. 2000).

The goal of the current study was to elucidate the relationship between CC structure and neurophysiological function, and their respective roles in motor control. Here I provide a comprehensive description of transcallosal fiber tracts connecting homologous sensorimotor cortical regions, as well as a mid-sagittal callosal atlas in normalized MNI space for future studies to use when investigating callosal macro- and microstructure. Additionally, I determined the relationship(s) between neurophysiological function of volitional interhemispheric inhibition and the microstructure of these fibers. Based upon our recent work (Fling, et al. In press) and that of others (Koerte et al., 2009) I hypothesized that there would be a negative

relationship between microstructure of fiber tracts connecting primary motor cortices and volitional interhemispheric inhibition.

Methods

Participants

Twenty-one young adults (range: 19-28 yr of age; mean: 22.1 ± 2.8 yr; 10 males and 11 females) participated in the current study. All individuals were right-hand dominant as assessed by the Edinburgh Handedness Inventory (mean: 77.0 ± 0.08 ; Oldfield, 1971). This experiment was approved by the Medical Institutional Review Board (IRBMED) of the University of Michigan. Participants gave their informed written consent prior to beginning the experiment and were compensated for their time.

I performed testing on 2 days, separated by less than one week. On the first day of testing I acquired structural magnetic resonance (MR) and diffusion weighted (DW) images (detailed in the following section). On the second day of testing I acquired iSP data from the first dorsal interosseous (FDI) muscle of the dominant hand as described below.

Image acquisition

Whole brain high-resolution structural MR images were collected on a 3T MRI scanner (General Electric, Waukesha, WI, USA) using a spoiled gradient echo sequence (124 slices, field-of-view: 24 cm, voxel size: $0.94 \times 0.94 \times 1.4$ mm, TR: 10.2 ms and TE: 3.4 ms). Diffusion weighted images were collected using a single shot echo-planar sequence (39 slices; TE/TR: 82.8 ms/9000 ms; field of view: 220 mm x 220 mm; voxel size $3 \times 3 \times 3$ mm; b -value = 800 s/mm^2 ; 15 diffusion-sensitizing directions). Images

were motion and eddy-current corrected. Using the averaged images with $b = 0$ and $b = 800 \text{ s/mm}^2$, the diffusion tensor was calculated and fractional anisotropy (FA) images were constructed off-line using ExploreDTI (Leemans et al., 2009). Diffusion tensors were calculated from the 15 DW images based upon a simple least squares fit of the tensor model to the diffusion data (Basser, et al. 2000). Diagonalization of the tensor yields three voxel-specific eigenvalues ($\lambda_1 > \lambda_2 > \lambda_3$) representing diffusivities along the three principle directions of the tensor. The three principal eigenvectors were then used to construct fiber tracts and the resultant diffusion properties as described below.

Tractography

Each participant's resultant FA map was co-registered into MNI space, aligned along the anterior/posterior commissure line with the coordinate 0, 0, 0 placed at the brain's center of mass, and voxel size was re-sampled to $2 \times 2 \times 2 \text{ mm}$ through the use of ExploreDTI (Leemans et al., 2009). The Human Motor Area Template (HMAT; Mayka et al., 2006), transformed from its original Talairach space, was co-registered to each individual's MNI-normalized FA image and subsequently used as a mask (**Figure 2.1A**). The HMAT is the result of a meta-analysis examining cortical activity assessed by functional MRI; strict inclusion criteria were used to identify six sensorimotor regions: dorsal and ventral premotor cortices (PMd and PMv, respectively), supplementary and pre-supplementary motor areas (SMA and pre-SMA, respectively), M1, and the primary somatosensory cortices (S1). Due to the large interindividual variability of the central sulcus location combined with the difficulty of normalizing this highly variable landmark, Mayka and colleagues (2006) suggest that the HMAT only serves as a functional guide in distinguishing between M1 and S1 cortical regions. Potentially as a

result of this variability, I could not reliably identify interhemispheric fiber tracts connecting S1 regions in all participants using the HMAT. Given this I included the cortical masks of Brodmann's areas (BA) 1, BA2, and BA3 provided by ExploreDTI (**Figure 2.1B**); I will refer to tracts identified by these masks as S1 tracts for the remainder of this paper. Fiber tracts were constructed based upon deterministic streamline tractography using the method of Mori and colleagues (cf. Mori and van Zijl, 2002). Tractography between seed and target regions of interest was performed using threshold parameters including a minimum fiber tracking threshold of 0.2 (e.g. 0.2 is the minimum FA of a voxel allowable in a fiber tract; this value is comparable to what has been used in other studies, Davis et al., 2009; Hofer and Frahm, 2006), a minimum fiber length of 50 mm, and a maximum deviation angle of 30° between contiguous voxels. Interhemispheric fiber tracts were identified by placing seed and target ROIs in homologous cortical regions identified by the HMAT (e.g. right and left M1; **Figure 2.1C**). Fiber tracking was performed for all regions identified by the HMAT plus the additional S1 masks, resulting in six possible interhemispheric tract bundles connecting homologous cortical regions (**Figure 2.1D**).

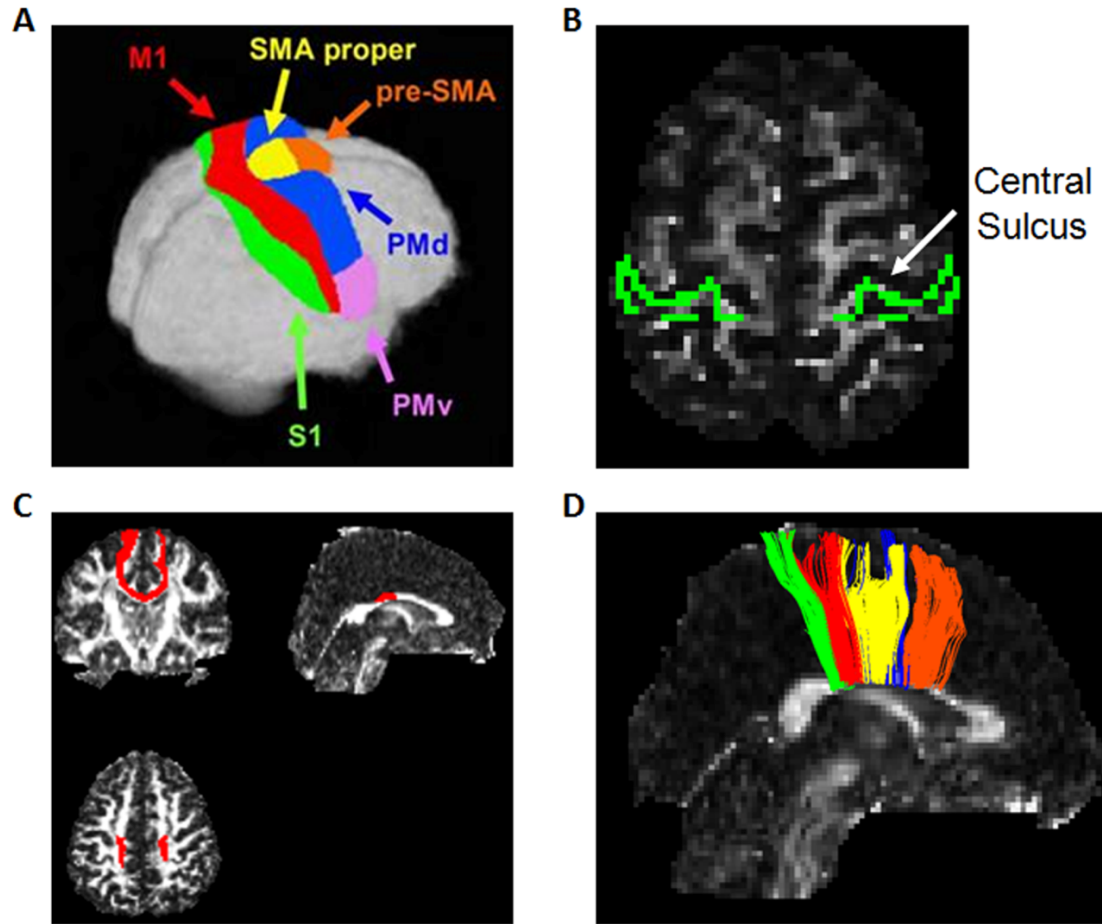


Figure 2.1 – Interhemispheric fiber tracts connecting homologous sensorimotor cortical regions. **A)** Human motor area template (HMAT; Mayka et al., 2006). The HMAT was co-registered to each individual's fractional anisotropy map and used as a mask to map homologous interhemispheric fiber tract connections. **B)** Masks of BA1, BA2, and BA3 used to identify interhemispheric tracts connecting S1 cortical regions ($Z = 48$). Masks are shown overlaid on one representative subject's fractional anisotropy map. **C)** One representative example of interhemispheric fiber tracts projecting between the bilateral primary motor cortices (0, -2, 30). **D)** All interhemispheric fiber tracts identified with the HMAT for one representative participant. Fiber tracts are color-coded to match the HMAT (Figure 1A) and represent fibers connecting S1 (green), M1 (red), SMA (yellow), PMd (blue) and pre-SMA (orange). No interhemispheric tracts between PMv were identified in any participants.

Interhemispheric Inhibition

On day 2 a subset of 16 participants from the initial imaging session underwent a TMS procedure to assess volitional interhemispheric inhibition. Five participants from the first day of testing were unable to undergo the TMS procedure based on screening (4 individuals were taking prescription medication with possible contraindications and 1 individual had a familial history of epilepsy; for screening questionnaire see Appendix 1). Participants were seated in a chair with both their dominant and non-dominant forearms resting on a table. Shoulders were abducted at approximately 45°, the elbows were flexed at approximately 90°, and forearms were pronated with the palms of the hand lying flat on the custom apparatus (**Figure 2.2**). The wrist, third, fourth, and fifth fingers were constrained from moving, isolating force production to the index finger. A pre-amplified force transducer (OMEGA LC509-015 Beam Load Cell) was positioned at the lateral aspect of the proximal interphalangeal joint of the isolated index finger to record compressive isometric force (output: 0.5-9.5 Vdc; excitation: 24 Vdc \pm 4 Vdc).



Figure 2.2 – Depiction of the force production set-up used in the current experiments.

Surface electromyography and motor evoked potentials (MEPs) were recorded from the FDI muscle of both hands using 4 mm Ag/AgCl electrodes placed on the muscle in a belly-tendon arrangement. Surface EMG and MEP data were recorded using Biopac hardware and AcqKnowledge software (BIOPAC Systems Inc., Goleta, CA). The raw EMG signal was collected and digitized at 2000 Hz, amplified and band pass filtered (10-1000 Hz). Data were collected at 2kHz as it has previously been shown to produce the most accurate estimate of mean consecutive difference (MCD) of pre-stimulus EMG activity, necessary to accurately calculate the iSP (Garvey et al., 2001).

Estimation of the maximal voluntary contraction (MVC) and resting motor threshold (RMT)

Participants were instructed to press as hard as possible on the load cell using index finger abduction of the dominant hand for three consecutive 6-second trials (Fling et al., 2009). The force applied to the load cell was displayed on the video monitor, providing online visual feedback during the MVC trials. The highest force sample in each trial was averaged across three MVC trials, providing an estimate of the participants' MVC. A 60-second rest period was provided in between each MVC trial.

Prior to performing the experimental paradigm, I used a Magstim Rapid magnetic stimulator (The Magstim Company Ltd, Spring Gardens, Whitland, Carmarthenshire, UK) and a focal figure of eight coil (diameter of each wing 70 mm) to identify the right M1 hotspot. The coil was placed tangential to the scalp with the handle pointing backwards and 45° away from the midline (Chen et al., 2003; **Figure 2.2**). The optimum site in the right M1 (hotspot) for eliciting motor responses in the left FDI was identified at supra-threshold intensity. This location was utilized to elicit iSPs from the right FDI as

it has previously been shown that the topography of the contralateral MEP and the iSP correspond closely (Wasserman et al., 1991). Resting motor threshold (RMT) was determined to the nearest 1% of the maximum stimulator output. Using the standard protocol, the RMT was defined as the minimum stimulus intensity which elicited MEPs > 50 μ V in at least 5 out of 10 consecutive trials (Triggs et al., 1994).

Experimental Task

The force target levels used in the experiment were scaled to 20% of each individual participant's MVC. Participants viewed a yellow, horizontal target line that spanned the width of a video monitor (placed at 20% of MVC). Force output was sampled at 200 Hz; for each instant in time that force was sampled (.005s), a green pixel appeared on the monitor corresponding to the amount of force produced providing the participant with on-line, real-time visual feedback of their performance. Using their dominant hand, participants were instructed to overlay their green force trace onto the yellow target line for three 40-second trials (**Figure 2.3**; colors changed for presentation purposes). Once participants reached the target force level, an iSP was elicited from the dominant hand by stimulation given at 120% of resting motor threshold to the right motor cortex (Giovannelli et al., 2009). During each 40-second trial, five iSPs were evoked with an interstimulus interval jittered between 5-8 seconds resulting in a total of 15 iSPs per participant (Garvey et al., 2001; Jung & Ziemann, 2006). Participants were provided rest breaks of five minutes in between each trial. EMG data were also collected and monitored from the non-dominant, left hand to ensure that the TMS coil was always in the appropriate location over the right M1. During one trial in two different participants, MEPs ceased to be elicited from the left FDI. On each occasion data collection was

halted and the right M1 hotspot for the FDI was re-located.

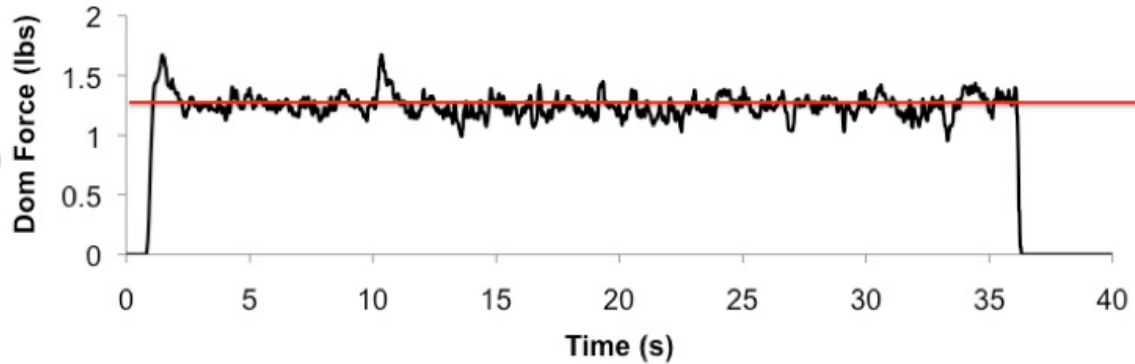


Figure 2.3 – An example force trace during the unimanual force production task. The horizontal red line is the target force goal.

Data Analysis

Fiber Tractography

Multiple descriptive metrics were calculated for each fiber tract including the number of identifiable points composing fiber tract streamlines connecting each homologous sensorimotor ROI pair (henceforth referred to as number of interhemispheric fiber tract connections), FA, and radial diffusivity ($(\lambda_2 + \lambda_3) / 2$). Fractional anisotropy, a rotationally invariant index that ranges from 0 (isotropic) to 1 (anisotropic), is a composite measure of the tensor ellipsoid derived from the tensor's eigenvectors on an intravoxel basis (Sullivan et al., 2010a). Therefore, higher FA values are interpreted as reflecting better white matter microstructure (Basser and Pierpaoli 1996). Conversely, *lower* radial diffusivity is interpreted as being indicative of better tract microstructure (Basser et al., 2000). Mean values of the aforementioned metrics were calculated for all identified interhemispheric fiber tracts within each participant. Additionally, the average coordinate position of each interhemispheric fiber tract within the corpus callosum was

identified on a mid-sagittal slice ($X = 0$) for all participants.

Ipsilateral Silent Period (iSP)

The iSP was calculated by using an objective, graphical method described in detail by Garvey and colleagues (2001). Single EMG trials (15 total per participant) were rectified and averaged across trials. Using a custom MATLAB program (The MathWorks Inc., Natick, MA), upper and lower variation limits of the EMG signal were calculated by determining the mean consecutive difference (MCD) of EMG data points 100ms prior to stimulation: mean pre-stimulus EMG \pm ($|MCD| \times 1.77$). These limits encompassed 95% of possible pre-stimulus EMG data points (equivalent to two standard deviations). Onset and offset of iSP were identified using the following criteria: (1) time of onset was the first of 5 consecutive data points to fall below the lower variation limit; (2) all subsequent data points were considered part of the iSP until there was a return of sustained EMG activity; (3) time of offset was defined as the first data point to rise above the lower variation limit if 50% or more of the data points in the following 5 ms window were also above the variation limit (See **Figure 2.4**: Garvey et al., 2001). In addition to measuring the onset, offset and duration of the iSP, the depth of the iSP was defined in two ways as previously described by Jung and Ziemann (2006): (1) the minimum EMG level during the iSP (diSP-max), and (2) the average EMG level during the iSP (diSP). The diSP and diSP-max were expressed as percentages of the mean prestimulus EMG. Therefore the greater the suppression of ipsilateral EMG activity during the iSP, the larger the diSP (and diSP-max). This is interpreted as increased interhemispheric inhibition (Garvey et al., 2001).

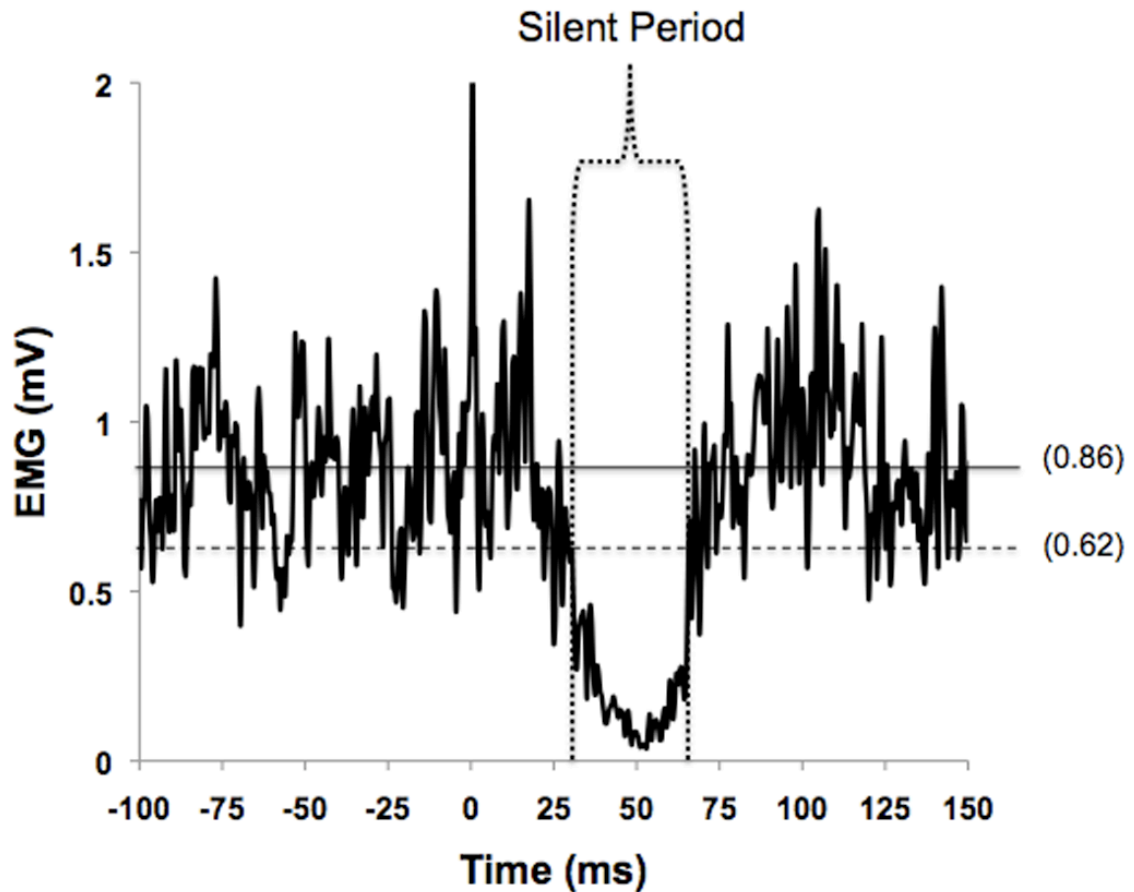


Figure 2.4 – Representative example of an ipsilateral silent period. Data displayed are the rectified average of 15 iSPs (stimulation applied at time 0) obtained during 20% MVC isometric contraction. The horizontal solid line represents mean pre-stimulus EMG activity (0.86 mV). The horizontal dotted line represents the lower variability limit (0.62 mV). Vertical dotted lines encompass the ipsilateral silent period.

Force data

The initial 5 seconds of each force time series was removed to eliminate the transitory period prior to force target attainment. Force data were digitally filtered using a 4th order Butterworth filter with a low-pass cutoff frequency of 20 Hz. All data processing and subsequent time and frequency analyses were performed using software written in MATLAB (The MathWorks Inc., Natick, MA). Similar to previous work, the

amount of force output variability was assessed by calculating the within-trial mean and the root mean square error (RMSE) from the target (Vaillancourt et al., 2003).

Statistical analysis

A repeated measures analysis of variance was used to analyze metrics of interhemispheric fiber tracts with fiber tract treated as a within-subject variable and significance set at an alpha of 0.05 (SPSS 17.0). The Huyn-Feldt epsilon was computed to test for sphericity; I interpreted corrected P values in cases of violation. Significant main effects were subjected to post-hoc paired t -tests and corrected for multiple comparisons ($\alpha = 0.05/4$). Additionally, I used linear regression analysis to investigate relationships between diSP and interhemispheric fiber tract microstructure (as assessed by FA), while correcting for multiple comparisons ($\alpha = 0.05/5$). Presented values are mean \pm standard deviation unless otherwise noted.

Results

The spatial distribution and ordering of fiber tracts depicted for the representative participant in Figure 1D was observed in all participants.

Sensorimotor Fiber Tractography

No interhemispheric fiber tracts were found between homologous ventral premotor cortices for any of the participants. Descriptive metrics of the five remaining interhemispheric fiber tracts are shown in **Table 2.1**. A main effect of fiber tract was found for fiber tract connections ($F_{4,76} = 64.2$, $P < 0.001$), fractional anisotropy ($F_{4,76} = 21.4$, $P < 0.001$), and radial diffusivity ($F_{4,76} = 20.77$, $P < 0.001$).

	<i>Fiber Tract Connections</i>	<i>FA</i>	<i>Radial Diffusivity ($\times 10^{-3} \text{ mm}^2/\text{s}$)</i>
S1	6657.5 ^d (922.8)	0.52 ^c (0.03)	0.57 ^c (0.05)
M1	13559.9 ^c (1428.1)	0.54 ^b (0.02)	0.54 ^b (0.03)
SMA	32377.7 ^a (2226.8)	0.56 ^a (0.02)	0.509 ^a (0.03)
PMd	7468.7 ^d (1365.7)	0.56 ^a (0.03)	0.53 ^a (0.04)
pre-SMA	21598.9 ^b (1206.9)	0.54 ^b (0.02)	0.52 ^b (0.03)

Table 2.1 – Interhemispheric sensorimotor fiber tract metrics. Data for fiber tract connections are mean (\pm s.e.m.), while all other data are presented as mean (\pm standard deviation). Significant differences between fiber tracts were assessed by paired *t*-tests - the same letter within each column indicates tracts that were not significantly different from each other.

Fiber Tract Connections

Paired *t*-tests revealed that there were significantly more fiber tracts connecting homologous SMA regions than M1, S1, PMd and pre-SMA ($P < 0.001$). There were also significantly more fibers connecting pre-SMA than M1, S1 or PMd ($P < 0.001$). Lastly, fibers connecting M1 were significantly greater in number than those connecting S1 or PMd ($P < 0.01$). No difference was noted in the number of fiber tracts connecting S1 or PMd ($P > 0.51$).

Fiber microstructure

Similar to previous work in young adults (Fling et al., in press), radial diffusivity and FA were highly correlated within all interhemispheric fiber tracts ($r > 0.8$). As a result I only discuss fiber microstructure in terms of FA; however, metrics of radial diffusivity within each fiber tract can be viewed in **Table 2.1**. Post-hoc paired t-tests revealed that FA values connecting the homologous SMAs were significantly greater than pre-SMA, M1 and S1 ($P < 0.001$ in all cases). No difference was found between SMA and PMd fiber microstructure ($P > 0.12$). The mean FA of fiber tracts connecting PMd was significantly greater than those connecting pre-SMA, M1 and S1 ($P < 0.01$ in all cases). Lastly, no differences were noted in microstructural integrity between tracts connecting pre-SMA and M1 cortical regions ($P > 0.77$), however both were significantly greater than fibers projecting between homologous S1s ($P < 0.01$ in both cases).

Homologous interhemispheric sensorimotor fiber tract locations within the CC

I identified the average y- and z- coordinate of each fiber tract on a mid-sagittal slice of the CC ($X = 0$) both at the individual- and group-level. The individual and mean group locations of these tracts are shown in MNI-space in **Figure 2.5**. The average location on the CC where each of the five interhemispheric sensorimotor tracts crosses can be viewed in **Table 2.2**. It should be noted that although there are gaps on the CC where no fiber tracts are displayed (e.g. between SMA and M1 fibers) this does not indicate that no fibers were identified within the CC at those specific locations. The depiction in **Figure 2.5** is solely providing the average tract location; a complete example of identified fiber pathways can be viewed in **Figure 2.1D**.

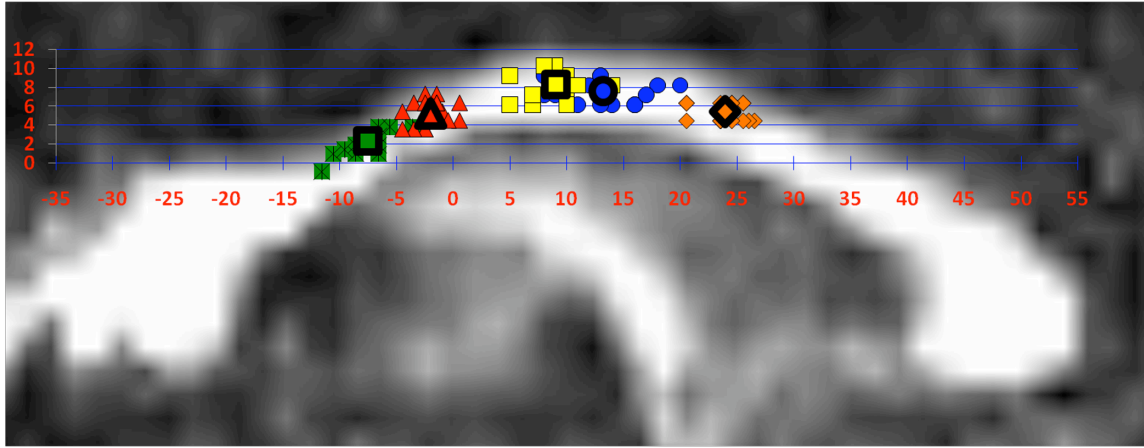


Figure 2.5 – Individual participants’ average y- and z- coordinates of transcalsal fiber pathways ($X = 0$). Average tract locations are depicted by symbols outlined in black. Data are displayed on a representative fractional anisotropy map normalized to MNI space with 0, 0, 0 placed at the brain’s center of mass. Fiber locations are color-coded to match the HMAT (Figure 1A) and represent fibers connecting S1 (green), M1 (red), SMA (yellow), PMd (blue) and pre-SMA (orange).

	<i>Average y (mm)</i>	<i>Average z (mm)</i>
S1	-8.0 (-15 – 1)	2.45 (-5 – 9)
M1	-1.64 (-9 – 8)	5.76 (1 – 11)
SMA	9.05 (-5 – 23)	8.1 (3 – 13)
PMd	13.1 (1 – 25)	7.45 (3 – 13)
Pre-SMA	24.6 (13 – 35)	5.86 (1 – 13)

Table 2.2 – Average interhemispheric fiber location on a mid-sagittal slice of the corpus callosum ($X = 0$). Data are reported in MNI space with 0, 0, 0 placed at the center of mass of the brain. Values are the group mean and ranges across participants are provided in parentheses.

Force Data

The group mean maximal voluntary contraction value from the FDI was 18.9 N (± 5.7). Participants were able to perform the unimanual isometric task in a consistent manner; force was maintained at 93.7% ($\pm 5.4\%$) of the target force goal. Further, the mean RMSE of 0.031 (± 0.02) indicates that variability was low across all participants.

TMS - Ipsilateral Silent Period

Ipsilateral silent periods were reliably produced in all 16 participants. I performed an average of 15.2 stimulations (range = 15-18 stimulations) to produce the 15 silent periods that I used to average iSP data per participant. Quantitative metrics of the iSP can be viewed in **Table 2.3**. Duration of iSP and diSP were significantly correlated with each other ($r = 0.70$; $P < 0.01$); therefore I use diSP to refer to strength of interhemispheric inhibition for the remainder of the chapters.

Relationships between sensorimotor fiber microstructure and interhemispheric inhibition

I found a significant relationship between metrics of M1 transcallosal fiber microstructure (FA) and diSP ($r = 0.76$; $P < 0.0001$; **Figure 2.6**). A trend was observed for a relationship between diSP and FA of fiber tracts connecting S1 ($r = 0.55$; $P < 0.05$) and PMd ($r = 0.54$; $P < 0.05$); however, neither association was significant after correcting for multiple comparisons. No relationships were noted between fiber microstructure of either SMA ($r = 0.28$) or pre-SMA ($r = 0.08$) with diSP ($P > 0.3$ in both cases; **Figure 2.7**).

RMT (%)	63.6 (4.9)
iSP Onset latency (ms)	38.4 (3.4)
iSP Duration (ms)	27.7 (8.8)
diSP (%)	73.6 (6.2)
diSP-max (%)	91.9 (4.6)

Table 2.3 – Resting motor threshold (RMT; relative to maximal stimulator output) and ipsilateral silent period (iSP) metrics. Values are mean (\pm standard deviation).

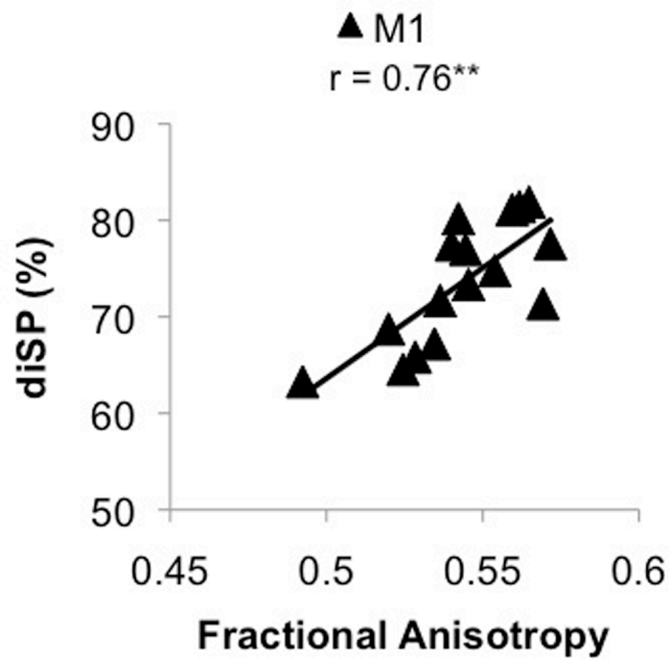


Figure 2.6 – Positive linear relationship ($**p < 0.001$) between strength of interhemispheric inhibition (diSP) and microstructure of fiber tracts connecting bilateral primary motor cortices (assessed by FA).

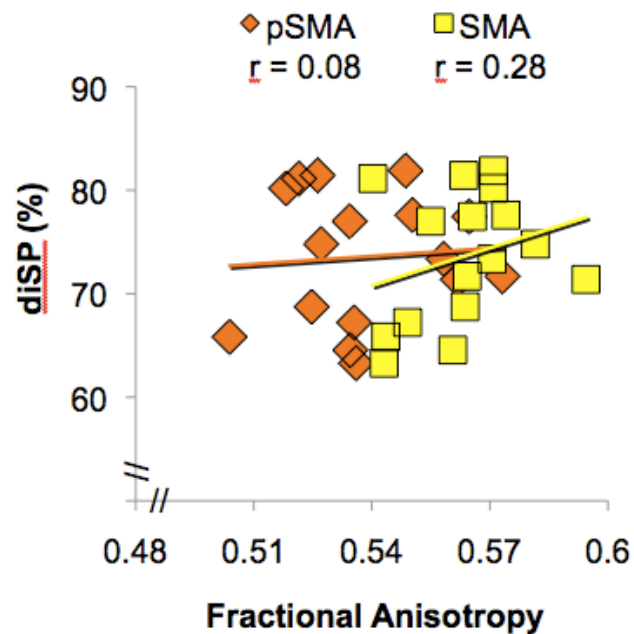


Figure 2.7 – No relationship ($p > 0.3$) was observed between strength of interhemispheric inhibition (diSP) and microstructure of fiber tracts connecting bilateral supplementary or pre-supplementary motor areas (SMA and pSMA, respectively).

Discussion

In the current study I mapped distinct transcallosal sensorimotor connections and identified quantitative metrics for each fiber tract. Additionally, I have provided a mid-sagittal callosal atlas in normalized MNI space for future studies to use when investigating callosal macro- and microstructure of sensorimotor connections. Finally, I observed a positive relationship between volitional interhemispheric inhibition and microstructure specific to fibers connecting homologous M1 regions.

Interhemispheric Sensorimotor Fiber Tractography

Interhemispheric Fiber Tract Connections

Several key findings from the current study provide information about sensorimotor connections that are in agreement with previous work in non-human primates as well as fiber tractography studies in humans. Anatomical tracer work in non-human primates has demonstrated that the main callosal connections of M1, SMA, PMd and PMv are with homotopic sites in the contralateral hemisphere (Dancause et al., 2007; Fang et al., 2009; Rouiller et al., 1994). Similar to anatomical tracer work performed in galagos (Fang et al., 2008) and macaque monkeys (Rouiller et al., 1994), the largest quantities of interhemispheric tracts in the current study were found between homologous SMA and pre-SMA cortical regions. Conversely, the fewest connections were observed in fiber tracts connecting PMd and S1 cortical areas. Again, this is in agreement with previous work demonstrating consistent, but relatively sparse transcallosal connections between homologous PMds (Fang et al., 2008) and S1s (Pandya and Vignolo, 1968). While I was unable to identify interhemispheric PMv connections in any individuals,

previous work has found meager transcallosal homotopic PMv fibers (Dancause et al., 2007; Fang et al., 2008). It is possible that due to the lateral location of PMv within each hemisphere, deterministic fiber tractography is unable to reliably identify fibers projecting to these cortical areas. That is to say, there are major crossing fiber pathways (e.g. the superior longitudinal fasciculus) that may result in too much diffusion signal loss for the current study to identify these lateral PMv connections.

A significant body of literature has identified transcallosal connections between homologous M1 regions, both in humans and other primates. While dense connections between right and left M1 face representations have reliably been identified, M1 forelimb and hand representations typically have scant callosal connections (Fang et al., 2009; Rouiller et al., 1994). These callosal connections appear to be fairly homotopic, although it should be noted that M1 appears to also have limited callosal connections with additional contralateral cortical regions including SMA and PMd (Fang et al., 2009). The current study demonstrates relatively dense M1 callosal connections, and although I do not identify the specific cortical target of these fiber tracts (e.g. hand, face or other regions of the precentral gyrus), the relationships with physiological function discussed below provide strong evidence that the M1 fiber pathways I have identified play a significant role in interhemispheric inhibitory function during volitional motor output to a finger muscle. The cortical termination sites of identified interhemispheric fiber tracts are relatively medial (Figure 1C), which is in agreement with previous research both in human and non-human primates (Bonzano et al., 2008; Fang et al., 2009; Rouiller et al., 1994; Sullivan et al., 2010a; 2010b; Wahl et al., 2007).

Fiber Microstructure

I report significant microstructural integrity differences of fiber tracts connecting homologous sensorimotor cortical regions. Previous studies have inferred metrics of interhemispheric microstructure from the data obtained solely within the CC (Fling et al., In press; Koerte et al., 2009; Wahl et al., 2007). However, it is likely that integrity of the entire interhemispheric tract influences transcallosal communication. For example, recent work has demonstrated that distal callosal fibers projecting to sensorimotor cortical areas show greater degradation than those within the body of the CC in healthy older adults (Sullivan et al., 2010a). Here I report metrics of transcallosal microstructure based upon the entirety of interhemispheric tracts.

Previous work has shown white matter integrity (as assessed by FA) to be low in areas of the CC containing fibers connecting primary and secondary motor regions in comparison to values within the genu and the splenium (Fling et al., in press; Hofer and Frahm, 2006). In the current study I show that there are significant differences in fiber microstructure even within the callosal midbody sensorimotor fiber tracts. Fractional anisotropy was observed to be the greatest for tracts connecting SMA and PMd in the current study. Importantly, fiber microstructure does not appear to be a function of the number of fiber connections; fibers connecting SMA were the most numerous whereas fibers connecting PMd were among the sparsest. Further supporting this finding, fibers connecting S1 regions (less numerous than PMd fibers) were found to have the poorest microstructure of the five interhemispheric tracts identified.

Sensorimotor Fiber Location Within the CC

A novel contribution from the current study is that I provide a mid-sagittal callosal atlas in normalized MNI space for future studies to use when investigating callosal macro- and microstructure of homologous sensorimotor connections. Moving through the CC posteriorly to anteriorly, our results are in line with previous tractography work identifying S1 connections traversing the isthmus, and M1 fiber pathways within the posterior mid-body of the CC (Hofer and Frahm, 2006; Wahl et al., 2007). Conversely, white matter tracts connecting homologous SMA regions were identified to traverse the midpoint of the CC (anterior to posterior), slightly more posterior than previous geometric segmentation approaches have suggested (Hofer and Frahm, 2006). The same was observed for fiber tracts within the anterior mid-body of the CC projecting to PMd and pre-SMA, respectively. Therefore, all of the fiber tracts projecting to secondary motor areas (SMA, PMd and pre-SMA) were identified as crossing more posteriorly within the CC than geometric segmentation approaches have suggested (**Figure 2.8**). An additional novel finding from the current study is that tracts connecting PMd cortical regions cross the CC posterior to pre-SMA fiber tracts. Again, this is at odds with previous geometric segmentation approaches reporting connections between premotor areas crossing the CC anterior to the SMA and pre-SMA fiber tracts (Witelson, 1989).

Previous studies have used a geometric segmentation scheme for parsing the CC when investigating relationships between behavior, physiology and callosal metrics. Oftentimes this geometric segmentation lumps together fibers projecting to multiple cortical targets; for example PMv, PMd, pre-SMA and SMA tracts are all included in one

CC segment by Hofer and Frahm (2006). This leaves the interpretation of results subject to a fair amount of speculation as it is unclear which interhemispheric fiber tracts are driving the observed relationship(s). Thus, solely using geometric segmentation to identify pertinent white matter tracts can result in the inclusion of multiple interhemispheric fiber tracts that may have little to no relevance. I provide MNI coordinates (**Table 2.2**) for future studies to utilize as seed regions when investigating transcallosal fiber pathways with specific sensorimotor cortical targets. I believe that using the seed regions identified with the current template will allow for more specific research questions to be addressed through the identification of relevant fiber tracts. For example, if one were to use region III as described by Hofer and Frahm (2006), not only would fiber tracts projecting to homologous M1 cortical areas be included, but a large volume of fiber tracts connecting bilateral SMAs would be as well (**Figure 2.8**). This is an important distinction as these cortical regions serve very different roles in the control of movement. For example, the S1 receives afferent input providing information about somatosensation, whereas the M1 outputs efferent commands of motor execution. Moreover, the premotor cortices, the pSMA and the SMA are involved at the motor planning stage and provide significant *intra*hemispheric input to the M1 for motor execution (Liuzzi et al., 2011). Finally, the PMd has been shown to facilitate the contralateral M1 prior to movement (Liuzzi et al., 2011; van den Berg et al., 2010). While the coordinates I provide give detailed locations of sensorimotor fibers within the CC, due to the large amount of overlap one likely cannot distinguish between fiber tracts connecting homologous SMA and PMd regions.

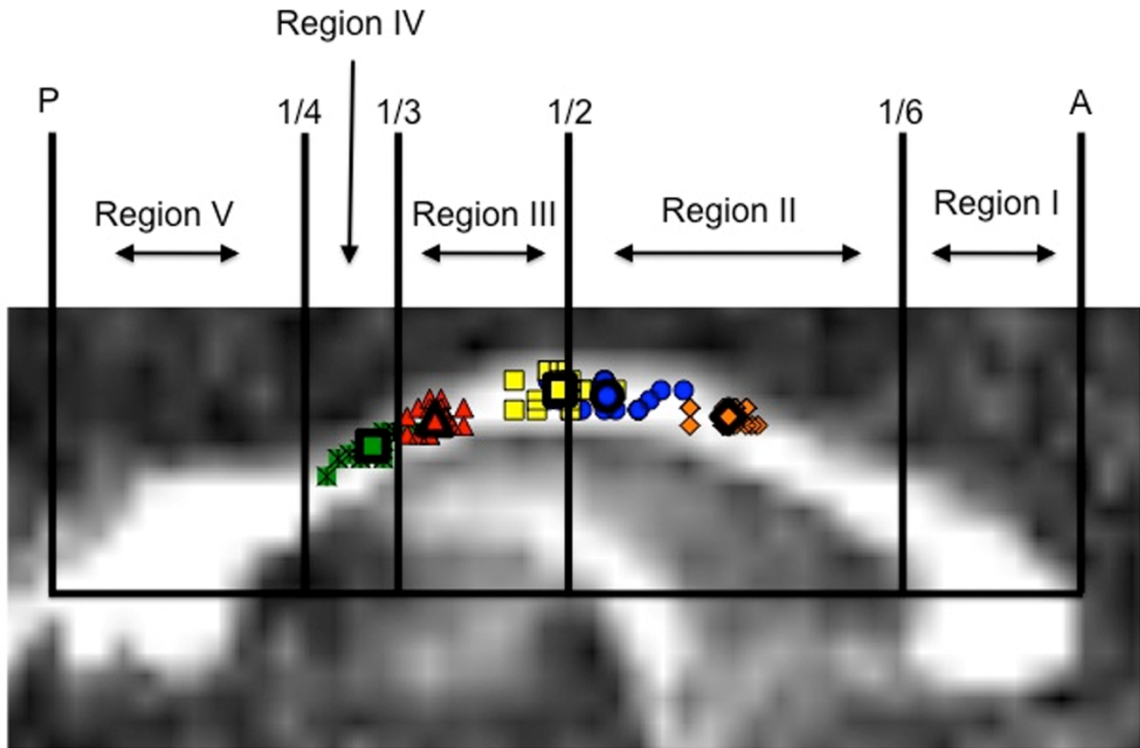


Figure 2.8 – Individual participants’ average y- and z- coordinates of transcalsal fiber pathways (color-coded to match Figure 3) with the geometric segmentation of Hofer and Frahm overlaid. The segmented regions are purported to contain fibers that project to Region I (anterior 1/6): prefrontal; region II (anterior 1/2 minus region I): premotor and supplementary motor; region III (posterior 1/2 minus region IV and V): motor; region IV (posterior 1/3 minus region V): sensory; region V (posterior 1/4): parietal, temporal, and occipital. It is clear from the current data that while this geometric segmentation provides a general rubric, the fibers projecting to sensorimotor cortical regions require a more specified approach. A, anterior; P, posterior.

Ipsilateral Silent Period

Giovannelli and colleagues (2009) have recently shown that the iSP is characterized by substantial topographical, temporal and neuronal circuit specificity. They also demonstrate the functional significance of the pathway(s) mediating iSP as they likely play pivotal roles in suppressing mirror activity during unimanual actions. While it is possible that the iSP relies on direct descending oligosynaptic pathways from the ipsilateral cortex, the most likely mechanism underlying the iSP involves

interhemispheric connections through the corpus callosum projecting to the contralateral motor cortex. This is supported by the fact that iSPs are preserved in patients with subcortical cerebro-vascular lesions that interrupt the corticospinal tract but not the corpus callosum (Boroojerdi et al. 1996). Furthermore, iSP is delayed or prolonged in neurological disorders affecting the CC such as multiple sclerosis (Schmierer et al. 2000) and no detectable iSP is found in preschool children who have yet to develop a functionally competent corpus callosum (Heinen et al. 1998), nor in patients with callosal agenesis (Meyer et al., 1995; 1998). Thus, the iSP has been proposed as a simple, clinical diagnostic tool for assessing callosal function (Meyer et al. 1999).

Contrary to our hypothesis, results from the current study show that the strength of interhemispheric inhibition (as assessed by diSP) is strongly *positively* correlated with FA of interhemispheric fibers. This relationship was restricted to transcallosal fibers connecting the primary motor cortices, although fiber tracts between homologous S1 and PMd cortical targets showed a similar trend. Previous work investigating similar relationships across early development revealed positive associations between iSP duration and microstructure of the posterior mid-body (Koerte et al., 2009), an area of the CC now reliably shown to contain fibers connecting bilateral M1 (Hofer and Frahm, 2006; Wahl et al., 2007). However, this relationship does not appear to exist in the subset of mature adults within Koerte and colleagues' (2009) data sample.

Why then, did I observe a positive relationship between M1 fiber tract microstructure and diSP? The current study provides information about transcallosal microstructure along the entire fiber tract, not just from a mid-sagittal slice. Furthermore, I did not use a callosal geometric segmentation approach; therefore our

results are not confounded by including transcallosal fibers that may be irrelevant to the relationships being studied (e.g. fibers connecting bilateral SMAs). Additionally, Koerte and colleagues (2009) provided stimulation to all participants at an absolute intensity (80% of stimulator output) as opposed to a relative intensity of each participant's motor threshold. Previous work has demonstrated that stimulator intensity has a significant effect on both iSP duration and area (Chen et al., 2003). Thus, not adjusting stimulator intensity to an individual's relative motor threshold poses a significant confound for Koerte and colleagues' results. Based upon the current work and taking into account the findings of Wahl et al., (2007), increased microstructure of transcallosal fibers connecting M1s appears to allow for an increased ability to inhibit the contralateral hemisphere in young adults. Thus, while SIHI and iSP reflect differing phenomena, both appear to be related to M1 callosal tract FA in a similar manner. It is worth noting that increased interhemispheric inhibitory capabilities (and increased callosal FA) may not always be beneficial for uni- and bimanual motor control (cf. Fling et al., 2011), whereas previous work suggests that increased interhemispheric inhibition is beneficial to prevent interference on cognitive tasks requiring cortical lateralization (Muller-Oehring et al., 2007).

Finally, I note a relationship, although not significant, between diSP & PMd tract microstructure. Multiple lines of research implicate the PMd in regulating interhemispheric communication, with particular emphasis on inhibitory projections to the contralateral M1 (Giovannelli et al., 2006; Koch et al., 2006; van den Berg et al., 2010). Recently, it was shown that functional connectivity between the left dorsal PMC to the right dorsal PMC and M1 is state dependent, such that its influence on the other

hemisphere is modulated as a function of motor task demands (Bestmann et al. 2008). Specifically, the interhemispheric coupling of PMd with the contralateral M1 appears to be more readily apparent during movement preparation. Therefore it is perhaps not surprising that in the current study where force production was constant, I do not report a significant relationship between PMd microstructure and strength of interhemispheric inhibition. Because motor planning demands are quite low, participants are likely operating under feedback control.

Conclusions and Future Directions

I have demonstrated the ability to map transcallosal sensorimotor fiber pathways and have provided an atlas in MNI space for future use. In addition I report a positive relationship between interhemispheric fiber microstructure and strength of volitional interhemispheric inhibition. Future work is still required to describe how modulation of these interhemispheric inhibitory effects relates to motor control. As there are sparse interhemispheric connections between the homologous hand M1 areas future work would also benefit by further describing muscle specificity of the iSP. For example, it may be that the iSP is stronger in more proximal muscles with more interhemispheric connections. Future work investigating topographical specificity of stimulation location on iSP would also be beneficial. For example, it would be of interest to identify whether stimulation of areas with known inhibitory effects on the contralateral M1, such as the ipsilateral SMA or PMd, also evokes an iSP.

References

- Bartels C, Mertens N, Hofer S, Merboldt KD, Dietrich J, Frahm J, Ehrenreich H. (2008): Callosal dysfunction in amyotrophic lateral sclerosis correlates with diffusion tensor imaging of the central motor system. *Neuromuscul Disord* 18(5):398-407.
- Basser PJ, Pajevic S, Pierpaoli C, Duda J, Aldroubi A. (2000): In vivo fiber tractography using DT-MRI data. *Magn Reson Med* 44(4):625-32.
- Basser PJ, Pierpaoli C. (1996): Microstructural and physiological features of tissues elucidated by quantitative-diffusion-tensor MRI. *J Magn Reson B* 111(3):209-19.
- Bestmann S, Swayne O, Blankenburg F, Ruff CC, Haggard P, Weiskopf N, Josephs O, Driver J, Rothwell JC, Ward NS. (2008): Dorsal premotor cortex exerts state-dependent causal influences on activity in contralateral primary motor and dorsal premotor cortex. *Cereb Cortex* 18(6):1281-91.
- Bonzano L, Tacchino A, Roccatagliata L, Abbruzzese G, Mancardi GL, Bove M. (2008): Callosal contributions to simultaneous bimanual finger movements. *J Neurosci* 28(12):3227-33.
- Bonzano L, Tacchino A, Roccatagliata L, Mancardi GL, Abbruzzese G, Bove M. (2011): Structural integrity of callosal midbody influences intermanual transfer in a motor reaction-time task. *Hum Br Map* 32(2):218-228.
- Boroojerdi B, Diefenbach K, Ferbert A. (1996): Transcallosal inhibition in cortical and subcortical cerebral vascular lesions. *J Neurol Sci* 144(1-2):160-70.
- Carson RG. (2005): Neural pathways mediating bilateral interactions between the upper limbs. *Brain Res Brain Res Rev* 49(3):641-62.
- Chen R. (2004): Interactions between inhibitory and excitatory circuits in the human motor cortex. *Exp Brain Res* 154(1):1-10.
- Chen R, Yung D, Li JY. (2003): Organization of ipsilateral excitatory and inhibitory pathways in the human motor cortex. *J Neurophysiol* 89(3):1256-64.
- Dancause N, Barbay S, Frost SB, Mahnken JD, Nudo RJ. (2007): Interhemispheric connections of the ventral premotor cortex in a new world primate. *J Comp Neurol* 505(6):701-15.
- Davis SW, Dennis NA, Buchler NG, White LE, Madden DJ, & Cabeza R. (2009): Assessing the effects of age on long white matter tracts using diffusion tensor tractography. *Neuroimage*, 46(2):530-541.
- De Gennaro L, Cristiani R, Bertini M, Curcio G, Ferrara M, Fratello F, Romei V, Rossini PM. (2004): Handedness is mainly associated with an asymmetry of corticospinal excitability and not of transcallosal inhibition. *Clin Neurophysiol* 115(6):1305-12.
- Eliassen JC, Baynes K, Gazzaniga MS. (1999): Direction information coordinated via the posterior third of the corpus callosum during bimanual movements. *Exp Brain Res* 128(4):573-7.

- Eliassen JC, Baynes K, Gazzaniga MS. (2000): Anterior and posterior callosal contributions to simultaneous bimanual movements of the hands and fingers. *Brain* 123 Pt 12:2501-11.
- Fang PC, Stepniewska I, Kaas JH. (2008): Corpus callosum connections of subdivisions of motor and premotor cortex, and frontal eye field in a prosimian primate, *Otolemur garnetti*. *J Comp Neurol* 508(4):565-78.
- Ferbert A, Caramia D, Priori A, Bertolasi L, Rothwell JC. (1992): Cortical projection to erector spinae muscles in man as assessed by focal transcranial magnetic stimulation. *Electroencephalogr Clin Neurophysiol* 85(6):382-7.
- Fling BW, Knight CA, Kamen G. (2009): Relationships between motor unit size and recruitment threshold in older adults: implications for size principle. *Exp Brain Res* 197(2):125-33.
- Fling BW, Peltier SJ, Bo J, Welsh RC, Seider RD. (2011): Age differences in interhemispheric interactions: callosal structure, physiological function, and behavior. *Front Neurosci* 5(38).
- Fling BW, Walsh CM, Bangert AS, Reuter-Lorenz PA, Welsh RC, Seidler RD. (In press): Differential Callosal Contributions to Bimanual Control in Young and Older Adults. *J Cogn Neurosci*.
- Garvey MA, Ziemann U, Becker DA, Barker CA, Bartko JJ. (2001): New graphical method to measure silent periods evoked by transcranial magnetic stimulation. *Clin Neurophysiol* 112(8):1451-60.
- Giovannelli F, Borgheresi A, Balestrieri F, Ragazzoni A, Zaccara G, Cincotta M, Ziemann U. (2006): Role of the right dorsal premotor cortex in "physiological" mirror EMG activity. *Exp Brain Res* 175(4):633-40.
- Giovannelli F, Borgheresi A, Balestrieri F, Zaccara G, Viggiano MP, Cincotta M, Ziemann U. (2009): Modulation of interhemispheric inhibition by volitional motor activity: an ipsilateral silent period study. *J Physiol* 587(Pt 22):5393-410.
- Grefkes C, Eickhoff SB, Nowak DA, Dafotakis M, Fink GR. (2008): Dynamic intra- and interhemispheric interactions during unilateral and bilateral hand movements assessed with fMRI and DCM. *Neuroimage* 41(4):1382-94.
- Hanajima R, Ugawa Y, Terao Y, Sakai K, Furubayashi T, Machii K, Kanazawa I. (1998): Paired-pulse magnetic stimulation of the human motor cortex: differences among I waves. *J Physiol* 509 (Pt 2):607-18.
- Heinen F, Glocker FX, Fietzek U, Meyer BU, Lucking CH, Korinthenberg R. (1998): Absence of transcallosal inhibition following focal magnetic stimulation in preschool children. *Ann Neurol* 43(5):608-12.
- Hofer S, Frahm J. (2006): Topography of the human corpus callosum revisited--comprehensive fiber tractography using diffusion tensor magnetic resonance imaging. *Neuroimage* 32(3):989-94.

- Johansen-Berg H, Della-Maggiore V, Behrens TE, Smith SM, Paus T. (2007): Integrity of white matter in the corpus callosum correlates with bimanual co-ordination skills. *Neuroimage* 36 Suppl 2:T16-21.
- Jung P, Ziemann U. (2006): Differences of the ipsilateral silent period in small hand muscles. *Muscle Nerve* 34(4):431-6.
- Kennedy KM, Raz N. (2009): Aging white matter and cognition: differential effects of regional variations in diffusion properties on memory, executive functions, and speed. *Neuropsychologia* 47(3):916-27.
- Kennerley SW, Diedrichsen J, Hazeltine E, Semjen A, Ivry RB. (2002): Callosotomy patients exhibit temporal uncoupling during continuous bimanual movements. *Nat Neurosci* 5(4):376-81.
- Kern KC, Sarcona J, Montag M, Giesser BS, Sicotte NL. Corpus callosal diffusivity predicts motor impairment in relapsing-remitting multiple sclerosis: A TBSS and tractography study. *Neuroimage*.
- Kobayashi M, Hutchinson S, Schlaug G, Pascual-Leone A. (2003): Ipsilateral motor cortex activation on functional magnetic resonance imaging during unilateral hand movements is related to interhemispheric interactions. *Neuroimage* 20(4):2259-70.
- Koch G, Franca M, Del Olmo MF, Cheeran B, Milton R, Alvarez Saucó M, Rothwell JC. (2006): Time course of functional connectivity between dorsal premotor and contralateral motor cortex during movement selection. *J Neurosci* 26(28):7452-9.
- Koerte I, Heinen F, Fuchs T, Laubender RP, Pomschar A, Stahl R, Berweck S, Winkler P, Hufschmidt A, Reiser MF and others. (2009): Anisotropy of callosal motor fibers in combination with transcranial magnetic stimulation in the course of motor development. *Invest Radiol* 44(5):279-84.
- Leemans A, Jeurissen B, Sijbers J, and Jones DK (2009): ExploreDTI: a graphical toolbox for processing, analyzing, and visualizing diffusion MR data. In: 17th Annual Meeting of Intl Soc Mag Reson Med, p. 3537, Hawaii, USA.
- Lenzi D, Conte A, Mainero C, Frasca V, Fubelli F, Totaro P, Caramia F, Inghilleri M, Pozzilli C, Pantano P. (2007): Effect of corpus callosum damage on ipsilateral motor activation in patients with multiple sclerosis: a functional and anatomical study. *Hum Brain Mapp* 28(7):636-44.
- Liuzzi G, Hornib V, Zimerman M, Gerloff C, Hummel FC (2011) Coordination of uncoupled bimanual movements by strictly timed interhemispheric connectivity. *J Neurosci* 42:9111-9117.
- Luders E, Thompson PM, Toga AW. (2010): The development of the corpus callosum in the healthy human brain. *J Neurosci* 30(33):10985-90.
- Mayka MA, Corcos DM, Leurgans SE, Vaillancourt DE. (2006): Three-dimensional locations and boundaries of motor and premotor cortices as defined by functional brain imaging: a meta-analysis. *Neuroimage* 31(4):1453-74.

- Meyer BU, Roricht S, Graf von Einsiedel H, Kruggel F, Weindl A. (1995): Inhibitory and excitatory interhemispheric transfers between motor cortical areas in normal humans and patients with abnormalities of the corpus callosum. *Brain* 118 (Pt 2):429-40.
- Meyer BU, Roricht S, Niehaus L. (1998): Morphology of acallosal brains as assessed by MRI in six patients leading a normal daily life. *J Neurol* 245(2):106-10.
- Meyer BU, Roricht S, Schmierer K, Irlbacher K, Meierkord H, Niehaus L, Grosse P. (1999): First diagnostic applications of transcallosal inhibition in diseases affecting callosal neurones (multiple sclerosis, hydrocephalus, Huntington's disease). *Electroencephalogr Clin Neurophysiol Suppl* 51:233-42.
- Mori S, van Zijl PC. (2002): Fiber tracking: principles and strategies - a technical review. *NMR Biomed* 15(7-8):468-80.
- Muller-Oehring EM, Schulte T, Raassi C, Pfefferbaum A, & Sullivan EV. (2007): Local-global interference is modulated by age, sex and anterior corpus callosum size. *Brain Res*, 1142:189-205.
- Netz J. (1999): Asymmetry in transcallosal inhibition. *Electroencephalogr Clin Neurophysiol Suppl* 51:137-44.
- Ni Z, Gunraj C, Nelson AJ, Yeh IJ, Castillo G, Hoque T, Chen R. (2009): Two phases of interhemispheric inhibition between motor related cortical areas and the primary motor cortex in human. *Cereb Cortex* 19(7):1654-65.
- Oldfield RC. (1971): The assessment and analysis of handedness: the Edinburgh inventory. *Neuropsychologia* 9(1):97-113.
- Pandya DN, Vignolo LA. (1968): Interhemispheric neocortical projections of somatosensory areas I and II in the rhesus monkey. *Brain Res* 7(2):300-3.
- Ridding MC, Brouwer B, Nordstrom MA. (2000): Reduced interhemispheric inhibition in musicians. *Exp Brain Res* 133(2):249-53.
- Rouiller EM, Babalian A, Kazennikov O, Moret V, Yu XH, Wiesendanger M. (1994): Transcallosal connections of the distal forelimb representations of the primary and supplementary motor cortical areas in macaque monkeys. *Exp Brain Res* 102(2):227-43.
- Schmierer K, Niehaus L, Roricht S, Meyer BU. (2000): Conduction deficits of callosal fibres in early multiple sclerosis. *J Neurol Neurosurg Psychiatry* 68(5):633-8.
- Serrien DJ, Strens LH, Oliviero A, Brown P. (2002): Repetitive transcranial magnetic stimulation of the supplementary motor area (SMA) degrades bimanual movement control in humans. *Neurosci Lett* 328(2):89-92.
- Stancak A, Cohen ER, Seidler RD, Duong TQ, Kim SG. (2003): The size of corpus callosum correlates with functional activation of medial motor cortical areas in bimanual and unimanual movements. *Cereb Cortex* 13(5):475-85.

- Sullivan EV, Rohlfing T, Pfefferbaum A. (2010a): Longitudinal study of callosal microstructure in the normal adult aging brain using quantitative DTI fiber tracking. *Dev Neuropsychol* 35(3):233-56.
- Sullivan EV, Rohlfing T, Pfefferbaum A. (2010b). Quantitative fiber tracking of lateral and interhemispheric white matter systems in normal aging: relations to timed performance. *Neurobiol Aging* 31(3):464-81.
- Triggs WJ, Calvanio R, Macdonell RA, Cros D, Chiappa KH. (1994): Physiological motor asymmetry in human handedness: evidence from transcranial magnetic stimulation. *Brain Res* 636(2):270-6.
- Tuller B, Kelso JA. (1989): Environmentally-specified patterns of movement coordination in normal and split-brain subjects. *Exp Brain Res* 75(2):306-16.
- Vaillancourt DE, Newell KM. (2003): Aging and the time and frequency structure of force output variability. *J Appl Physiol* 94(3):903-12.
- van den Berg FE, Swinnen SP, Wenderoth N. (2010): Hemispheric Asymmetries of the Premotor Cortex are Task Specific as Revealed by Disruptive TMS During Bimanual Versus Unimanual Movements. *Cereb Cortex* 20(12):2842-51.
- Wahl M, Lauterbach-Soon B, Hattingen E, Jung P, Singer O, Volz S, Klein JC, Steinmetz H, Ziemann U. (2007): Human motor corpus callosum: topography, somatotopy, and link between microstructure and function. *J Neurosci* 27(45):12132-8.
- Wassermann EM, Fuhr P, Cohen LG, Hallett M. (1991): Effects of transcranial magnetic stimulation on ipsilateral muscles. *Neurology* 41(11):1795-9.
- Werhahn KJ, Kunesch E, Noachtar S, Benecke R, Classen J. (1999): Differential effects on motorcortical inhibition induced by blockade of GABA uptake in humans. *J Physiol* 517 (Pt 2):591-7.
- Witelson SF. (1989): Hand and sex differences in the isthmus and genu of the human corpus callosum. A postmortem morphological study. *Brain* 112 (Pt 3):799-835.

CHAPTER III

Task-dependent effects of interhemispheric inhibition on motor control

Published with stylistic modifications as - Fling BW & Seidler RD. (*In press*). Task-dependent effects of interhemispheric inhibition on motor control. *Behavioural Brain Research*

Abstract:

Interhemispheric inhibition (IHI) is the ability to mitigate the spread of neuronal excitability between cortical hemispheres. Previous work has demonstrated that IHI is increased during both unimanual and independent bimanual movements of the upper limbs in comparison to synchronous bimanual movements, likely to minimize interference between the hands. The goal of the current study was to investigate the relationship(s) between motor performance and individual differences in inhibitory capacity of the corpus callosum. To assess IHI, I utilized the ipsilateral silent period technique (iSP; evoked by suprathreshold transcranial magnetic stimulation), which elicits inhibition of volitional motor activity. Participants performed three force production tasks: 1) unimanual (right hand) constant force, 2) bimanual constant force, (bimanual synchronous) and 3) bimanual with right hand constant force and left hand sine wave tracking (bimanual independent). I found that individuals with greater IHI capacity demonstrated reduced mirror EMG activity in the left hand during unimanual right hand contraction. However, these same individuals demonstrated the poorest performance during the bimanual independent force production task. I suggest that a

high capacity for IHI from one motor cortex to another can effectively prevent “motor overflow” during unimanual tasks, but it can also limit the ability for optimal control during independent bimanual tasks, possibly due to a reduced capability for interhemispheric cooperation.

Introduction

Imagine a concert pianist with exceptional bimanual coordination yet exquisite individuated finger control. This skillful act requires that hand movements are coordinated in time and space, while minimizing intermanual crosstalk or interference. The ability of the brain's two hemispheres to coordinate such movements relies heavily upon callosally mediated communication. Interhemispheric communication consists of a complex balance of facilitatory and inhibitory interactions. Decades of research has provided insight into the role of the corpus callosum and interhemispheric communication for a wide array of cognitive, motor, sensory, and perceptual tasks. Previous work in the cognitive literature has demonstrated that the degree to which interhemispheric cooperation underlies performance varies with the complexity of the task being performed. Specifically, interhemispheric interaction aids the performance of complex tasks more than simpler ones (e.g., Banich & Belger, 1990; Reuter-Lorenz et al., 1999). The results of Weismann & Banich (2000) demonstrate that even when within- and across-hemisphere processing are equally possible, the hemispheres couple their processing when tasks are complex but not when they are relatively simple.

The ability to minimize interference between hemispheres, often referred to as “motor overflow”, is termed interhemispheric inhibition (IHI; cf. Hoy et al. 2004). IHI is the suppression of activity of a brain region by the contralateral cortex with impulses transmitted via the corpus callosum. While some degree of IHI is necessary to prevent interference of control processes between the two cortices (cf. Bloom & Hynd 2005; Fling et al. 2011), emerging work has begun to indicate that low levels of IHI may be beneficial for the performance of some complex bimanual tasks (Ridding et al. 2000; Shim et al. 2005).

Interhemispheric inhibition has been shown to increase during tasks when the upper limbs have different movement goals. For example, during unilateral movement IHI increases to suppress unwanted motor (or mirror) activity in the opposite limb (cf. Cincotta & Ziemann, 2008; Vercauteren et al. 2008). Furthermore, several studies report increased IHI during multi-limb movements where each effector has different movement goals as compared to movements where the limbs move symmetrically (Stinear & Byblow, 2002; Fujiyama et al. 2009; Giovannelli et al. 2009). Thus it stands to reason that by increasing IHI during such movements, individuals are able to maintain partitioned cortical activity resulting in less interference between the right and left motor cortices. Giovannelli and colleagues (2009) demonstrated that IHI (assessed by inducing an ipsilateral silent period (iSP)) is modulated across task conditions. Specifically, the amount of IHI (assessed by iSP of the dominant hand during maximal contraction) increased as non-dominant index finger movement changed from i) full relaxation to ii) maximal isometric contraction; iii) repetitive thumb-to-index tapping, and iv) sequential tapping of different targets. While the authors demonstrate that IHI is modulated across task conditions, no motor performance metrics were analyzed. Thus it remains unclear how the amount of IHI, or individual differences in the capacity to modulate IHI across conditions, is related to performance.

Although IHI is increased during bimanual independent tasks, emerging work in musicians as well as training interventions in neurologically healthy young adults have begun to indicate that the relationship between IHI and performance on such tasks may follow an inverted-U relationship. That is to say there may be an optimal amount of IHI above which performance begins to decline in a similar fashion to those individuals with

compromised inhibitory capacity such as children with premyelinated interhemispheric fibers (Koerte et al. 2009) or patients with multiple sclerosis (Boroojerdi et al. 1998). In accordance with this notion, IHI is *reduced* in musicians compared to non-musicians (Ridding et al. 2000). While it is unclear whether this reduction in IHI represents an adaptive change related to exceptional control of finger movements or a maladaptive change brought about by overuse of the hand from extensive training (Nordstrom & Butler, 2002), recent training interventions appear to support the former hypothesis (Hortobagyi et al. in press; Shim et al. 2005). These studies demonstrate that interhemispheric inhibitory projections can show plastic changes that favor the execution of a practiced task by decreasing the amount of IHI. Based on the literature reviewed here I believe it is possible that increased levels of IHI are beneficial during unimanual movement to prevent motor overflow, whereas greater IHI may be detrimental to motor performance during asymmetrical bimanual tasks due to “over-inhibition” of the contralateral cortex. To my knowledge this has yet to be investigated.

The capacity for IHI is highly correlated with the microstructure of callosal fibers connecting bilateral M1's in young adults (as reported in Chapter 2 and in Wahl et al. 2007). Recent work investigating corpus callosum microstructure (assessed with diffusion tensor imaging) has lent insight into the relationship between callosal structure and motor performance across a range of unimanual and bimanual tasks. Johansen-Berg and colleagues (2007) reported that young adults with increased microstructure of callosal fibers connecting primary and secondary motor cortices were better able to coordinate the two hands during a synchronous tapping task (a task requiring relatively low IHI). Conversely, I have recently shown that young adults with increased

microstructural quality of callosal regions connecting sensorimotor cortical areas perform more poorly on unimanual and asynchronous bimanual finger tapping tasks (which require relatively high IHI) (Fling et al., in press). Although neither of the aforementioned studies measured IHI, it appears that interhemispheric connections and inhibition are integral for the performance of both unilateral and coordinated bilateral tasks. The relationship of these variables to motor performance may be task dependent.

There is a gap in the current literature describing the relationship(s) between interhemispheric inhibitory capacity and motor performance. The use of individual differences approaches to study the neural bases of motor behavior has recently been touted as a fruitful avenue for understanding how brain structural and neurophysiological characteristics affect motor performance (Kanai and Rees, 2011). Here I utilized such an approach to investigate the relationship(s) between inhibitory capacity of the corpus callosum in young adults and performance on three different force production tasks: 1) unimanual (right hand) constant force production, 2) bimanual constant force production (bimanual synchronous), and 3) bimanual with the right hand performing constant force and the left hand tracking a sine wave target (bimanual independent). Capacity for IHI was assessed by eliciting iSPs in the dominant hand during all force production conditions. Regardless of any condition effect I hypothesized that individuals with greater IHI capacity would be able to inhibit motor overflow during unimanual contraction to a greater extent. However, I predicted that these same individuals would demonstrate poorer performance on the bimanual independent task.

Methods

Participants

Sixteen young adults (range: 19-28 yr of age; mean: 22.1 ± 3.1 yr; 8 males) participated in the current study. All individuals were right-hand dominant as assessed by the Edinburgh Handedness Inventory (mean: 77.4 ± 0.09 ; Oldfield, 1971). Any individuals with a history of neurological insult (e.g. stroke, epilepsy) or those taking medications with contraindications for transcranial magnetic stimulation were excluded, as were any individuals with musical training greater than 3 years (see screening questionnaire in Appendix 1). This experiment was approved by the Medical Institutional Review Board (IRBMED) of the University of Michigan. Participants gave their informed written consent prior to the experiment and were compensated for their time.

Experimental Task

Participants were seated in a chair with both their dominant and non-dominant forearms resting on a table. Shoulders were abducted at approximately 45° , the elbows were flexed at approximately 90° , and the forearms were pronated with the palms of the hand lying flat on the custom apparatus. The wrist, third, fourth, and fifth fingers were constrained from moving, isolating force production to the index finger. A pre-amplified force transducer (OMEGA LC509-015 Beam Load Cell) was positioned at the lateral aspect of the proximal interphalangeal joint of the isolated index finger to record compressive isometric force (output: 0.5-9.5 Vdc; excitation: $24 \text{ Vdc} \pm 4 \text{ Vdc}$).

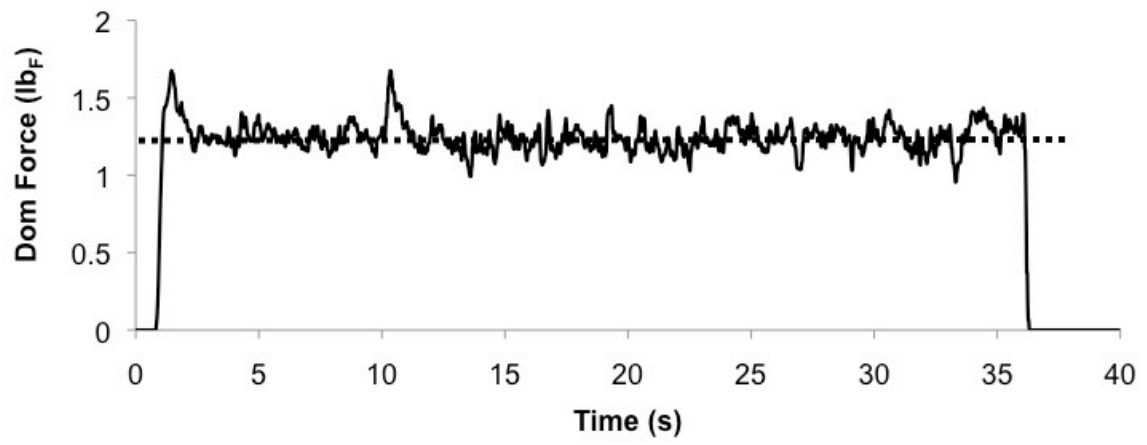
Surface electromyography and motor evoked potentials (MEPs) elicited with transcranial magnetic stimulation (TMS) were recorded from the first dorsal interosseous (FDI) muscle of both hands using 4 mm Ag/AgCl⁻ electrodes placed on the muscle in a belly-tendon arrangement. Task-related surface EMG and MEP data were recorded using Biopac hardware and AcqKnowledge software (BIOPAC Systems Inc., Goleta, CA).

The raw EMG signal was collected and digitized at 2000 Hz, amplified and band pass filtered (10-1000 Hz). Data were collected at 2kHz as it has previously been shown to produce the most accurate estimate of mean consecutive difference (MCD) of pre-stimulus EMG activity, which is used to calculate the iSP (Garvey et al. 2001). To assess maximal voluntary contractile (MVC) force of the FDI, participants were instructed to press as hard as possible on the load cell using index finger abduction of the dominant hand for three consecutive 6-second trials. The force applied to the load cell was displayed on the video monitor, providing online visual feedback during the MVC trials. The highest force sample in each trial was averaged across three MVC trials providing an estimate of the participants' MVC. A minimum 90-second rest period was provided in between each MVC trial. The same procedure was subsequently performed on the non-dominant hand.

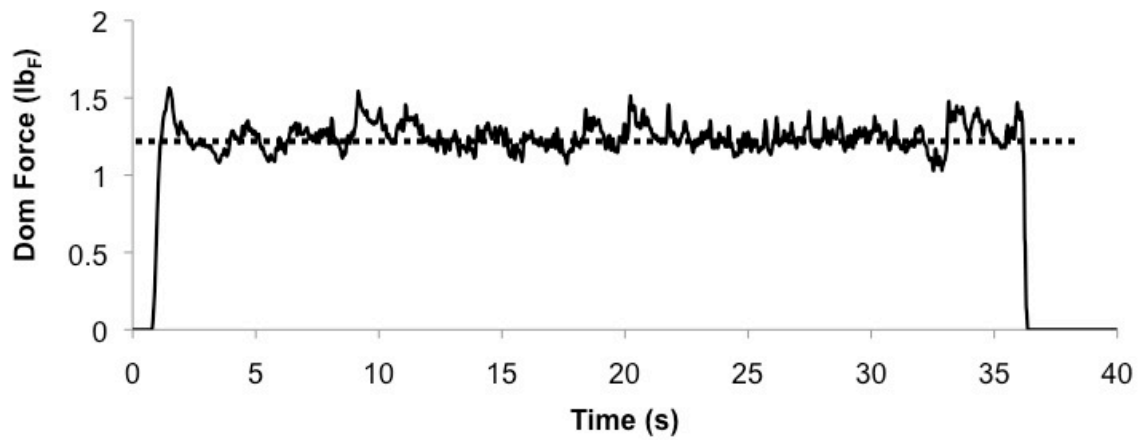
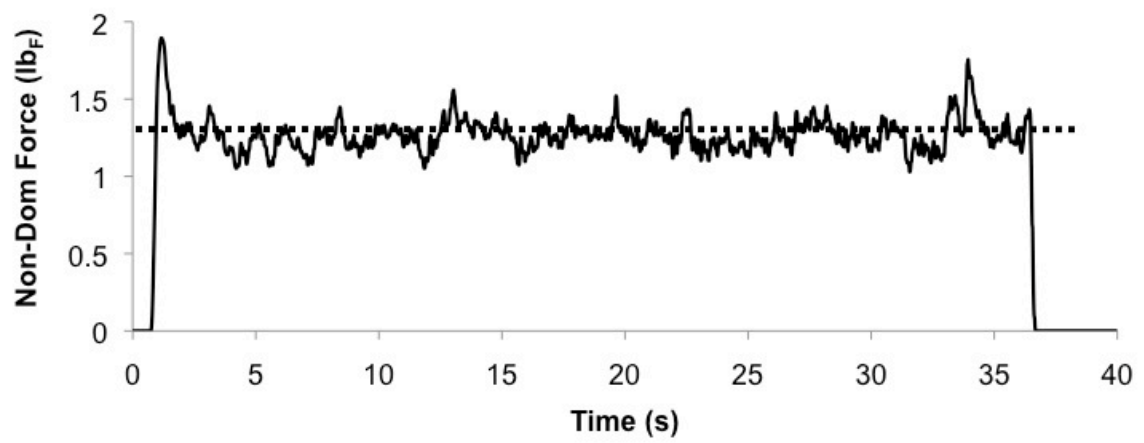
Participants performed three different force production tasks: 1) unimanual isometric force of the dominant hand at a constant force target level (**Figure 3.1A**), 2) bimanual synchronous isometric force with both hands producing the same constant force target level (bimanual synchronous task; **Figure 3.1B**), and 3) dominant hand isometric force at a constant force target level while the non-dominant hand matched a 1 HZ sine wave (bimanual independent task; **Figure 3.1C**). Thus, in all conditions the dominant hand always performed the same constant force production task while the non-dominant hand's involvement varied across the three conditions. The order of conditions was counter-balanced across participants. For all conditions the force target levels used in the experiment were scaled to 20% of each individual subject's MVC (during the bimanual independent task the peak force of the non-dominant sine wave-matching hand was also

20% MVC). Thus the dominant hand always produced a constant isometric force at 20% MVC across the three conditions while the varying role of the non-dominant hand (i.e. the right M1) was expected to modulate IHI demands. Feedback windows were presented on one video monitor and were aligned parallel on top of each other with the upper window providing feedback of the non-dominant hand force trace while the lower window provided feedback for the dominant hand. During the unimanual and bimanual synchronous force production tasks participants viewed a yellow, horizontal target line that spanned the width of a video monitor (placed at 20% of MVC for each respective hand). During the bimanual independent movement condition the target for the dominant hand was identical to the other two conditions while the target for the non-dominant hand was a yellow 1-Hz sine wave target line with the peak force of each sine wave placed at 20% of MVC. Force output was sampled at 200 Hz; for each instant in time that force was sampled (.005s), a green pixel appeared in the center of the respective feedback window corresponding to the amount of force produced. This provided participants with on-line, real-time visual feedback of their performance with minimal horizontal saccades required. For each condition participants were instructed to match their green force trace to the respective yellow target line for three 35-second trials per condition. Participants were provided five minute rest breaks in between each trial (a total of 9 trials) in an attempt to minimize fatigue. Fatigue minimization is supported by the fact that no behavioral differences were noted across trials within a given condition.

A



B



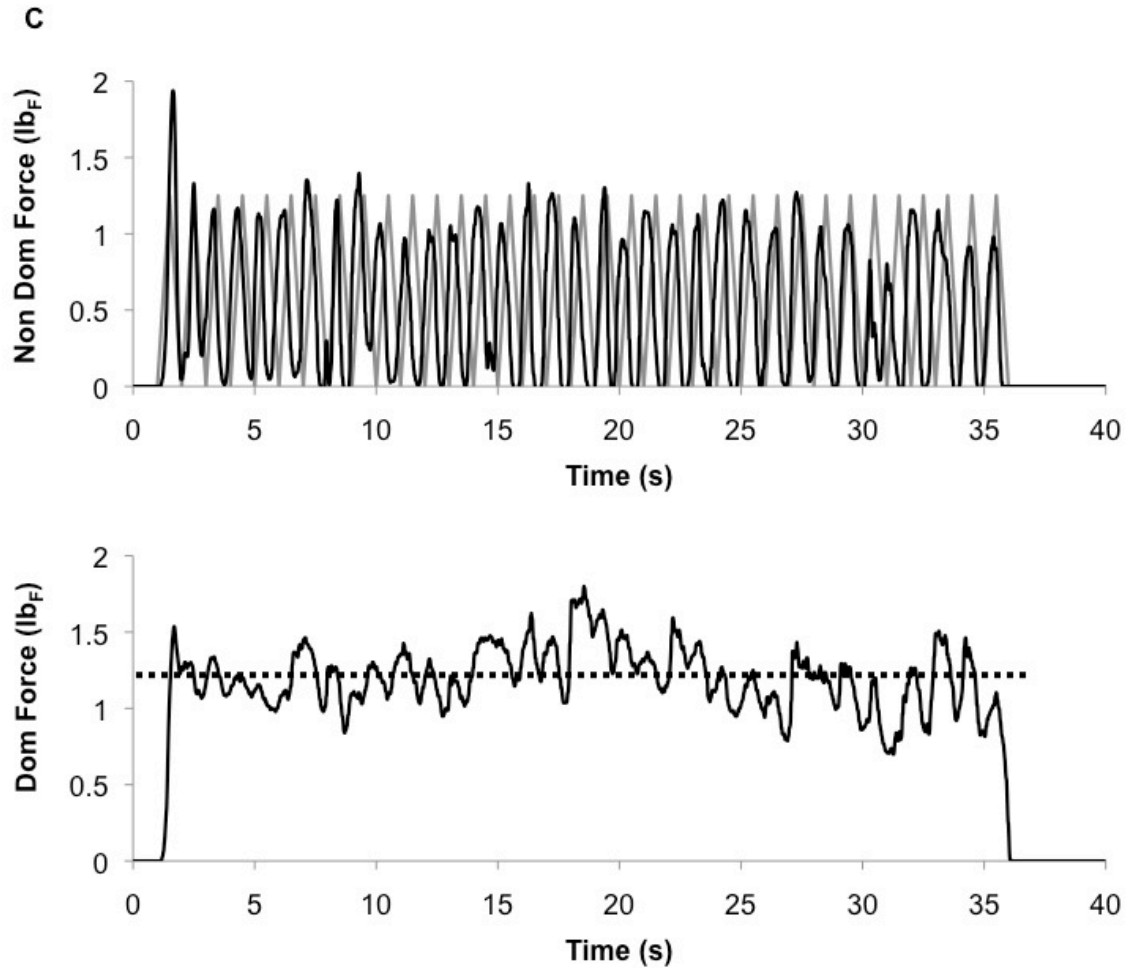


Figure 3.1 – Representative force traces for the: **A)** dominant hand unimanual force condition, **B)** non-dominant (upper panel) and dominant hand (lower panel) during a bimanual synchronous force production trial and, **C)** non-dominant (upper panel) and dominant hand (lower panel) during the bimanual independent force production task. For all isometric force conditions the horizontal dotted line indicates the force target, during the bimanual independent force task the gray line indicates the 1 Hz sine wave target for the non-dominant hand. Dom = dominant hand; Non-Dom = non-dominant hand.

Interhemispheric Inhibition

Interhemispheric inhibition was measured by evoking an ipsilateral silent period (iSP) in the dominant hand FDI. The iSP is elicited by focal TMS of the M1 ipsilateral to the hand making a voluntary contraction, leading to a brief suppression of voluntary

activity in the electromyogram signal of this muscle (Meyer et al. 1995). The iSP reflects transcallosal inhibition of volitional motor activity, and appears to be particularly well-suited to investigate interhemispheric control of voluntary cortical motor output (Giovannelli et al. 2009).

Prior to performing the experimental paradigm, I used a Magstim Rapid magnetic stimulator (The Magstim Company Ltd, Spring Gardens, Whitland, Carmarthenshire, UK) and a focal figure of eight coil (diameter of each wing 70 mm) to identify the right M1 hotspot for the left FDI. The coil was placed tangential to the scalp with the handle pointing backwards and 45° away from the midline (Chen et al. 2003). The optimum site in the right M1 (hotspot) for eliciting motor responses in the left FDI was identified at supra-threshold intensity. This location was utilized to elicit iSPs from the right FDI as it has previously been shown that the topography of the contralateral MEP and the iSP correspond closely (Wasserman et al. 1991). Resting motor threshold (RMT) was determined to the nearest 1% of the maximum stimulator output. Using standard protocol, the RMT was defined as the minimum stimulus intensity which elicited MEPs > 50 μ V in at least 5 out of 10 consecutive trials (Triggs et al. 1994).

During the unimanual and bimanual synchronous force conditions, iSPs were elicited from the dominant hand once participants reached the target force level by stimulation given at 120% of resting motor threshold to the right motor cortex (See Chapter 2). During the bimanual independent condition stimulations were always applied during the upward phase of the non-dominant hand sine wave force production task. During each 35-second trial, a minimum of five iSPs were evoked with an interstimulus interval jittered between 5-8 seconds (Garvey et al. 2001; Jung & Ziemann, 2006).

During the unimanual condition, EMG data were also collected and monitored from the non-dominant hand to ensure full relaxation and that the TMS coil was always in the appropriate location over the right M1. During one trial in two different participants, MEPs ceased to be elicited from the left FDI. On both occasions data collection was halted and the right M1 hotspot for the FDI was re-located.

Data Analysis

Force data

The initial 5 seconds of each force time series was removed to eliminate the transitory performance in achieving the force target. Force data were digitally filtered using a 4th order dual pass Butterworth filter with a low-pass cutoff frequency of 20 Hz. All data processing and subsequent time and frequency analyses were performed using software written in MATLAB (The MathWorks Inc., Natick, MA). Similar to previous work, the amount of force output variability was assessed by calculating the within-trial mean (normalized to the force target goal and expressed as a percentage throughout the remainder of this chapter) and the root mean square error (RMSE) from the target (Vaillancourt et al. 2003). I also performed a power spectral density analysis to assess peak frequency of the non-dominant hand during the bimanual independent condition to ensure that individuals were adhering to the 1 Hz frequency.

Finally, the structure of force variability was assessed by calculating the approximate entropy (ApEn) of the dominant hand's force output in each condition. ApEn returns a single value (between 0 and 2) that reflects the predictability of future values in a time series based on previous values and has been used to assess force

production during both constant isometric and 1 Hz sine wave tasks (Slifkin and Newell, 1999; Vaillancourt and Newell, 2003). An increase in the ApEn of a signal reflects increased noisiness or complexity in its time domain structure (Pincus, 1991). Thus, for a completely random signal (e.g. white Gaussian noise) each value in the time series is independent from the previous value and the ApEn trends toward 2. The algorithm and parameter settings ($m = 2$; $r = 0.2 * \text{standard deviation of the signal}$) used in the current study reflect previous work (Slifkin and Newell, 1999; Vaillancourt and Newell, 2003). A detailed description of the multi-step algorithm is available elsewhere (see Appendix of Slifkin and Newell, 1999).

Ipsilateral Silent Period (iSP)

The iSP was calculated by using an objective, graphical method described in detail by Garvey and colleagues (2001). Single EMG trials (15 total per participant) were rectified and averaged across trials. Using a custom MATLAB program (The MathWorks Inc., Natick, MA), upper and lower variation limits of the EMG signal were calculated by determining the mean consecutive difference (MCD) of EMG data points 100ms prior to stimulation: mean pre-stimulus EMG \pm ($|\text{MCD}| \times 1.77$). These limits encompassed 95% of possible pre-stimulus EMG data points (equivalent to two standard deviations). Onset and offset of iSP were identified using the criteria described in Chapter 2. In addition to measuring the onset, offset and duration of the iSP, the depth of the iSP was defined in two ways as previously described by Jung and Ziemann (2006): (1) the minimum EMG level during the iSP (diSP-max), and (2) the average EMG level during the iSP (diSP). The diSP and diSP-max were expressed as percentages of the

mean prestimulus EMG. Therefore, the larger the diSP and diSP-max, the greater the suppression of ipsilateral EMG activity during the iSP. This is interpreted as increased interhemispheric inhibition (Garvey et al. 2001).

Statistical Analysis

Separate repeated measures analyses of variance were used to analyze measures of IHI and dominant hand force production with iSP onset, iSP duration, diSP, diSP-max, RMSE, ApEn, and normalized mean force production treated as within-subject variables across the three conditions. Significance was set at an alpha of 0.05 (SPSS 18.0) and the Huyn-Feldt epsilon was computed to test for sphericity; I interpreted corrected *P* values in cases of violation. Significant main effects were subjected to post-hoc paired *t*-tests and Bonferroni-corrected for multiple comparisons. I performed linear regression to investigate the relationship between diSP and dominant hand variability (RMSE) on the three different force production tasks. I also correlated non-dominant hand EMG activity during the unimanual force condition (i.e. motor overflow) with diSP. Motor overflow was calculated by taking the integral of non-dominant hand EMG during unimanual dominant hand contraction. All correlation analyses using diSP as a predictor were corrected for multiple comparisons. Additionally, I used linear regression to test for associations between each hand's force output during the bimanual synchronous and bimanual independent force production tasks. Thus, I correlated force output between the dominant and non-dominant hand within each participant for the two bimanual conditions. All data are presented as mean \pm S.E.M. unless otherwise noted.

Results

Force Data

The maximal voluntary contraction values from the dominant and non-dominant FDI were 4.3 ± 0.6 lb_F and 3.9 ± 0.5 lb_F, respectively. While a paired *t*-test revealed a trend towards higher MVC in the dominant hand, no statistical difference was observed ($t_{1,15} = 2.1$; $P < 0.07$).

Participants' force production parameters including accuracy, variability (RMSE) and ApEn can be viewed in **Table 3.1**. Additionally, during the bimanual independent condition participants' non-dominant hand average frequency was 0.93 ± 0.01 Hz, indicating that they were able to adhere to this relatively difficult bimanual force production task (**Figure 3.1C**).

A repeated measures ANOVA revealed a significant main effect of condition on dominant hand force variability ($F_{2,30} = 45.8$; $P < 0.001$), mean normalized force ($F_{2,30} = 31.8$; $P < 0.001$), and ApEn ($F_{2,30} = 41.8$; $P < 0.001$). Post hoc tests for dominant hand force variability revealed a significant difference between all conditions ($t_{1,15} > 5.0$; $P < 0.001$; **Table 3.1**), such that variability was greatest during the bimanual independent task and lowest during the unimanual task. Post hoc paired *t*-tests for normalized dominant hand mean force revealed that force production was significantly lower during the bimanual independent condition than either the unimanual ($t_{1,15} = 6.7$; $P < 0.001$) or the bimanual synchronous conditions ($t_{1,15} = 5.3$; $P < 0.001$). No difference in normalized mean force was observed between the unimanual and bimanual synchronous conditions ($t_{1,15} = 1.7$; $P > 0.15$; **Table 3.1**). Paired *t*-tests for dominant hand ApEn also revealed a significant difference between all conditions ($t_{1,15} > 5.6$; $P < 0.001$ for all conditions;

Table 3.1), such that ApEn was lowest during the bimanual independent condition and highest during the unimanual task. Further, I note that dominant hand force variability and ApEn were significantly correlated in all conditions in an inverse fashion, i.e. higher variability was related to lower ApEn ($r > -0.6$; $P < 0.01$ for all conditions).

Force Condition	Normalized Mean Force (%)	Variability (RMSE)	ApEn	B/w Hand Correlations (r)
Unimanual	93.7 ± 1.5^a	0.031 ± 0.004^a	0.53 ± 0.06^a	-
Bim. Synchronous	90.9 ± 2.0^a	0.048 ± 0.005^b	0.47 ± 0.08^b	0.69*
Bim. Independent	74.2 ± 3.4^b	0.088 ± 0.008^c	0.36 ± 0.06^c	0.34

Table 3.1 – Constant isometric force production variables describing dominant hand performance across the three conditions. The dominant hand was most accurate (normalized mean force) and demonstrated the least variability (RMSE) during the unimanual condition. Conversely, dominant hand approximate entropy was lowest during the bimanual independent task. The force output timecourse was significantly correlated between the two hands during the bimanual synchronous condition, but not during the bimanual independent condition. Values are mean \pm standard deviation. Bim. = bimanual; ApEn = approximate entropy; B/w = between. The same letter within each column indicates metrics of force performance that were not significantly different from each other. * $P < 0.01$.

iSP Data

Resting motor threshold (RMT) was $63.6\% \pm 4.9\%$ of maximal stimulator output, thus average stimulation intensity to elicit iSPs was $76.3\% \pm 5.7\%$ (i.e. 120% of RMT). Ipsilateral silent periods were reliably produced in all 16 participants. An average of 15.6 stimulations (and a maximum of 19) were required to elicit the 15 iSPs used for data analysis within each condition. Participants' IHI characteristics including iSP onset, iSP duration, diSP and diSP-max can be viewed in **Table 3.2**. A repeated measures ANOVA revealed no significant main effect of condition on iSP onset ($F_{2,30} = .37$; $P > 0.68$), iSP duration ($F_{2,30} = 0.02$; $P > 0.96$), diSP ($F_{2,30} = 1.3$; $P > 0.27$), nor diSP-max ($F_{2,30} = .45$; $P > 0.62$). Due to the fact that no differences were observed, I used the iSP metrics

obtained during the unimanual force production task for the remainder of this chapter as a measure of individual differences in IHI capacity.

Force Condition	iSP Onset (ms)	iSP Duration (ms)	diSP (%)	diSP-max (%)
Unimanual	38.4 (3.2)	27.4 (8.7)	73.6 (6.3)	91.9 (4.4)
Bim. Synchronous	37.9 (2.6)	27.1 (10.1)	71.4 (9.6)	92.4 (4.2)
Bim. Independent	38.2 (2.7)	26.9 (7.5)	70.0 (9.2)	91.2 (5.4)

Table 3.2 – Characteristics of dominant hand iSPs across the three force production conditions. No differences were noted among any of the dependent measures. Values are mean \pm standard deviation. Bim. = bimanual.

Relationships between EMG activity, force variability and IHI

I first performed linear regression relating the capacity for IHI, as assessed by diSP, to the amount of non-dominant EMG activity (motor overflow) observed during the dominant hand unimanual force production task. Although non-dominant hand EMG activity was relatively small in all participants (0.19 ± 0.008 mV*s), motor overflow and IHI were significantly negatively correlated ($r = -0.76$; $P < 0.001$). This suggests that during unimanual contraction those participants with greater IHI capacity were able to more effectively inhibit activity in the contralateral M1 and as a result had less muscle activity in the non-dominant hand (**Figure 3.2**). In addition, I regressed diSP against dominant hand force variability during the three different conditions. I found no relationship between diSP and dominant hand variability during the unimanual ($r = -0.13$; $P > 0.4$) or the bimanual synchronous condition ($r = -0.19$; $P > 0.25$). In contrast, a significant relationship was observed between diSP and dominant hand variability during the bimanual independent condition ($r = 0.59$; $P < 0.01$; **Figure 3.3**) indicating that

individuals with increased inhibitory capacity were poorer at maintaining steady force during this particular task.

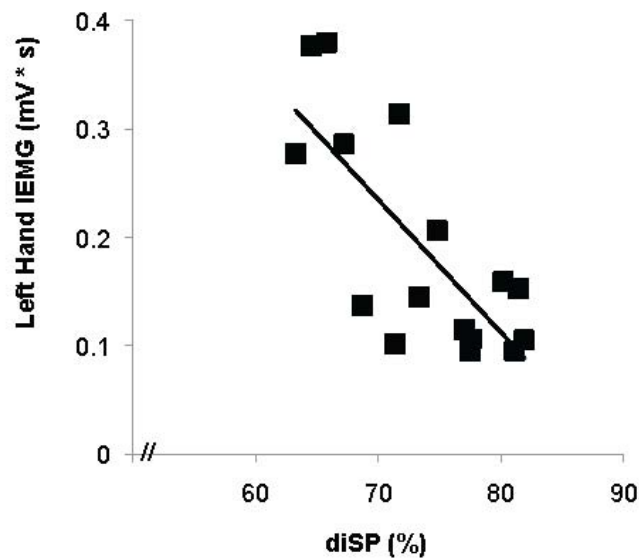


Figure 3.2 – Scatterplot of interhemispheric inhibition, as assessed by diSP, and non-dominant hand EMG (motor overflow) during unimanual dominant hand contraction. A significant, negative association was found ($r = -0.76$; $P < 0.001$) indicating that individuals with greater IHI were able to suppress activity in the resting non-dominant hand (motor overflow) during unimanual dominant hand force production. IEMG = integral of the rectified EMG.

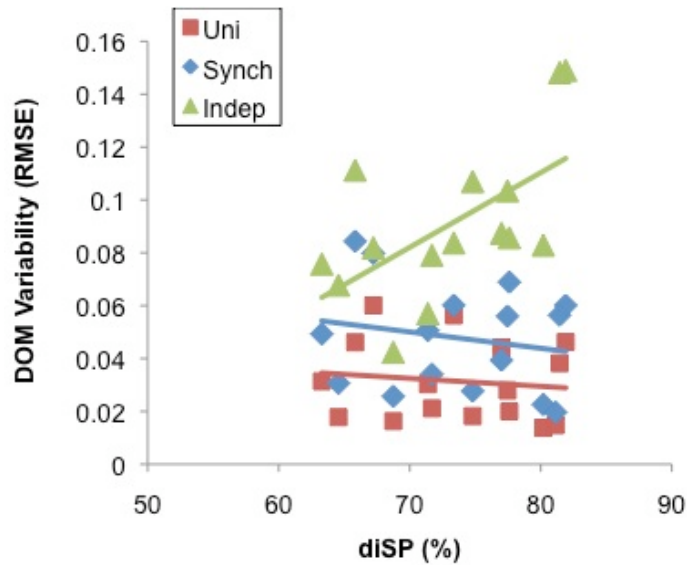


Figure 3.3 – Scatterplot of interhemispheric inhibition, as assessed by diSP, and dominant hand variability during all conditions. A significant, positive relationship was observed for the independent condition indicating that individuals with greater IHI had greater dominant hand force variability during the bimanual independent task ($r = 0.59$; $P < 0.01$). No relationship was observed for the unimanual or the bimanual synchronous task. Bim; = bimanual; Indep = independent; Synch = synchronous; Uni = unimanual; DOM = dominant hand.

For both bimanual tasks I also performed linear regression to describe associations between dominant and non-dominant hand force output. The time course of force produced by each hand was significantly correlated during the bimanual synchronous condition ($r = 0.69$; $P < 0.01$), but not during the bimanual independent condition ($r = 0.34$; $P > 0.1$). For each of these correlations I performed an r-to-Z transformation and regressed dominant hand force variability (RMSE) against between-hand force relationships (as assessed by their Z-score) within each bimanual condition. The extent to which the time course of force production was correlated between the two hands during the bimanual synchronous condition was significantly inversely related to dominant hand variability ($r = -0.7$; $P < 0.001$; **Figure 3.4**). That is, participants with greater linked bimanual force output performed the task with less dominant hand

variability during the synchronous condition. A similar trend was observed for the bimanual independent condition, however the relationship was not significant ($r = -0.33$; $P > 0.1$).

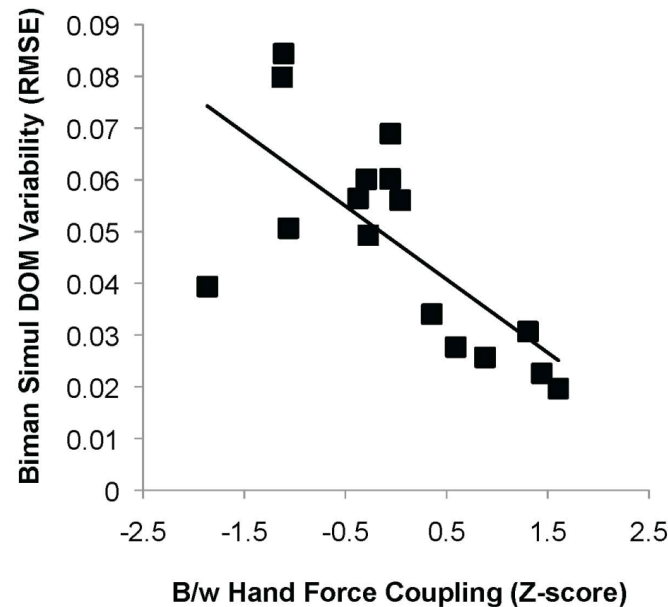


Figure 3.4 – Scatterplot of dominant hand force variability (RMSE) during the bimanual synchronous force production task and between-hand force coupling (assessed with a Fisher r-to-Z transformation). A significant, inverse association ($r = -0.70$; $P < 0.01$) was observed demonstrating that individuals performed the task better when they coupled the output of the two hands to a greater extent. Biman = bimanual; Simul = synchronous; DOM = dominant hand.

Discussion

In the current study I observed task-dependent relationships between manual motor performance and interhemispheric inhibitory capacity. I found a continuum of variability in dominant hand force production across the three conditions investigated. Specifically, dominant hand variability increased (with a concomitant decrease in mean force production) when the non-dominant hand was required to produce either an identical or an independent force trajectory as compared to the unimanual task. In agreement with the results of Slifkin and Newell (1999) I also found that increases in

force variability were accompanied by decreases in approximate entropy. Contrary to my hypothesis, I found no modulation of IHI across the three force production tasks. Despite the lack of condition effects on the iSP, I found several relationships with motor performance. Consistent with my hypotheses, during unimanual force production, individuals with greater IHI capacity were able to more effectively reduce motor overflow activity from the active to the resting hand. Conversely, those individuals with greater IHI were poorer at the bimanual independent task. I interpret this to mean a high level of IHI is detrimental during tasks where the two hands are performing independent movements.

Interhemispheric interactions vary with task conditions (Verstynen and Ivry, *in press*). Inhibition between the primary motor cortices is a necessity for the skilled performance of unimanual and bimanual motor control, particularly for tasks that require independent spatio-temporal paths for each hand. While some level of IHI is necessary, I show that greater inhibitory capacity is negatively associated with the ability to maintain steady force production when the contralateral hand is performing an independent action. This is in agreement with previous work demonstrating that interference related to bimanual force production arises from callosal interactions (Diedrichsen et al., 2003). These results suggest that individuals with greater IHI likely have a reduced capacity for interhemispheric cooperation, resulting in poorer performance on independent bimanual motor tasks. That is to say, these individuals may be “over-inhibiting” the contralateral cortex, thereby preventing each hemisphere from accurately activating its respective neuronal circuitry. Thus, while some level of IHI is required to coordinate movement, it

appears that the ability to suppress IHI and increase interhemispheric cooperation favors the execution of bimanual tasks.

Studies conducted with highly trained (and developing) musicians support the hypothesis that reduced IHI is beneficial for bimanual tasks where the two hands have independent movement goals (Nordstrom & Butler 2002; Ridding et al. 2000). Long-term training within critical developmental periods has the potential to induce regionally specific neural adaptations, both at the anatomical and functional level. The anterior half of the corpus callosum is larger in adult musicians who began training prior to the age of 7 when compared to control participants (Schlaug et al. 1995). In addition to structural changes in the corpus callosum, representations within the sensorimotor cortices are significantly altered by musical or athletic training (Schwenkreis et al. 2007; Tyc et al. 2005). Whereas musical training appears to *increase* the size of anatomically specific regions in the brain, IHI is *reduced* in musicians (Ridding et al. 2000). Thus, as I show in the current study, reduced IHI appears to lend itself to better individuated bimanual control. While it is informative that long-term musical training has the capability to induce such plastic changes, rehabilitation protocols would benefit from shorter interventions or through the use of non-invasive stimulation protocols.

Studies using non-invasive stimulation paradigms such as repetitive TMS (Meehan et al. 2011), transcranial direct current stimulation (Vines et al. 2006) or cortico-cortical paired-associative stimulation (Rizzo et al. 2009) have demonstrated that interhemispheric interactions can be transiently altered with resulting behavioral consequences. An exciting, though meager, body of literature indicates that interhemispheric physiology is also malleable over a relatively short time-course by

manual training. Shim and colleagues (2005) investigated the effects of practice on callosal physiology. Following just two days of practice on a novel bimanual force production task, participants demonstrated task-selective reductions in IHI. Furthermore, Hortobagyi et al. (*in press*) reported a significant decrease in IHI and a concomitant increase in ipsilateral primary motor cortex excitability following 20 sessions of unimanual submaximal force production. A recent study revealed a reduction in asymmetry of cortical activity, assessed by functional MRI, following just five 1-hour training sessions in older adults (mean age = 66.1 years old), suggesting that the capability for plasticity of interhemispheric interactions remains even with advanced age (Erickson et al. 2007). The question of what modulates this inhibitory capacity still requires further investigation.

Interhemispheric inhibition is mediated by transcallosal glutamatergic pathways that synapse onto pyramidal tract neurons through gamma-aminobutyric acid (GABA) inhibitory interneurons (Werhahn et al. 1999). Stagg and colleagues (2011) reported that participants with higher baseline levels of GABA in M1 had slower reaction times. Furthermore, a positive correlation was observed between transcranial direct current stimulation (tDCS)-induced GABA decrease in M1 and degree of motor learning, such that subjects who demonstrated a greater decrease in M1 GABA following stimulation showed faster short-term learning (Stagg et al., 2011). It is possible that training-related decreases in IHI (Shim et al., 2005; Hortobagyi et al., 2011) and GABA levels (Stagg et al., 2011; Floyer-Lea et al., 2006) represent a change in the balance of interhemispheric facilitatory and inhibitory communication. In the current study, individuals who coupled the force output of the two hands to a greater extent, potentially via greater

interhemispheric facilitation, performed the bimanual simultaneous task with less force variability. Future work would benefit from exploring an apparent increase in cooperative action between bilateral motor cortices as a result of manual training and/or non-invasive stimulation.

It was somewhat surprising that I did not observe modulation of IHI across the different force production tasks in the current study as has previously been shown (Giovannelli et al. 2009). The current study and that of Giovannelli utilized identical stimulation parameters (120% of resting motor threshold) and both elicited iSPs from the dominant hand FDI. However, there is a clear difference in the force production tasks between the two studies. Participants in the Giovannelli study were required to produce maximal force with the dominant hand FDI across all conditions, whereas participants in the current study were only producing force at 20% of their maximal output. This was necessary to ensure that fatigue did not contaminate condition effects in the current study. It may be that extremely high levels of interhemispheric and descending motor output (associated with maximal force production) are required to see task-dependent modulation of IHI as reported by Giovannelli et al. (2009). At sub-maximal contractions, such as those used in the current study, iSPs appear not to be modulated across tasks and may solely be an indicator of individual differences in inhibitory capacity.

An additional caveat to note is the attentional demand required to perform two tasks synchronously, particularly during the bimanual independent force production task in the current study. It is well established that performing two tasks simultaneously often degrades performance of one or both tasks, potentially due to competition for shared attentional resources (Hiraga et al. 2009). In the current study performance of the

dominant hand became more variable as the involvement of the non-dominant hand increased. Therefore, while the increase in dominant hand variability may be due to interhemispheric M1 interactions, it is also quite possible that the dual-task nature of the bimanual condition played a significant role. This concern is somewhat tempered by the fact that I did not observe any association between IHI and dominant hand force variability during the bimanual synchronous condition.

Conclusions

Skillful bimanual control requires that hand movements are coordinated in time and space, while minimizing intermanual interference through interhemispheric inhibition. Our current findings revealed that isometric dominant hand force variability was increased when the non-dominant hand was required to produce either an identical or an independent force trajectory as compared to the dominant hand. Our results shed light on the task-specific nature of interhemispheric inhibition for tasks with different movement requirements. As shown in the current chapter, IHI is necessary for the performance of unimanual movements to reduce motor overflow. Furthermore, although some level of IHI is necessary for the performance of bimanual tasks where each hand is performing an independent movement (Kennerley et al., 2002), it is clear that reduced IHI is beneficial to performance in this context. Conversely, interhemispheric communication and IHI are not a necessity for the performance of bimanual movements where the two hands have identical movement goals (Kennerley et al. 2002).

References

- Banich MT, and Belger A. Interhemispheric interaction: how do the hemispheres divide and conquer a task? *Cortex* 26: 77-94, 1990.
- Bloom JS, and Hynd GW. The role of the corpus callosum in interhemispheric transfer of information: excitation or inhibition? *Neuropsychol Rev* 15: 59–71, 2005.
- Boroojerdi B, Hungs M, Mull M, Topper R, and Noth J. Interhemispheric inhibition in patients with multiple sclerosis. *Electroencephalogr Clin Neurophysiol* 109(3): 230-237, 1998.
- Chen R, Yung D, and Li JY. Organization of ipsilateral excitatory and inhibitory pathways in the human motor cortex. *J Neurophysiol* 89: 1256-1264, 2003.
- Cincotta M, and Ziemann U. Neurophysiology of unimanual motor control and mirror movements. *Clin Neurophys* 119: 744-762, 2008.
- Diedrichsen J, Hazeltine E, Nurss WK, and Ivry RB. The role of the corpus callosum in the coupling of bimanual isometric force pulses. *J Neurophysiol* 90: 2409-2418. 2003.
- Erickson KI, Colcombe SJ, Wadhwa R, Bherer L, Peterson MS, Scalf PE, Kim JS, Alvarado M, and Kramer AF. Training-induced plasticity in older adults: effects of training on hemispheric asymmetry. *Neurobiol Aging* 28: 272-283, 2007.
- Fling BW, Peltier SJ, Bo J, Welsh RC, Seidler RD. Age differences in interhemispheric interactions: callosal structure, physiological function, and behavior. *Front in Neurosci* 5(38), 2011.
- Fling BW, Walsh CM, Bangert AS, Reuter-Lorenz PA, Welsh RC, and Seidler RD. Differential Callosal Contributions to Bimanual Control in Young and Older Adults. *J Cogn Neurosci* (October 18, 2010). doi:10.1162/jocn.2010.21600.
- Fujiyama H, Garry MI, Levin O, Swinnen SP, and Summers JJ. Age-related differences in inhibitory processes during interlimb coordination. *Brain Res* 1262: 38-47, 2009.
- Garvey MA, Ziemann U, Becker DA, Barker CA, and Bartko JJ. New graphical method to measure silent periods evoked by transcranial magnetic stimulation. *Clin Neurophysiol* 112: 1451-1460, 2001.
- Giovannelli F, Borgheresi A, Balestrieri F, Zaccara G, Viggiano MP, Cincotta M, and Ziemann U. Modulation of interhemispheric inhibition by volitional motor activity: an ipsilateral silent period study. *J Physiol* 587: 5393-5410, 2009.
- Hiraga CY, Garry MI, Carson RG, and Summers JJ. Dual-task interference: attentional and neurophysiological influences. *Behav Br Res* 205: 10-18, 2009.
- Hortobagyi T, Richardson SP, Lomarev M, Shamim E, Meunier S, Russman H, Dang N, and Hallett M. Interhemispheric Plasticity in Humans. *Med Sci Sports Exerc* 2010.
- Hoy KE, Fitzgerald PB, Bradshaw JL, Armatas CA, and Georgiou-Karistianis N. Investigating the cortical origins of motor overflow. *Brain Res Brain Res Rev* 46: 315-327, 2004.

- Johansen-Berg H, Della-Maggiore V, Behrens TE, Smith SM, and Paus T. Integrity of white matter in the corpus callosum correlates with bimanual co-ordination skills. *Neuroimage* 36 Suppl 2: T16-21, 2007.
- Jung P, and Ziemann U. Differences of the ipsilateral silent period in small hand muscles. *Muscle Nerve* 34: 431-436, 2006.
- Kanai R, and Rees G. The structural basis of inter-individual differences in human behavior and cognition. *Nat Rev Neurosci* 12(4): 231-242, 2011.
- Kennerley SW, Diedrichsen J, Hazeltine E, Semjen A, and Ivry RB. Callosotomy patients exhibit temporal uncoupling during continuous bimanual movements. *Nat Neurosci* 5: 376-381, 2002.
- Koerte I, Heinen F, Fuchs T, Laubender RP, Pomschar A, Stahl R, Berweck S, Winkler P, Hufschmidt A, Reiser MF, and Ertl-Wagner B. Anisotropy of callosal motor fibers in combination with transcranial magnetic stimulation in the course of motor development. *Invest Radiol* 44(5):279-84, 2009.
- Mark RF, and Sperry RW. Bimanual coordination in monkeys. *Exp Neurol* 21: 92-104, 1968.
- Meehan SK, Linsdell MA, Handy TC, and Boyd LA. Interhemispheric enhancement of somatosensory cortical excitability through contralateral repetitive transcranial magnetic stimulation. *Clin Neurophysiol* 2011.
- Meyer BU, Roricht S, Graf von Einsiedel H, Kruggel F, and Weindl A. Inhibitory and excitatory interhemispheric transfers between motor cortical areas in normal humans and patients with abnormalities of the corpus callosum. *Brain* 118 (Pt 2): 429-440, 1995.
- Murase N, Duque J, Mazzocchio R, and Cohen LG. Influence of interhemispheric interactions on motor function in chronic stroke. *Ann Neurol* 55: 400-409, 2004.
- Nordstrom MA, and Butler SL. Reduced intracortical inhibition and facilitation of corticospinal neurons in musicians. *Exp Brain Res* 144: 336-342, 2002.
- Oldfield RC. The assessment and analysis of handedness: the Edinburgh inventory. *Neuropsychologia* 9: 97-113, 1971.
- Pincus SM. Approximate entropy as a measure of system complexity. *Proc Nat Acad Sci* 88: 2297-2301, 1991.
- Reuter-Lorenz PA, Stanczak L, and Miller AC. Neural recruitment and cognitive aging: two hemispheres are better than one, especially as you age. *Psychological Science* 10(6): 494-500, 1999.
- Ridding MC, Brouwer B, and Nordstrom MA. Reduced interhemispheric inhibition in musicians. *Exp Brain Res* 133: 249-253, 2000.
- Rizzo V, Siebner HS, Morgante F, Mastroeni C, Girlanda P, and Quartarone A. Paired associative stimulation of left and right human motor cortex shapes interhemispheric motor inhibition based on a Hebbian mechanism. *Cereb Cortex* 19: 907-915, 2009.

- Schlaug G, Jancke L, Huang Y, Staiger JF, and Steinmetz H. Increased corpus callosum size in musicians. *Neuropsychologia* 33: 1047-1055, 1995.
- Schwenkreis P, El Tom S, Ragert P, Pleger B, Tegenthoff M, and Dinse HR. Assessment of sensorimotor cortical representation asymmetries and motor skills in violin players. *Eur J Neurosci* 26: 3291-3302, 2007.
- Shim JK, Kim SW, Oh SJ, Kang N, Zatsiorsky VM, and Latash ML. Plastic changes in interhemispheric inhibition with practice of a two-hand force production task: a transcranial magnetic stimulation study. *Neurosci Lett* 374: 104-108, 2005.
- Slifkin AB, and Newell KM. Noise, information transmission, and force variability. *J Exp Psych: Hum Per Perf* 25(3): 837-851. 1999.
- Stagg CJ, Bachtar V, and Johansen-Berg H. The Role of GABA in Human Motor Learning. *Curr Biol* 2011.
- Stinear JW, and Byblow WD. Disinhibition in the human motor cortex is enhanced by synchronous upper limb movements. *J Physiol* 543: 307-316, 2002.
- Triggs WJ, Calvanio R, Macdonell RA, Cros D, and Chiappa KH. Physiological motor asymmetry in human handedness: evidence from transcranial magnetic stimulation. *Brain Res* 636: 270-276, 1994.
- Tyc F, Boyadjian A, and Devanne H. Motor cortex plasticity induced by extensive training revealed by transcranial magnetic stimulation in human. *Eur J Neurosci* 21: 259-266, 2005.
- Vaillancourt DE, and Newell KM. Aging and the time and frequency structure of force output variability. *J Appl Physiol* 94: 903-912, 2003.
- Vercauteren K, Pleysier T, Van Belle L, Swinnen SP, and Wenderoth N. Unimanual muscle activation increases interhemispheric inhibition from the active to the resting hemisphere. *Neurosci Lett* 445: 209-213, 2008.
- Verstynen T, and Ivry RB. Network dynamics mediating ipsilateral motor cortex activity during unimanual actions. *J Cogn Neurosci* (January 26, 2011). doi:10.1162/jocn.2011.21612.
- Vines BW, Nair DG and Schlaug G. Contralateral and ipsilateral motor effects after transcranial direct current stimulation. *Neuroreport* 17: 671-674, 2006.
- Wahl M, Lauterbach-Soon B, Hattingen E, Jung P, Singer O, Volz S, Klein JC, Steinmetz H, and Ziemann U. Human motor corpus callosum: topography, somatotopy, and link between microstructure and function. *J Neurosci* 27: 12132-12138, 2007.
- Wassermann EM, Fuhr P, Cohen LG, Hallett M. Effects of transcranial magnetic stimulation on ipsilateral muscles. *Neurology* 41(11): 1795-1799, 1991.
- Weissman DH, and Banich MT. The cerebral hemispheres cooperate to perform complex but not simple tasks. *Neuropsychology* 14: 41-59, 2000.
- Werhahn KJ, Kunesch E, Noachtar S, Benecke R, and Classen J. Differential effects on motorcortical inhibition induced by blockade of GABA uptake in humans. *J Physiol* 517 (Pt 2): 591-597, 1999.

CHAPTER IV

Fundamental differences in callosal structure, neurophysiologic function, and bimanual control in young and older adults

Currently under review with stylistic modifications as - Fling BW & Seidler RD (Under review). Fundamental differences in callosal structure, neurophysiologic function, and bimanual control in young and older adults. *Cerebral Cortex*

Abstract:

Bimanual actions involve coordinated motion in time and space, but often rely on the movements performed with each hand to be different. Older adults exhibit differentially greater variability for bimanual actions in which each hand has an independent movement goal. Such actions rely on interhemispheric communication via the corpus callosum including both facilitatory and inhibitory interactions. Here I investigated whether age differences in callosal structure and interhemispheric interactions contribute to this selective movement difficulty. Participants performed three force production tasks: 1) unimanual 2) bimanual simultaneous and 3) bimanual independent. Older adults had significantly greater interhemispheric facilitation and trended towards less interhemispheric inhibition during voluntary muscle activation. I also report a fundamental shift with age in the relationship between callosal tract microstructure and interhemispheric inhibition. Specifically, older adults with greater callosal tract microstructure have less interhemispheric inhibition. Further, greater interhemispheric inhibition was related to poorer bimanual performance in older adults on all tasks, whereas this relationship was only observed in young adults for the bimanual

independent condition. These findings indicate changes in interhemispheric communication with advancing age such that older adults may rely on bilateral cortical cooperation to a greater extent than young adults for manual actions.

Introduction

Many activities of daily living require the two hands to perform movements with independent sub-goals to accomplish a unified goal. Consider buttoning your shirt; each hand works independently to accomplish a mutual goal. Such movements involve coordinated motion in time and space, but also rely on independent control of each hand (Perrig et al., 1999). Interhemispheric transfer via the corpus callosum plays a key role in the production of such coherently integrated behavior, assuring the appropriate balance of excitatory and inhibitory processes. My recent work suggests that this interhemispheric excitatory / inhibitory balance may be altered in older adults (cf. Fling et al., 2011a).

Both the size (Fling et al., in press; 2011b) and white matter integrity (Davis et al., 2009; Sullivan et al., 2010a) of the corpus callosum are reduced in older adults. These differences are typically reported as being specific to the anterior regions of the corpus callosum; however, a recent study by Sullivan and colleagues (2010b) demonstrated age-related declines in white matter microstructure (assessed with diffusion tensor imaging) of callosal fiber tracts connecting more posterior cortical regions such as the primary and secondary sensorimotor areas. Furthermore, recent work from our laboratory has demonstrated that the size and microstructure of callosal regions connecting these sensorimotor cortical targets are related to motor performance in a differential fashion for young and older adults. Specifically, on an asynchronous bimanual timing task better callosal microstructure was related to *poorer* performance in young adults, yet *better* performance in older adults (Fling et al., 2011b). A change in neurophysiologic function, specifically interhemispheric inhibition, as a result of poorer callosal tract structure is one potential mechanism underlying this age-related difference.

Interhemispheric inhibition is mediated by transcallosal glutamatergic pathways that synapse onto pyramidal tract neurons through gamma-aminobutyric acid (GABA) inhibitory interneurons (Werhahn et al., 1999). Structural integrity of callosal tracts connecting the primary motor cortices is predictive of interhemispheric inhibition in young adults (see Chapter 2). A decline in interhemispheric inhibition with age has been reported (Talelli et al., 2008), however relationships between inhibition and callosal structure have yet to be described in older adults. Thus, while a converging body of literature indicates declines in both interhemispheric inhibition and callosal tract microstructure with advancing age, relationships between callosal structure and function and their collective impact on bimanual control have yet to be studied in combination.

Here I used diffusion tensor imaging (DTI) and transcranial magnetic stimulation (TMS) to quantify the integrity of callosal sensorimotor fibers and interhemispheric inhibition in young and older adults. I hypothesized that better microstructure of callosal tracts connecting the two primary motor cortices would be positively related to bimanual independent task performance in older adults, but negatively related to performance in young adults. Further, I hypothesized that less interhemispheric inhibition would be related to better bimanual independent task performance in both young and older adults. Finally, I expected to find less interhemispheric inhibition and greater interhemispheric facilitation in older adults. This pattern of results would provide support for the notion that callosal structure-function relationships, as well as the balance of interhemispheric inhibition and facilitation, undergo a fundamental shift with age.

Materials and Methods

Participants

Twenty-one young adults (10 males; mean age 22.1 ± 2.8 years; range 18-28 years) were recruited from the population at the University of Michigan. Eighteen community-dwelling older adults (8 males; 67.2 ± 5.2 years; range 65-76 years) also participated in this study (all older adults had a minimum high school education). This experiment was approved by the Medical Institutional Review Board (IRBMED) of the University of Michigan. Participants gave their informed written consent prior to beginning the experiment and were compensated for their time.

I performed testing on 2 days, separated by less than one week. On the first day of testing I acquired structural magnetic resonance (MR) and diffusion weighted (DW) images (detailed in the following section). I also administered the Edinburgh Handedness Inventory (Oldfield, 1971; all participants were strongly right-handed, (mean = 0.89) and the Montreal Cognitive Assessment (MoCA) to assess general cognitive function. To assess dexterity using both clinical and functional tasks, all participants completed the unimanual (dominant and non-dominant hand), bimanual and assembly tasks on the Purdue Pegboard as well as timed tasks of shoelace tying and buttoning a 5-button dress shirt using a custom-built board composed of a dress shirt and a set of shoelaces. On the second day of testing I assessed interhemispheric inhibition through the use of the ipsilateral silent period (iSP) technique during three different force production paradigms.

Image acquisition

Using identical procedures to those previously reported (Chapter 2), whole brain

high-resolution structural MR images were collected on a 3T MRI scanner (General Electric, Waukesha, WI, USA) using a spoiled gradient echo sequence (124 slices, field-of-view: 24 cm, voxel size: 0.94 x 0.94 x 1.4 mm, TR: 10.2 ms and TE: 3.4 ms). Diffusion weighted images were collected using a single shot echo-planar sequence in the axial plane (39 slices; TE/TR: 82.8 ms/9000 ms; field of view: 220 mm x 220 mm; voxel size 0.9 x 0.9 x 3.1 mm; b -value = 800 s/mm²; 15 diffusion-sensitizing directions). Images were motion and eddy-current corrected to account for drifts in scanner acquisition. Using the averaged images with $b = 0$ and $b = 800$ s/mm², the diffusion tensor was calculated and fractional anisotropy (FA) images were constructed off-line using ExploreDTI (Tournier et al., 2011). Diffusion tensors were calculated from the 15 DW images based upon a simple least squares fit of the tensor model to the diffusion data (Basser, et al. 2000). Diagonalization of the tensor yields three voxel-specific eigenvalues ($\lambda_1 > \lambda_2 > \lambda_3$) representing diffusivities along the three principle directions of the tensor. The three principal eigenvectors were then used to construct fiber tracts and the resultant diffusion properties as described below.

Fiber Tractography

Interhemispheric fiber tractography between sensorimotor regions of interest was performed using a previously described technique (Chapter 2). Briefly, each participant's FA map was co-registered into MNI space, aligned along the anterior/posterior commissure line with the coordinate 0, 0, 0 placed at the brain's center of mass, and voxel size was re-sampled to 2 x 2 x 2 mm through the use of ExploreDTI (Tournier et al., 2011). The Human Motor Area Template (HMAT; Mayka et al., 2006) was co-registered to each individual's MNI-normalized FA image and subsequently used as a

mask of the primary motor cortex (M1). Interhemispheric fiber tracts were identified by placing seed and target ROIs in homologous M1 regions as identified by the HMAT. Fiber tracts were constructed based upon deterministic streamline tractography using the method of Mori and colleagues (cf. Mori and van Zijl, 2002).

Interhemispheric Inhibition & Facilitation

Five young adults and three older adults from the first day of testing were unable to undergo the TMS procedure based on screening (Appendix A, 6 individuals were taking prescription medication with possible contraindications and 2 individuals had a familial history of epilepsy). Thus, on day 2 a subset of 16 young adults and 15 older adults from the initial imaging session underwent a TMS procedure to assess interhemispheric inhibition.

Experimental Task

Participants were seated in a chair with both their dominant and non-dominant forearms resting on a table. The shoulders were abducted at approximately 45°, the elbows were flexed at approximately 90°, and the forearms were pronated with the palms of the hand lying flat on the custom apparatus. The wrist, third, fourth, and fifth fingers were constrained from moving, isolating force production to the index finger. A pre-amplified force transducer (OMEGA LC509-015 Beam Load Cell) was positioned at the lateral aspect of the proximal interphalangeal joint of the isolated index finger to record compressive isometric force (output: 0.5-9.5 Vdc; excitation: 24 Vdc \pm 4 Vdc).

Surface electromyography and motor evoked potentials (MEPs) were recorded from the first dorsal interosseous (FDI) muscle of both hands using 4 mm Ag/AgCl⁺ electrodes placed on the muscle in a belly-tendon arrangement. Surface EMG and MEP

data were recorded using Biopac hardware and AcqKnowledge software (BIOPAC Systems Inc., Goleta, CA). The raw EMG signal was collected and digitized at 2000 Hz, amplified and band pass filtered (10-1000 Hz). Data were collected at 2kHz as it has previously been shown to produce the most accurate estimate of mean consecutive difference (MCD) of pre-stimulus EMG activity, necessary to accurately calculate the iSP (Garvey et al. 2001). To assess maximal voluntary contractile (MVC) force of the FDI, participants were instructed to press as hard as possible on the load cell using index finger abduction of the dominant hand for three consecutive 6-second trials. The force applied to the load cell was displayed on the video monitor, providing online visual feedback during the MVC trials. The highest force sample in each trial was averaged across three MVC trials providing an estimate of the participants' MVC. A minimum 90-second rest period was provided in between each MVC trial. The same procedure was subsequently performed on the non-dominant hand.

Participants performed three different force production tasks: 1) unimanual isometric force of the dominant hand at a constant force target level, 2) bimanual simultaneous isometric force with both hands producing the same constant force target level (bimanual simultaneous task); and 3) dominant hand isometric force at a constant force target level while the non-dominant hand matched a 1 Hz sine wave (bimanual independent task; **Figure 4.1**). The order of conditions was counter-balanced across participants. For all conditions the force target levels used in the experiment were scaled to 20% of each individual subject's MVC (during the bimanual independent task the peak force of the non-dominant sine wave-matching hand was also 20% MVC). Thus, in all conditions the dominant hand always produced a constant isometric force at 20% MVC

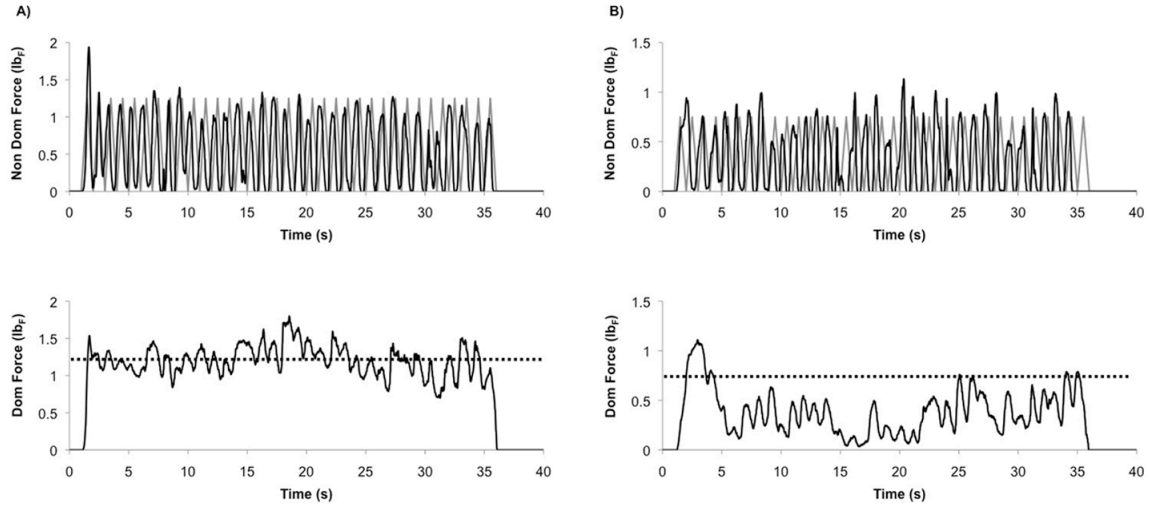


Figure 4.1 - Bimanual independent force production performance for a representative young (**A**) and older adult (**B**). For each participant the top panel represents the non-dominant hand attempting to produce a 1 Hz sine wave, whereas the bottom panel represents the dominant hand attempting to maintain a constant isometric force. The horizontal dotted line indicates the force target of the dominant hand (20% MVC), whereas the gray line indicates the 1 Hz sine wave target for the non-dominant hand (peak = 20% MVC). Non-Dom = non-dominant hand; Dom = dominant hand; lb_F = pound-force.

while the activity of the non-dominant hand (i.e. the right M1) was expected to modulate inhibitory demands. Feedback windows were presented on one video monitor and were aligned parallel on top of each other with the upper window providing feedback to the non-dominant hand while the lower window provided feedback for the dominant hand. During the unimanual and bimanual simultaneous force production tasks participants viewed a yellow, horizontal target line that spanned the width of a video monitor (placed at 20% of MVC for each respective hand). During the bimanual independent movement condition the target for the dominant hand was identical to the other two conditions while the target for the non-dominant hand was a yellow 1-Hz sine wave target line with the peak force of each sine wave placed at 20% of MVC. Force output was sampled at 200 Hz; for each instant in time that force was sampled (.005s), a green pixel appeared in the

center of the respective feedback window corresponding to the amount of force produced. This provided participants with on-line, real-time visual feedback of their performance with minimal horizontal saccades required. For each condition, participants were instructed to match their green force trace to the respective yellow target line for three 35-second trials per condition. Participants were provided rest breaks of five minutes in between each trial (a total of 9 trials) in an attempt to minimize fatigue.

Ipsilateral Silent Period (iSP)

Interhemispheric inhibition (IHI) was measured by evoking an ipsilateral silent period (iSP) in the dominant hand FDI. The iSP is elicited by focal TMS of the M1 ipsilateral to the hand making a voluntary contraction, leading to a brief suppression of voluntary activity in the electromyogram signal of this muscle (Meyer et al. 1995). The iSP reflects inhibition of volitional motor activity, and thus is particularly well-suited to investigate interhemispheric control of voluntary cortical motor output (Giovannelli et al. 2009).

Prior to performing the experimental paradigm, I used a Magstim Rapid magnetic stimulator (The Magstim Company Ltd, Spring Gardens, Whitland, Carmarthenshire, UK) and a focal figure of eight coil (diameter of each wing 70 mm) to identify the right hemisphere M1 hotspot for the left FDI. The coil was placed tangential to the scalp with the handle pointing backwards and 45° away from the midline (Chen et al. 2003). The optimum site in the right M1 (hotspot) for eliciting motor responses in the left FDI was identified at supra-threshold intensity. This location was marked on the scalp and subsequently utilized to elicit iSPs from the right FDI as it has previously been shown that the topography of the contralateral MEP and the iSP correspond closely (Wasserman

et al. 1991). Resting motor threshold (RMT) was determined to the nearest 1% of the maximum stimulator output. Using standard protocol, the RMT was defined as the minimum stimulus intensity that elicited MEPs of 50 μ V in at least 5 out of 10 consecutive trials (Triggs et al. 1994).

Once participants reached the target force level during the unimanual task, I applied stimulation at 120% of resting motor threshold to the right motor cortex to elicit dominant hand iSPs. During each 35-second trial, a minimum of five iSPs were evoked with an interstimulus interval jittered between 5-8 seconds (Garvey et al. 2001; Jung & Ziemann, 2006). During the unimanual condition, EMG data were also collected and monitored from the non-dominant hand to ensure full relaxation and that the TMS coil was always in the appropriate location over the right M1. During one trial in four different participants (two young adults and two older adults), MEPs ceased to be elicited from the left FDI. On these occasions data collection was halted and the right M1 hotspot for the FDI was re-located.

Interhemispheric Facilitation

Interhemispheric facilitation was assessed by measuring the motor evoked potential in the resting non-dominant hand during unimanual isometric contraction. Ongoing activity of one motor cortex has previously been shown to transcallosally facilitate the contralateral M1 (Carson et al., 2004; Sohn et al., 2003), which is reflected by an increase in the size of the contralateral MEP (i.e. the non-dominant resting hand in this context).

Data Analysis

Fiber Tractography

Descriptive metrics were calculated for the microstructure of M1 fiber tracts including fractional anisotropy and radial diffusivity $((\lambda_2 + \lambda_3) / 2)$. Fractional anisotropy (FA), a rotationally invariant index that ranges from 0 (isotropic) to 1 (anisotropic), is a measure of the magnitude and orientation of principle eigenvectors on an intravoxel basis (Sullivan et al., 2010a). Therefore, higher FA values are interpreted as reflecting better white matter microstructure (Basser and Pierpaoli 1996). Conversely, *lower* radial diffusivity is interpreted as being indicative of better tract microstructure (Basser et al., 2000).

Force data

The initial 5 seconds of each force time series was removed to eliminate the transitory performance in achieving the force target. Force data were digitally filtered using a 4th order Butterworth filter with a low-pass cutoff frequency of 20 Hz. All data processing and subsequent time and frequency analyses were performed using software written in MATLAB (The MathWorks Inc., Natick, MA). Similar to previous work, the amount of force output variability was assessed by calculating the within-trial mean (normalized to the force target goal and expressed as a percentage throughout the remainder of this chapter) and the root mean square error (RMSE) from the target (Vaillancourt et al. 2003). I also performed a power spectral density analysis to assess peak frequency of the non-dominant hand during the bimanual independent condition to ensure that individuals were adhering to the 1 Hz frequency target.

Interhemispheric Inhibition

The ipsilateral silent period (iSP) was calculated by using an objective, graphical method described in detail by Garvey and colleagues (2001). EMG trials were rectified and analyzed offline using a custom MATLAB program (The MathWorks Inc., Natick, MA). For each iSP (15 total per participant), upper and lower variation limits of the EMG signal were calculated by determining the mean consecutive difference (MCD) of EMG data points 100ms prior to stimulation: mean pre-stimulus EMG \pm ($|MCD| \times 1.77$). These limits encompassed 95% of possible pre-stimulus EMG data points (equivalent to two standard deviations). Onset and offset of iSP were identified using the following criteria: (1) time of onset was the first of 5 consecutive data points to fall below the lower variation limit; (2) all subsequent data points were considered part of the iSP until there was a return of sustained EMG activity; (3) time of offset was defined as the first data point to fall above the lower variation limit if 50% or more of the data points in the following 5 ms window were also above the variation limit (Garvey et al. 2001). In addition to measuring the onset, offset and duration of the iSP, the depth of the iSP was defined in two ways as previously described by Jung and Ziemann (2006): (1) the maximum amount of EMG suppression during the iSP (diSP-max), and (2) the average EMG level during the iSP (diSP). The diSP and diSP-max were expressed as percentages of the mean prestimulus EMG. Therefore the larger the diSP (and diSP-max), the greater the suppression of ipsilateral EMG activity during the iSP. This is interpreted as increased interhemispheric inhibition (Garvey et al. 2001).

Similar to previous work, “motor overflow” was assessed for both groups during the unimanual dominant hand force production condition by taking the rectified integral

of the non-dominant (resting) hand EMG normalized to baseline measures of EMG activity for the same hand (Carey et al., 1983). Thus motor overflow is expressed as a percentage of the baseline EMG to decrease the chance of higher inter-subject variability due to differences in skin-electrode impedance, background noise, or arousal.

Interhemispheric Facilitation

Peak-to-peak amplitude was quantified for each MEP elicited from the non-dominant hand during the unimanual force production task (15 total per participant). Because MEPs were standardized to 50 μ V when identifying the resting motor threshold, those elicited during the task result in a normalized value comparable across participants.

Statistical Analysis

Independent *t*-tests were performed to compare between-group performance on the MoCA, timed shoelace tying and shirt buttoning, contralateral MEP amplitude (interhemispheric facilitation), and all metrics of IHI: iSP onset, iSP duration, diSP, and diSP-max. A mixed-model repeated measures analysis of variance was used to analyze measures of fiber tract microstructure, manual dexterity and dominant hand force production with FA, radial diffusivity, RMSE, normalized mean force production, and number of pegs for each condition of the Purdue Pegboard treated as within-subject variables and age group treated as the between-subject variable. Significance was set at an alpha of 0.05 (SPSS 18.0) and the Huyn-Feldt epsilon was computed to test for sphericity; I interpreted corrected *P* values in cases of violation. Significant main effects were subjected to post-hoc paired *t*-tests and Bonferroni-corrected for multiple comparisons. I have previously shown a fiber tract specific relationship between microstructure and inhibition (Chapter 2); thus within each age group I performed linear

regression to investigate the relationship(s) between microstructure of fiber tracts connecting the primary motor cortices, diSP, and dominant hand variability (RMSE) on the three different force production tasks. Therefore M1 fiber tract microstructure was used as a predictor of diSP and behavioral performance, and diSP was also used separately as a predictor of behavioral performance. I also used linear regression to investigate the association between interhemispheric facilitation and motor overflow. All correlation analyses using either fiber microstructure or diSP as a predictor were Bonferroni-corrected for multiple comparisons ($\alpha = 0.05/4$). Finally, for all significant relationships I used a Fisher r-to-Z transformation to compare the strength of correlations between age groups. All data are presented as mean \pm standard deviation unless otherwise noted.

Results

Behavioral testing

Descriptive metrics of cognitive performance (MoCA), manual dexterity (Purdue Pegboard) and functional manual control tasks (timed shoelace tying & shirt buttoning) are shown in **Table 4.1**. While both groups demonstrated similar MoCA scores and performance on the shoelace-tying task, young adults were significantly better at all manual dexterity tasks assessed with the Purdue Pegboard (a significant group and condition main effect, but no group x condition interaction; $P < 0.001$ for all comparisons), as well as significantly faster on the timed shirt-buttoning task ($P < 0.01$).

	Young Adults	Older Adults
MoCA	28.8 (1.3)	28.4 (1.3)
Purdue Pegboard (# of pegs)		
<i>Dominant</i>	16.0 (1.9)*	12.8 (1.7)
<i>Non-Dominant</i>	14.9 (2.1)*	12.2 (2.1)
<i>Bimanual</i>	12.6 (1.8)*	9.9 (1.6)
<i>Assembly</i>	39.8 (8.2)*	29.5 (3.8)
Shirt Buttoning (s)	13.9 (2.3)*	18.8 (5.0)
Shoelace Tying (s)	4.7 (0.9)	5.0 (1.0)

Table 4.1 – Group performance on tasks assessing general cognitive performance, manual dexterity, and manual performance of daily functional tasks. For the MoCA and Purdue Pegboard, higher values are indicative of better performance. For timed shoelace tying and shirt buttoning, lower times are indicative of faster performance. Young adults demonstrated significantly better performance on all components of the Purdue Pegboard, and were significantly faster on the shirt-buttoning task. No group differences were noted for the MoCA or in timed shoelace tying. Data are mean (standard deviation). MoCA = Montreal Cognitive Assessment; s = seconds. * $P < 0.05$.

Behavioral Performance

Maximal voluntary contractile force was similar between groups for both the dominant (YA: 4.3 lb_F; OA: 4.6 lb_F) and non-dominant (YA: 3.9 lb_F; OA: 4.3 lb_F) FDI with no statistical differences noted. As a result, during the force production tasks both groups were producing not only the same relative forces, but also similar absolute forces. A repeated measures ANOVA of dominant hand force variability across the three conditions revealed a significant main effect of RMSE for condition ($F_{2,58} = 303.8$, $P < 0.001$) and for group, such that older adults had significantly more variability ($F_{1,29} = 23.7$, $P < 0.001$). Post hoc paired-sample t tests showed that dominant hand variability was significantly lower during the unimanual condition than for either bimanual condition ($t > 6.6$; $P < 0.001$ for both comparisons). When comparing the two bimanual conditions (simultaneous & independent), dominant hand variability was significantly lower during the simultaneous condition ($t_{1,30} = 8.3$; $P < 0.001$). Finally, I found a significant condition x group interaction for RMSE ($F_{1,29} = 75.4$, $P < 0.001$) such that

variability was differentially increased in older adults during the bimanual independent condition ($t_{1,29} = 7.9$; $P < 0.001$; **Figure 4.2**). No differences were noted between groups for either the unimanual or bimanual simultaneous conditions ($t_{1,29} < 0.7$; $P > 0.5$ for both comparisons).

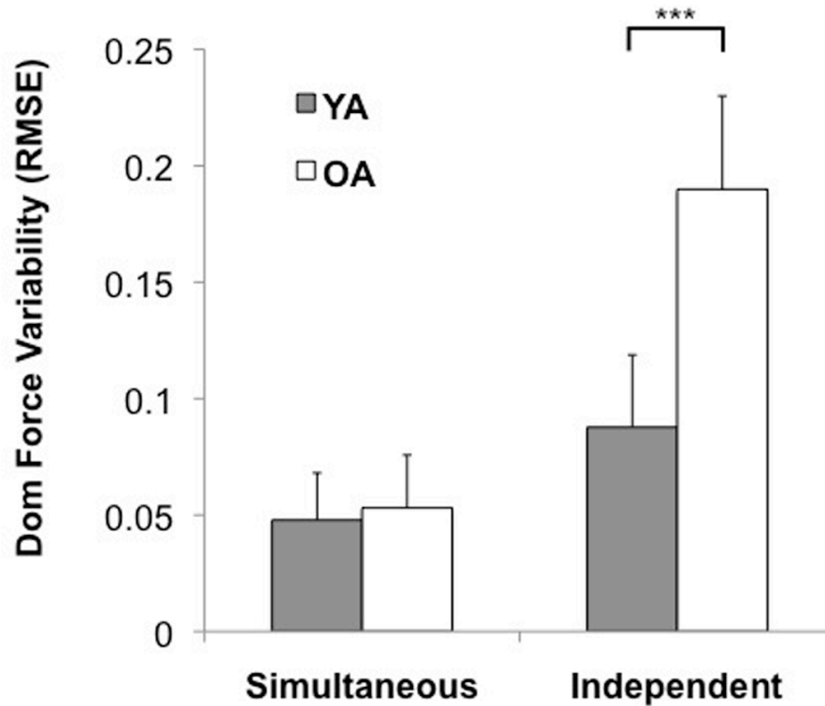


Figure 4.2 – Dominant hand variability during the two bimanual conditions. Data show an age x task interaction with older adults disproportionately impaired at maintaining steady force production during the bimanual independent condition. *** $P < 0.001$. YA = young adult; OA = older adult; Dom = dominant hand.

For dominant hand force accuracy (mean force output normalized to the target goal) I report a significant main effect of condition ($F_{2,56} = 16.7$, $P < 0.001$), but no group main effect ($F_{1,28} = 0.9$; $P > 0.35$) or group x condition interaction ($F_{2,56} = 1.3$; $P > 0.26$). No difference in accuracy was found between the unimanual (91.9%) and bimanual simultaneous (91.5%) force conditions. Dominant hand accuracy on both these conditions was significantly better than during the bimanual independent task (77.6%; $t_{1,29} > 4.0$; $P < 0.001$ for both comparisons).

Two additional behavioral metrics demonstrate that participants were able to adhere to each bimanual force condition. During the bimanual simultaneous condition, non-dominant hand variability (RMSE = 0.057) and accuracy (89.06%) were similar to the dominant hand during the same task (RMSE = 0.054; accuracy = 91.5%). Furthermore, during the bimanual independent force condition, both groups were able to approximate a 1 Hz sine wave with the non-dominant hand (mean frequency YA: 0.93 Hz; OA mean: 0.89 Hz).

Interhemispheric Sensorimotor Fiber Tracts

A significant age group difference was noted for FA ($F_{1,30} = 21.5$, $P < 0.001$) and radial diffusivity ($F_{1,30} = 11.1$, $P < 0.001$) with higher FA and lower radial diffusivity in young adults, both indicative of better fiber tract microstructure. FA and radial diffusivity were highly correlated across individuals ($r > 0.7$); therefore I use FA as the sole measure of fiber tract microstructure for the remainder of the current chapter.

Interhemispheric Inhibition (IHI) and Facilitation

All TMS measures can be viewed in **Table 4.2**. Briefly, no difference in resting motor threshold (RMT) was noted between groups ($P > 0.4$); thus, stimulation intensity to elicit iSPs (120% RMT) was similar for young (76% of maximal stimulator output) and older adults (78% of maximal stimulator output). To elicit the 15 iSPs necessary for analysis, an average of 15.3 stimulations and 15.5 stimulations were required for the young and older groups, respectively. Although not significant, I report a trend for greater interhemispheric inhibition in young adults ($t_{1,29} = 1.7$; $P = 0.07$) compared to

older adults, as assessed by diSP (**Figure 4.3A**). The age groups did not differ on diSP-max, iSP onset or iSP duration ($P > 0.25$ for all comparisons).

	Young Adults	Older Adults
RMT – %	63.6 (2.3)	64.9 (3.1)
Pre-stim EMG – mV	1.03 (0.14)	0.93 (0.13)
iSP Onset – ms	38.4 (0.8)	39.8 (0.9)
iSP Duration – ms	27.4 (2.2)	27.9 (1.8)
diSP – %	73.6 (1.6)	68.9 (2.3)
diSP-max – %	91.9 (1.1)	91.5 (1.3)
Contralateral MEP mV	3.98 (1.7)	10.3 (4.8)***

Table 4.2 – Measures evoked using transcranial magnetic stimulation. No age group differences were noted for any measure, although a trend was observed towards decreased interhemispheric inhibition (assessed with diSP) in older adults ($P < 0.08$). Older adults had significantly greater interhemispheric facilitation (assessed by contralateral MEP). Values are mean (S.D.). RMT = resting motor threshold; EMG = electromyography; iSP = ipsilateral silent period; diSP = depth of ipsilateral silent period; MEP = motor evoked potential. *** $P < 0.001$.

Older adults had significantly larger contralateral MEPs than their younger counterparts ($t_{1,29} = 7.2$; $P < 0.001$) during the unimanual force production task, indicative of greater interhemispheric facilitation (**Figure 4.3B**). Furthermore, interhemispheric inhibition (assessed with diSP) was inversely correlated with facilitation in young adults ($r = -0.74$; $P < 0.001$) indicating that those with greater interhemispheric inhibition had less facilitation. This relationship between inhibition and facilitation was not present in older adults ($r = -0.03$; $P > 0.5$).

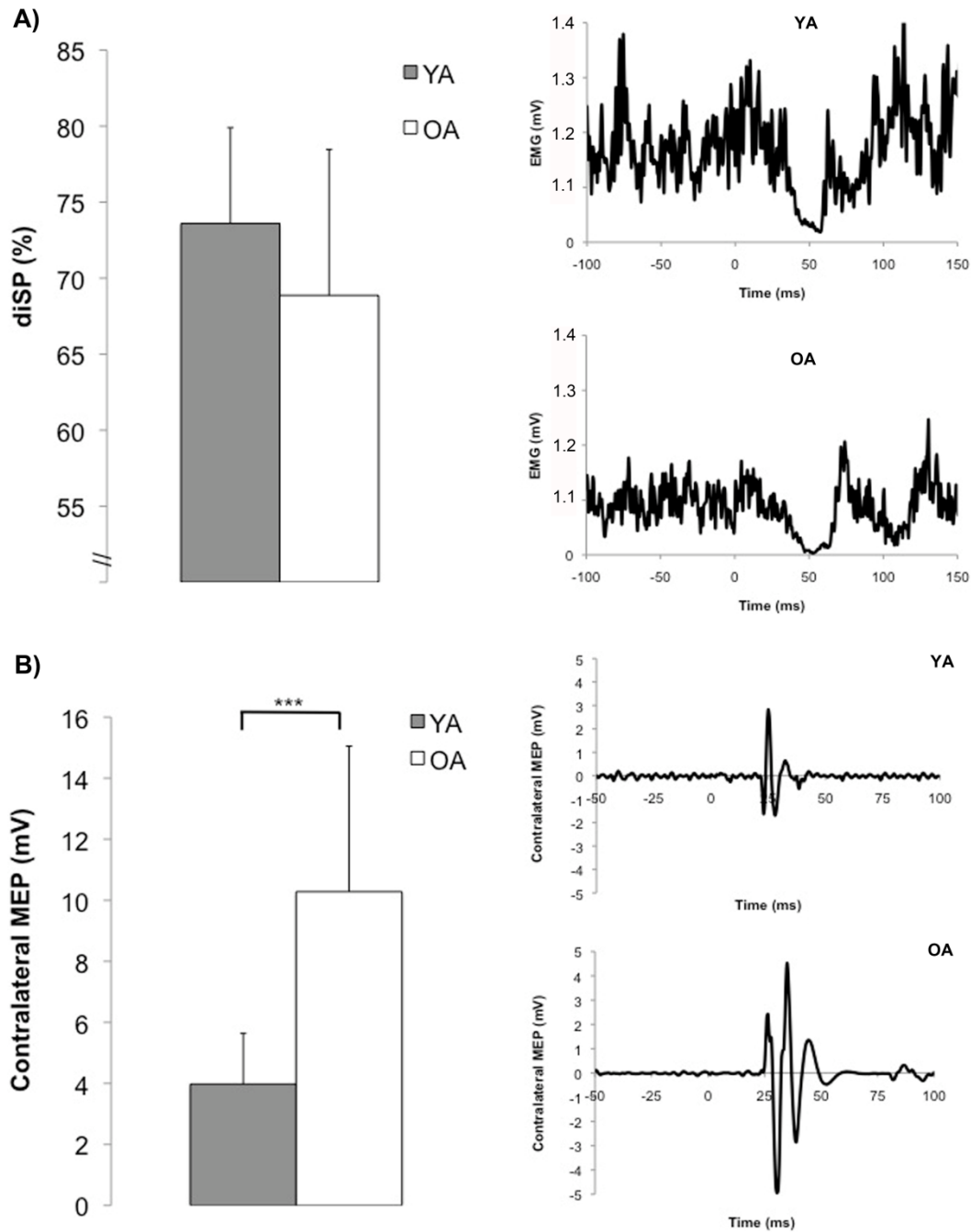


Figure 4.3 - Age-related differences in interhemispheric inhibition (A) and facilitation (B). There was a trend for greater interhemispheric inhibition in young adults ($P < 0.08$) and significantly greater facilitation in older adults ($P < 0.001$). For both age groups a representative example of the ipsilateral silent period (mean of 15 stimulations) and contralateral MEP (one stimulation) are provided. For each instance the young adult example is the top panel and the older adult example is the bottom panel. In each of these instances stimulation is applied at time point 0. diSP = depth of ipsilateral silent period; MEP = motor evoked potential. *** $P < 0.001$.

Non-dominant hand EMG activity (normalized to baseline levels) from the unimanual force production task was used as an index of motor overflow (**Figure 4.4A** presents representative examples for each age group). An independent t test showed that older adults had significantly greater motor overflow than their younger counterparts ($t_{1,29} = 2.4$; $P < 0.03$; **Figure 4.4B**). Furthermore, greater interhemispheric facilitation (larger MEP amplitude) was significantly, positively correlated with motor overflow for both young ($r = 0.57$; $P < 0.02$) and older adults ($r = 0.59$; $P < 0.01$).

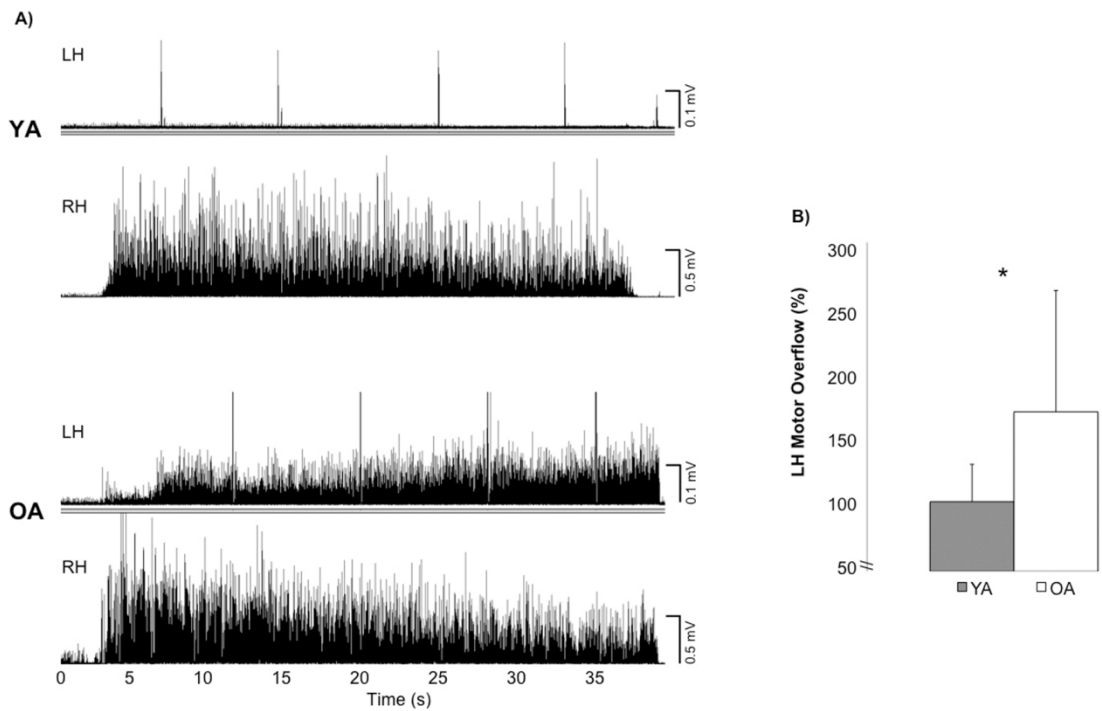


Figure 4.4 - A) Rectified EMG activity during a unimanual force production trial from one representative young (top two panels) and older adult (bottom two panels) illustrating motor overflow for the older adult. For each participant the top panel reflects EMG activity from the non-dominant resting hand's FDI, whereas the bottom panel is EMG from the dominant, force producing hand's FDI. Observable spikes in each participant's non-dominant hand EMG activity profile reflect stimulator artifact during iSP elicitation. Note that different scales are used on the y-axis for non-dominant as opposed to dominant hand EMG activity to better illustrate motor overflow. **B)** Average EMG during the unimanual force production task from the non-dominant FDI normalized to baseline EMG activity. Older adults had significantly greater motor overflow than young adults. $*P < 0.02$. LH = left hand (non-dominant); RH = right hand (dominant).

Relationships Between Fiber Tract Structure, IHI, Facilitation, and Behavior

I performed linear regression using the microstructure (assessed with FA) of interhemispheric fiber tracts connecting the primary motor cortices as a predictor of IHI (assessed with diSP) within each age group. Young adults demonstrated a significant relationship, such that individuals with better fiber tract microstructure have increased IHI ($r = 0.76$; $P < 0.001$). Conversely, older adults with greater FA have *decreased* interhemispheric inhibition ($r = -0.72$; $P < 0.002$; **Figure 4.5**). The strength of these relationships was significantly different between groups as assessed with a Fisher r-to-Z transformation ($Z = 4.8$; $P < 0.001$). Thus I report what appears to be a fundamental shift with age in the relationship between interhemispheric fiber tract structure and IHI.

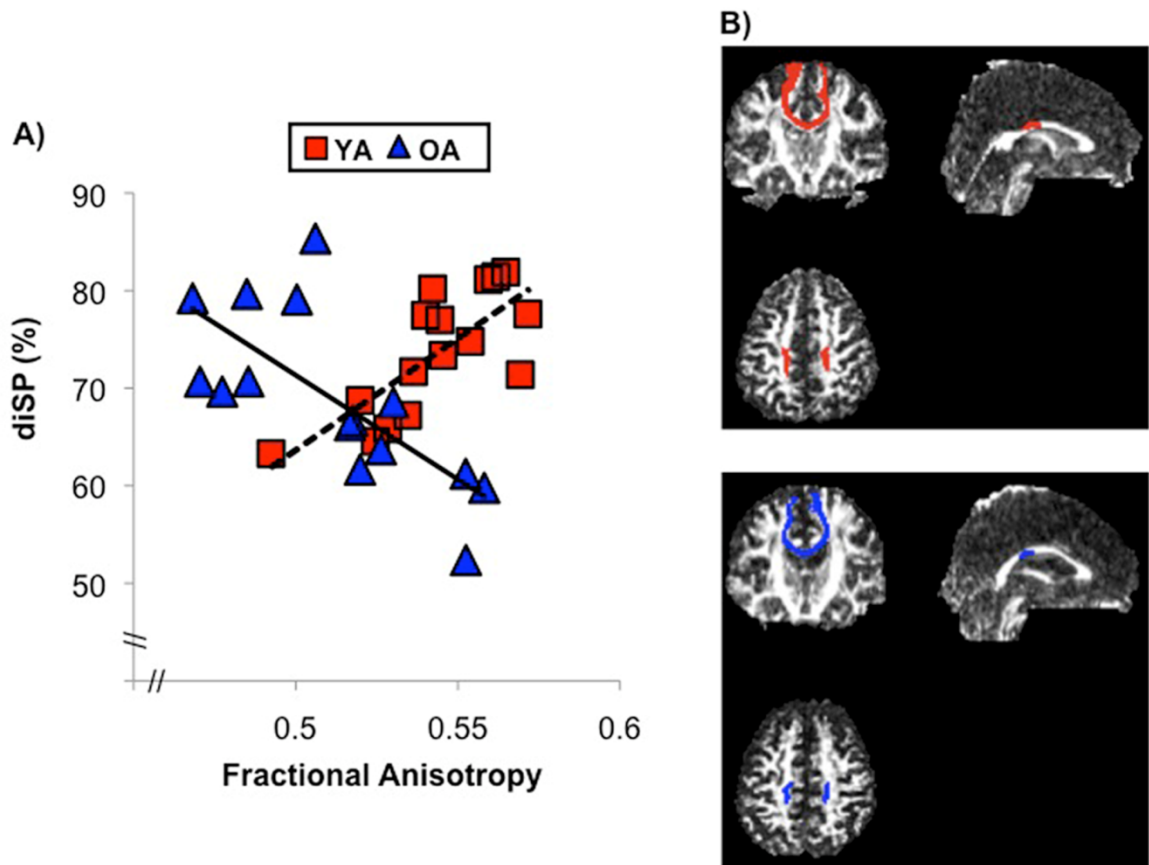


Figure 4.5 - A) Age differences in the relationship between microstructure of interhemispheric fiber tracts connecting primary motor cortices and interhemispheric

inhibition. While young adults demonstrate a significant linear relationship ($r = 0.76$; $P < 0.001$; red), older adults show an inverse relationship ($r = -0.72$; $P < 0.002$; blue). Using a Fisher r -to- Z transform, the strength of correlation is also significantly different between groups ($P < 0.001$). The dashed line represents linear regression fit for young adults, while the solid line represents linear regression fit for older adults. **B)** Interhemispheric fiber tracts connecting bilateral primary motor cortices in a representative young (red) and older (blue) adult. Coordinates for both images are ($x = 0$, $y = -2$, $z = 30$) in normalized MNI space.

I also evaluated measures of interhemispheric fiber tract structure and IHI as predictors of dominant hand variability for each of the three force conditions. Fractional anisotropy was not significantly related to dominant hand variability on either the unimanual ($r = 0.02$) or the bimanual simultaneous condition ($r = 0.08$) in young adults. Although not significant, I observed a trend such that FA was negatively correlated with variability for older adults on both the unimanual ($r = -0.33$; $P < 0.1$) and bimanual simultaneous ($r = -0.34$; $P < 0.1$) condition. Finally, I found that during the bimanual independent condition FA was positively associated with dominant hand variability ($r = 0.41$; $P < 0.06$) in young adults at a level trending towards significance, but negatively associated with variability in older adults ($r = -0.57$; $P < 0.01$). The strength of these correlations was also significantly different between groups when assessed using a Fisher r -to- Z transformation ($Z = 2.7$; $P < 0.01$; **Figure 4.6**). Therefore I show that structural integrity of interhemispheric fiber tracts is related to complex bimanual motor performance in a differential fashion for young and older adults.

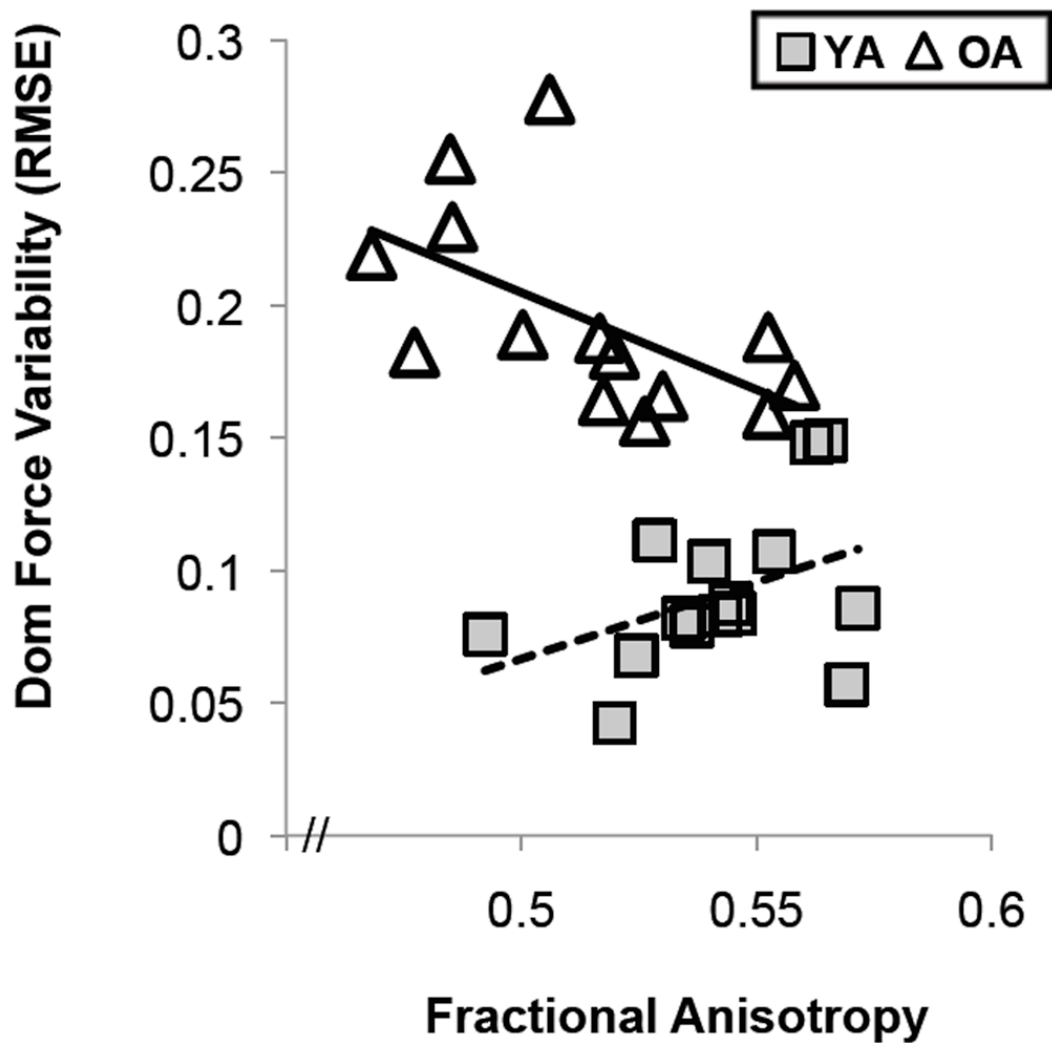


Figure 4.6 – Age differences in the relationship between microstructure of interhemispheric fiber tracts connecting primary motor cortices and dominant hand force variability during the bimanual independent force task. In young adults, greater microstructure was related to poorer performance ($r = 0.41$; $P < 0.06$), whereas in older adults greater microstructure was related to better performance ($r = -0.57$; $P < 0.01$). Using a Fisher r -to- Z transform, the strength of correlation is significantly different between groups ($P < 0.01$). The dashed line represents linear regression fit for young adults, while the solid line represents linear regression fit for older adults. Bim. = bimanual; Indep = independent.

Similar to the observed structural relationships, IHI was not related to performance in young adults during either the unimanual ($r = -0.13$) or bimanual

simultaneous ($r = -0.19$) condition. Conversely, in older adults increased IHI was significantly related to poorer performance of both the unimanual ($r = 0.59$; $P < 0.01$) and the bimanual simultaneous ($r = 0.55$; $P < 0.01$) condition. I also report that increased IHI is correlated with increased dominant hand variability during the bimanual independent condition for both age groups (YA: $r = 0.59$; OA: $r = 0.63$). Thus, higher IHI is associated with poorer performance on only the most difficult bimanual condition in young adults. Conversely, increased IHI is related to poorer performance across all conditions in the older adult contingent. Finally, no relationship was observed in young or older adults between interhemispheric facilitation and motor performance ($P > 0.1$), nor between facilitation and fiber tract microstructure ($P > 0.1$).

Discussion

This is the first study to simultaneously investigate the effects of age on interhemispheric microstructure and physiologic function along fiber tracts connecting the primary motor cortices. I employed a comprehensive approach to investigate callosal sensorimotor fiber tract structure, interhemispheric inhibition (IHI), facilitation, and their combined impact on motor control in young and older adults. I report that older adults exhibit disproportionately greater variability for bimanual actions when the two hands have independent force production goals. Additionally, I have shown that IHI is negatively associated with performance on the bimanual independent condition in both age groups; however, interhemispheric fiber tract microstructure is related to performance in a differential fashion for young and older adults. A novel finding of the current study is that higher radial diffusivity (i.e. poorer microstructure) is strongly

correlated with decreased IHI in older adults. This is the opposite of what has previously been observed in young adults (Wahl et al., 2007), and opposite of what I report for young adults in the current chapter. Thus this is the first work to report a qualitative shift in the relationship between sensorimotor fiber tract microstructure and IHI with age.

Multiple studies report declines in callosal size and microstructure with advancing age (cf. Seidler et al., 2010), which are associated with significant behavioral deficits. For example, less lateralized task processing during both cognitive (Muller-Oehring et al., 2007) and motor (Langan et al., 2010) tasks is associated with reductions in callosal size in older adults. In the current study I found that older adults exhibit differentially greater variability for bimanual tasks when the two hands have independent movement goals. This was evidenced by increased dominant hand variability during the bimanual independent force production task, as well as poorer performance on clinical (Purdue Pegboard) and functional (timed shirt buttoning) tasks of manual dexterity in older adults. On the other hand, older adults demonstrated comparable performance to young adults during the unimanual and bimanual simultaneous force conditions. Although previous studies report that increased callosal microstructure is beneficial to speeded, synchronous bimanual tasks in young adults (Johansen-Berg et al., 2007), recent work from our lab demonstrates that this relationship is task-specific. Specifically, *asynchronous* bimanual performance and callosal microstructure are negatively related in young adults, whereas they are positively correlated in older adults (Fling et al., 2011b). These findings strongly implicate age differences in size and integrity of callosal microstructure as key contributors to bimanual control deficits, potentially due to a reduced ability to inhibit motor overflow to the contralateral sensorimotor cortex.

These findings suggest a shift in the balance of interhemispheric inhibition and facilitation with advanced age. A converging body of literature indicates there are reductions in cortical inhibition with advancing age. Declines in both intrahemispheric (Peinemann et al., 2001; Sale and Semmler, 2005) and interhemispheric (Talelli et al., 2008) inhibition have been reported in older adults, as well as a reduced ability to modulate intracortical inhibition to meet task demands (Fujiyama et al., 2009). Age differences in IHI have not previously been investigated using the ipsilateral silent period technique, nor have there been reports of age differences in interhemispheric facilitation. I found that older adults had significantly greater interhemispheric facilitation, coupled with a trend for less interhemispheric inhibition. Furthermore, whereas stronger inhibition was predictive of decreased facilitation in the young adults, no such relationship existed in their older counterparts. Multiple studies have previously indicated that older adults have increased bilateral cortical activity (Ward and Frackowiak, 2003; Ward et al., 2008) and interhemispheric motor network connectivity (Langan et al., 2010; Zuo et al., 2010) potentially reflective of increased excitability within these motor regions, and a release from their typically inhibitory interactions. This study provides physiological evidence supporting this hypothesis; however the underlying mechanisms resulting in this potential shift in interhemispheric communication have yet to be fully elucidated.

Interhemispheric inhibition is mediated through gamma-aminobutyric acid (GABA) inhibitory interneurons (Werhahn et al., 1999). Older adults exhibit reduced glutamate levels in the motor cortex (assessed by ^1H MR spectroscopy; Kaiser et al., 2005), however less is known about changes in GABA with age. A recent study of the

visual cortex in post-mortem human brains highlights both pre- and post-synaptic losses of GABA_A signaling in the aging visual cortex (Pinto et al., 2010). The authors report two significant shifts in GABAergic signaling that accompany advanced age: 1) older adults have a greater capacity to traffic GABA_A to the synapse (more GABA vesicular transporter) while young adults have a greater capacity to produce GABA_A (more glutamic acid decarboxylase 65); and 2) older adults have relatively more pre-synaptic (more glutamic acid decarboxylase 65) expression while young adults have relatively more post-synaptic (more Gephyrin) expression (Pinto et al., 2010). Both of these changes point to alterations in functioning of GABAergic synapses in the visual cortex of older adults. To my knowledge, age-related differences in the concentration of GABA_B receptors (such as those mediating the iSP) have yet to be explored, nor has GABAergic signaling been studied in the aging motor cortex. Both phenomena could underlie decreased IHI in older adults.

Inter-individual variability in motor control is frequently treated as a source of 'noise' and discarded by averaging data from a group of participants. Kanai and Rees (2011) recently proposed that inter-individual differences can be used as a source of information to link human behavior to brain anatomy. Indeed, I report that increased IHI was related to poorer performance across all force production tasks in older adults, whereas increased IHI was only related to poorer performance during the bimanual independent task in young adults. Similarly, previous work has shown that older adults benefit from bihemispheric processing across all levels of task complexity on a divided visual field letter-matching task, whereas young adults only demonstrate similar benefits on the most complex tasks (Reuter-Lorenz et al., 1999). Taken together these results

suggest that older adults benefit from bilateral cortical cooperation (decreased IHI) across all tasks, whereas young adults only benefitted from such cooperation during the bimanual independent task.

While IHI is necessary to prevent interference of control processes between the two cortices (cf. Bloom & Hynd 2005; Carson, 2005), emerging work demonstrates that reduced IHI is beneficial for performance of asynchronous bimanual tasks (Shim et al. 2005). For example, musicians have decreased IHI compared to non-musicians (Ridding et al., 2000). The fact that IHI and fiber tract microstructure are related to performance in a differential fashion for young and older adults strongly supports my finding of an age-related shift in the relationship between interhemispheric fiber tract structure and IHI.

While studies combining DTI and TMS have previously shown that fiber tract microstructure is a strong predictor of IHI capacity in young adults (Fling et al., in press; Wahl et al., 2007), I am unaware of any studies that have assessed this relationship in older adults. Here I report a fundamental shift with age in the relationship between microstructure of fiber tracts connecting bilateral primary motor cortices and IHI such that older adults with increased microstructure have decreased IHI. I suggest that these results implicate a change in the balance of interhemispheric excitatory and inhibitory communication with age. Such a change may be a (nonconscious) strategic shift; that is to say, older adults who are able to maintain interhemispheric fiber tract integrity may rely more on interhemispheric facilitation and less on IHI in order to facilitate improved motor control. It remains unclear whether this decreased IHI represents an adaptive change related to better motor control across the lifetime, or an explicit neural strategy adopted at a later point in life to facilitate improved performance. Either explanation is

plausible, however it is important to note that even in those older adults with relatively decreased IHI, motor performance was still notably poorer than young adults. Thus, this strategy alone would not insulate older adults from experiencing declines in performance.

Interhemispheric interactions between additional sensorimotor cortices (both homologous and non-homologous) were beyond the scope of the current paper, but are clearly worthy of further investigation. For example, movement-related facilitation from the right PMd to the left M1 has recently been shown to predict performance during anti-phase bimanual movements, suggesting that these connections contribute to independent yet coordinated control of the two hands (Liuzzi et al., 2011; van den Berg et al., 2010).

Conclusions

I report a qualitative shift in the balance of interhemispheric communication with age. This is evidenced by increased interhemispheric facilitation, increased motor overflow, and decreased interhemispheric inhibition in older adults relative to their younger counterparts. Further, I report that older adults have significantly reduced microstructure of interhemispheric fiber tracts connecting primary motor cortices. Greater microstructure of fiber tracts connecting primary motor cortices was related to *better* performance on the bimanual independent force production task in older adults, but *poorer* performance in young adults on the same task. Additionally, increased interhemispheric inhibition was related to poorer performance on all force production tasks in older adults, but only on the bimanual independent task in young adults. Finally, I report an age-related shift in the relationship between interhemispheric inhibition and callosal fiber tract microstructure connecting bilateral primary motor cortices. Increased

structural integrity was positively associated with interhemispheric inhibition in young adults, whereas the relationship was negative in older adults. These findings suggest changes in interhemispheric communication with advancing age such that older adults rely on bilateral cortical cooperation to a greater extent than young adults on both unimanual and bimanual motor tasks.

References:

- Bangert AS, Reuter-Lorenz PA, Walsh CM, Schachter AB, Seidler RD. 2009. Bimanual coordination and aging: neurobehavioral implications. *Neuropsychologia* 48:1165-1170.
- Basser PJ, Pierpaoli C. 1996. Microstructural and physiological features of tissues elucidated by quantitative-diffusion-tensor MRI. *J Magn Reson B* 111:209-219.
- Basser PJ, Pajevic S, Pierpaoli C, Duda J, Aldroubi A. 2000. In vivo fiber tractography using DT-MRI data. *Magn Reson Med* 44:625-632.
- Bloom JS, Hynd GW. 2005. The role of the corpus callosum in interhemispheric transfer of information: excitation or inhibition? *Neuropsychol Rev* 15:59-71.
- Carey JR, Allison JD, Mundale MO. 1983. Electromyographic study of muscular overflow during precision handgrip. *Phys Ther* 63:505-511.
- Carson RG. 2005. Neural pathways mediating bilateral interactions between the upper limbs. *Brain Research Reviews* 49:641-62.
- Carson RG, Riek S, Mackey DC, Meichenbaum DP, Willms K, Forner M, Byblow WD. 2004. Excitability changes in human forearm corticospinal projections and spinal reflex pathways during rhythmic voluntary movement of the opposite limb. *J Physiol* 560:929-940.
- Chen R, Yung D, Li JY. 2003. Organization of ipsilateral excitatory and inhibitory pathways in the human motor cortex. *J Neurophysiol* 89:1256-1264.
- Davis SW, Dennis NA, Buchler NG, White LE, Madden DJ, Cabeza R. 2009. Assessing the effects of age on long white matter tracts using diffusion tensor tractography. *Neuroimage* 46:530-541.
- Fling BW, Benson BL, Seidler RD (In press) Transcallosal sensorimotor fiber tract structure-function relationships. *Hum Br Map*.
- Fling BW, Chapekis M, Reuter-Lorenz PA, Anguera, J, Bo J, Langan J, Welsh RC, Seidler RD. 2011a. Age differences in callosal contributions to cognitive processes. *Neuropsychologia* 49(9):2564-9..
- Fling BW, Walsh CM, Bangert AS, Reuter-Lorenz PA, Welsh RC, Seidler RD. 2011b. Differential Callosal Contributions to Bimanual Control in Young and Older Adults. *J Cogn Neurosci* 23(9):2151-2165.
- Fujiyama H, Garry MI, Levin O, Swinnen SP, Summers JJ. 2009. Age-related differences in inhibitory processes during interlimb coordination. *Brain Res* 1262:38-47.
- Garvey MA, Ziemann U, Becker DA, Barker CA, Bartko JJ. 2001. New graphical method to measure silent periods evoked by transcranial magnetic stimulation. *Clin Neurophysiol* 112:1451-1460.
- Giovannelli F, Borgheresi A, Balestrieri F, Zaccara G, Viggiano MP, Cincotta M, Ziemann U. 2009. Modulation of interhemispheric inhibition by volitional motor activity: an ipsilateral silent period study. *J Physiol* 587:5393-5410.
- Johansen-Berg H, Della-Maggiore V, Behrens TE, Smith SM, Paus T. 2007. Integrity of white matter in the corpus callosum correlates with bimanual co-ordination skills. *Neuroimage* 36 Suppl 2:T16-21.
- Jung P, Ziemann U. 2006. Differences of the ipsilateral silent period in small hand muscles. *Muscle Nerve* 34:431-436.
- Kaiser LG, Schuff N, Cashdollar N, Weiner MW. 2005. Age-related glutamate and glutamine concentration changes in normal human brain: ¹H MR spectroscopy

- study at 4 T. *Neurobio of Aging* 26:665-672.
- Kanai R, Rees G. 2011. The structural basis of inter-individual differences in human behaviour and cognition. *Nat Rev Neurosci* 12(4):231-42.
- Langan J, Peltier SJ, Bo J, Fling BW, Welsh RC, Seidler RD. 2010. Functional implications of age differences in motor system connectivity. *Front Syst Neurosci* 4:17.
- Liuzzi G, Hornib V, Zimerman M, Gerloff C, Hummel FC. 2011. Coordination of uncoupled bimanual movements by strictly timed interhemispheric connectivity. *J Neurosci* 42:9111-9117.
- Mayka MA, Corcos DM, Leurgans SE, Vaillancourt DE. 2006. Three-dimensional locations and boundaries of motor and premotor cortices as defined by functional brain imaging: a meta-analysis. *Neuroimage* 31:1453-1474.
- Meyer BU, Roricht S, Graf von Einsiedel H, Kruggel F, Weindl A. 1995. Inhibitory and excitatory interhemispheric transfers between motor cortical areas in normal humans and patients with abnormalities of the corpus callosum. *Brain* 118 (Pt 2):429-440.
- Mori S, van Zijl PC. 2002. Fiber tracking: principles and strategies - a technical review. *NMR Biomed* 15:468-480.
- Muller-Oehring EM, Schulte T, Raassi C, Pfefferbaum A, Sullivan EV. 2007. Local-global interference is modulated by age, sex and anterior corpus callosum size. *Brain Res* 1142:189-205.
- Oldfield RC. 1971. The assessment and analysis of handedness: the Edinburgh inventory. *Neuropsychologia* 9:97-113.
- Pinto JGA, Hornby KR, Jones DG, Murphy KM. 2010. Developmental changes in GABAergic mechanisms in human visual cortex across the lifespan. *Front Cell Neurosci* 4:16.
- Reuter-Lorenz PA & Park DC. 2005. Brain aging: reorganizing discoveries about the aging mind. *Curr Opin Neurobiol* 15(2):245-51.
- Reuter-Lorenz PA, Stanczak L, Miller AC. 1999. Neural Recruitment and Cognitive Aging: Two Hemispheres Are Better Than One, Especially as You Age. *Psychological Science* 10:494-500.
- Ridding MC, Brouwer B, Nordstrom MA. 2000. Reduced interhemispheric inhibition in musicians. *Exp Brain Res* 133:249-253.
- Sale MV, Semmler JG. 2005. Age-related differences in corticospinal control during functional isometric contractions in left and right hands. *J Appl Physiol* 99:1483-1493.
- Seidler RD, Bernard JA, Burutolu TB, Fling BW, Gordon MT, Gwin JT, Kwak Y, Lipps DB. 2010. Motor control and aging: links to age-related brain structural, functional, and biochemical effects. *Neurosci Biobehav Rev* 34:721-733.
- Shim JK, Kim SW, Oh SJ, Kang N, Zatsiorsky VM, Latash ML. 2005. Plastic changes in interhemispheric inhibition with practice of a two-hand force production task: a transcranial magnetic stimulation study. *Neurosci Lett* 374:104-108.
- Sohn YH, Jung HY, Kaelin-Lang A, Hallett M. 2003. Excitability of the ipsilateral motor cortex during phasic voluntary hand movement. *Exp Brain Res* 148(2):176-85.
- Sullivan EV, Rohlfing T, Pfefferbaum. 2010a. A quantitative fiber tracking of lateral and interhemispheric white matter systems in normal aging: relations to timed

- performance. *Neurobiol Aging* 31:464-481.
- Sullivan EV, Rohlfing T, Pfefferbaum A. 2010b. Longitudinal study of callosal microstructure in the normal adult aging brain using quantitative DTI fiber tracking. *Dev Neuropsychol* 35:233-256.
- Swinnen SP. 2002. Intermanual coordination: from behavioural principles to neural-network interactions. *Nat Rev Neurosci* 3:350-361.
- Talelli P, Ewas A, Waddingham W, Rothwell JC, Ward NS. 2008. Neural correlates of age-related changes in cortical neurophysiology. *Neuroimage* 40:1772-1781.
- Tournier JD, Mori S, Leemans A. 2011. Diffusion tensor imaging and beyond. *Magn Reson Med*. Epub Ahead of print.
- Triggs WJ, Calvanio R, Macdonell RA, Cros D, Chiappa KH. 1994. Physiological motor asymmetry in human handedness: evidence from transcranial magnetic stimulation. *Brain Res* 636:270-276.
- Vaillancourt DE, Newell KM. 2003. Aging and the time and frequency structure of force output variability. *J Appl Physiol* 94:903-912.
- van den Berg FE, Swinnen SP, Wenderoth N. 2010. Hemispheric Asymmetries of the Premotor Cortex are Task Specific as Revealed by Disruptive TMS During Bimanual Versus Unimanual Movements. *Cereb Cortex* 20(12):2842-51.
- Wahl M, Lauterbach-Soon B, Hattingen E, Jung P, Singer O, Volz S, Klein JC, Steinmetz H, Ziemann U. 2007. Human motor corpus callosum: topography, somatotopy, and link between microstructure and function. *J Neurosci* 27:12132-12138.
- Ward NS, and Frackowiak RS. 2003. Age-related changes in the neural correlates of motor performance. *Brain* 126:873-88.
- Ward NS, Swayne OB, Newton JM. 2008. Age-dependent changes in the neural correlates of force modulation: an fMRI study. *Neurobiol Aging* 29(9):1434-46.
- Wassermann EM, Fuhr P, Cohen LG, Hallett M. 1991. Effects of transcranial magnetic stimulation on ipsilateral muscles. *Neurology* 41:1795-1799.
- Werhahn KJ, Kunesch E, Noachtar S, Benecke R, Classen J. 1999. Differential effects on motorcortical inhibition induced by blockade of GABA uptake in humans. *J Physiol* 517:591-7.
- Zuo, X., Kelly, C., DiMartino, A., Mennes, M., Margulies, D.S., Bangaru, S., Grzadzinski, R., Evans, A.C., Zang, Y., Castellanos, F.X., & Milham, M.P. (2010). Growing together and growing apart: regional and sex differences in the lifespan developmental trajectories of functional homotopy. *J Neurosci*, 30(45), 15034-43.

CHAPTER V

General discussion and conclusions

Overview

The overarching goal of my dissertation was to determine whether age-related declines in callosal structure and interhemispheric inhibition contribute to previously described age deficits in uni- and bimanual control. I collected diffusion weighted images to identify homologous interhemispheric connections between primary and secondary sensorimotor areas to further our understanding of the contributions of callosal fiber tract structure to motor control. I have generated a mid-sagittal callosal spatial atlas in normalized MNI space for future studies to use when investigating callosal fiber tracts connecting primary and secondary sensorimotor cortices. Additionally, I found a positive relationship between strength of interhemispheric inhibition and microstructure of interhemispheric fibers that is specific to tracts connecting the primary motor cortices in young adults. Thus, increased fiber microstructure in young adults predicted higher interhemispheric inhibitory capacity (Chapter 2). In assessing the contributions of IHI to motor control I demonstrated that individuals with greater inhibitory capacity had reduced mirror EMG activity in the left hand during unimanual right hand contraction. However, these same individuals demonstrated the poorest performance during the bimanual independent force production task. I suggest that a high capacity for IHI from

one motor cortex to another can effectively prevent “motor overflow” during unimanual tasks, but it can also limit the ability for optimal control during bimanual independent tasks, possibly due to a reduced capability for interhemispheric cooperation (Chapter 3). Finally, I showed that better fiber tract structural integrity was related to *poorer* independent bimanual motor control in young adults, but *better* control in older adults on the same task (Chapter 4). Using TMS in the same individuals I have shown that increased interhemispheric inhibition was related to poorer bimanual task performance in older adults across all levels of uni- and bimanual control, whereas this relationship was only observed in young adults for the bimanual independent task. Finally, I found a fundamental shift with age in the relationship between callosal fiber tract microstructure and inhibitory function. Specifically, older adults with better callosal tract microstructure had reduced interhemispheric inhibition, potentially to facilitate performance on independent bimanual tasks. Collectively, these findings contribute to a comprehensive understanding of structural connectivity and neurophysiologic function of interhemispheric sensorimotor fibers and their respective contributions to motor control.

General discussion

In my first study I delineated mutually exclusive interhemispheric sensorimotor fiber tracts. Following callosal fiber tract identification, I investigated the relationship between callosal tract microstructure and interhemispheric inhibition. To accomplish this I utilized a multi-modal neuroimaging approach using DTI to assess structural connectivity and TMS to assess interhemispheric inhibition. Based on previous work by myself (Fling et al., in press b) and others (Koerte et al., 2009) I hypothesized that

callosal microstructure would be negatively associated with interhemispheric inhibition in a young adult cohort. This hypothesis is supported by my recent work demonstrating that higher CC microstructural integrity is associated with *poorer* performance on bimanual tasks requiring a large degree of interhemispheric inhibition (Fling et al., in press b).

I mapped mutually exclusive transcallosal connections between homologous sensorimotor regions and computed quantitative metrics of each fiber tract (Chapter 2). Paralleling work in non-human primates (Danceuse et al., 2007; Fang et al., 2009; Pandya and Vignolo, 1968; Rouiller et al., 1994) I found the densest interhemispheric sensorimotor connections to be between the SMA and pre-SMA. Additionally, I provided a mid-sagittal callosal atlas in normalized MNI space for future studies to use when investigating callosal fiber tracts connecting primary and secondary sensorimotor cortices. Contrary to my hypothesis, I report a strong, positive relationship between strength of interhemispheric inhibition and microstructure of interhemispheric fibers that is specific to tracts connecting the primary motor cortices in young adults. These results, taken together with my previous work (Fling et al., in press b), suggest that greater interhemispheric inhibition and fiber tract microstructure are detrimental to independent bimanual performance in young adults regardless of whether the independent manual control is focused on temporal replication (tapping) or force production.

Previous work has demonstrated that IHI is increased during both unimanual and independent bimanual movements of the upper limbs in comparison to synchronous bimanual movements, likely to minimize interference between the hands (Fujiyama et al. 2009; Giovannelli et al. 2009; Stinear & Byblow, 2002; Vercauteren et al. 2008). Thus

my second study investigated the relationship(s) between motor performance and individual differences in inhibitory capacity of the corpus callosum (Chapter 3). I hypothesized that individuals with greater IHI capacity would be able to inhibit motor overflow during unimanual contraction to a greater extent. Furthermore, I predicted that these same individuals would demonstrate poorer performance on the bimanual independent task. In agreement with these hypotheses I found that individuals with greater IHI capacity demonstrated reduced mirror EMG activity in the left hand during unimanual right hand contraction. These same individuals demonstrated the poorest performance during the bimanual independent force production task. I suggest that a high capacity for IHI from one motor cortex to another can effectively prevent “motor overflow” during unimanual tasks. However, taken together, the results of Chapters 2 and 3 suggest that increased callosal microstructure and IHI likely limits the ability for optimal control during independent bimanual tasks, possibly due to a reduced capability for interhemispheric cooperation.

I have previously reported that older adults’ performance is differentially impaired during bimanual movements where each hand has an independent movement goal (Fling et al., in press b). Such asynchronous bimanual actions purportedly rely on interhemispheric communication via the corpus callosum. Considering that callosal microstructure declines with advancing age (Fling et al., 2011a; b), I evaluated the hypothesis that age-related degradation of callosal structure and inhibitory function contribute to the selective difficulty older adults have with performing asynchronous actions (Chapter 4). Specifically, I hypothesized that better microstructure of callosal tracts connecting the two primary motor cortices would be positively related to

independent bimanual task performance in older adults, but negatively related to performance in young adults. Further, I hypothesized that increased interhemispheric inhibition would be related to poorer independent bimanual task performance in both young and older adults. Consistent with my hypotheses, I found that better microstructure of callosal tracts connecting the two primary motor cortices was positively related to bimanual task performance in older adults, but negatively related to performance in young adults. Further, increased interhemispheric inhibition was related to poorer bimanual task performance in older adults across all tasks, whereas this relationship was only observed in young adults for the independent bimanual task. Finally, I report a fundamental shift with age in the relationship between callosal fiber tract microstructure and inhibitory function. Specifically, older adults with better callosal tract microstructure have reduced interhemispheric inhibition, potentially to facilitate performance on independent bimanual tasks.

The series of studies in the current dissertation collectively demonstrates the differential contributions of interhemispheric inhibition and fiber tract structure to motor control in young and older adults. Based upon the results of these studies, I suggest that in young adults, increased interhemispheric inhibitory function is associated with larger callosal size and increased fiber tract microstructure, whereas the inverse relationship is true in older adults. Furthermore, a parsimonious and testable hypothesis that builds upon my recent findings is that performance on bimanual tasks falls along a continuum, which demonstrates a shared optimal region of callosal microstructure and IHI for young and older adults. That is, young and older adults exhibit maximal performance for a comparable range of callosal microstructure and IHI values. However, structure-

physiological function-performance relationships differentially diverge from this range for the two age groups (**Figure 5.1**).

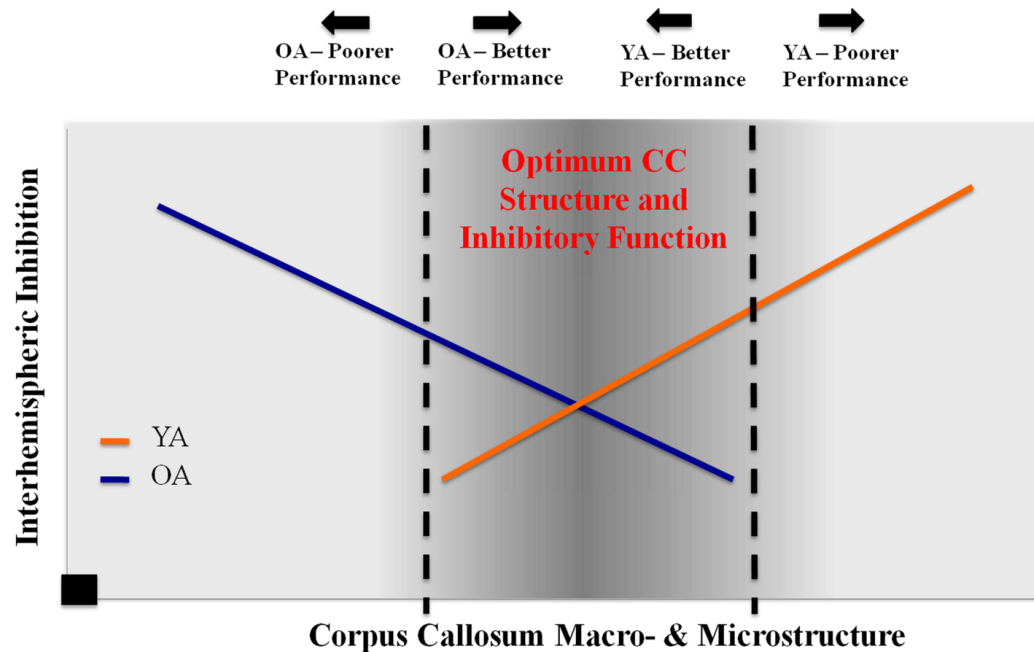


Figure 5.1 - This diagram provides a graphic representation of my hypothesis that performance on bimanual tasks falls along a continuum which demonstrates a shared optimal region of callosal microstructure and interhemispheric inhibition for young and older adults (darker gray central zone). Structure-physiological function-performance relationships differentially diverge from this range for the two age groups, with greater interhemispheric inhibition and reduced callosal structure associated with poorer performance in older adults and greater interhemispheric inhibition and greater callosal structure associated with poorer performance in young adults. The black square data point at $x, y=0$ indicates that there is no capacity for interhemispheric inhibition in the complete absence of the corpus callosum.

Caveats & Limitations

A few limitations should be taken into account when interpreting the findings of my experiments. The most notable is my choice of deterministic tractography to identify interhemispheric callosal fiber tracts. Currently, DTI is most commonly used to extract

fiber orientations from the diffusion-weighted signal as done in the current dissertation (Basser et al., 1994a,b). However, in voxels containing multiple fiber orientations, this model has been shown to be inadequate (Alexander et al., 2002; Frank, 2001, 2002; Tuch et al., 2002). Such voxels occur frequently throughout the white matter due to partial volume effects between adjacent tracts. A recent study estimated that a third of the white matter voxels contain complex fiber architecture (Behrens et al., 2007). This has important implications for fiber tractography, as most white matter tracts will traverse regions with multiple fiber orientations at some point along their path. In such regions, the orientation extracted from the diffusion tensor is unreliable and may cause false negatives, in which tracking terminates (Behrens et al., 2007), or false positives, in which tracking switches to an unrelated adjacent tract (Pierpaoli et al., 2001).

While it is true that deterministic tractography can be susceptible to a decreased signal-to-noise ratio as a result of crossing fiber tracts, this technique has been utilized extensively to describe organization and microstructure of large white matter fiber bundles such as the corpus callosum and the cortical-spinal tract (Davis et al., 2009; Hofer and Frahm, 2006; Sullivan et al., 2010). Furthermore, I have made a concerted effort in the Discussion section of Chapter 2 to relate the results to previous anatomical studies performed in animal and post-mortem human brains to help support my interpretations of “relative density”. My results align quite nicely with the existing literature in this respect. Additionally, previous work using probabilistic tractography to assess interhemispheric sensorimotor connections has produced very similar results to those in the current study, demonstrating largely medial cortical projections to sensorimotor cortices (e.g. Bonzano et al., 2011; Johansen-Berg et al., 2007).

It should be noted that although I have demonstrated significant contributions from both interhemispheric structure and function to motor control, these studies are still indirect assessments of the true underlying neural mechanisms. That is to say, the current dissertation is not able to describe causal effects at the neurotransmitter level, nor are the studies able to describe the mechanism of callosal microstructural decline. For example, while the iSP is mediated through GABA_B neurotransmitter receptors (Werhahn et al., 1999), the current studies are unable to determine whether the observed declines in IHI in older adults are the results of reduced density of inhibitory neurotransmitters or a shift in the balance of inhibitory and excitatory interhemispheric communication with age. Further, DTI is an indirect metric of white matter microstructure and while increases in radial diffusivity, as observed in older adults (Chapter 4), are suggested to reflect myelin deterioration (Gulani et al., 2001), this interpretation must be made with caution.

An additional limitation of the current work is the use of a correlational approach utilizing both fiber tract microstructure and interhemispheric inhibition as predictors of manual motor performance. That is to say, correlational analysis alone cannot infer causality of the observed relationships. Future studies would benefit by incorporating more direct assessments at the neurotransmitter level to describe the underlying age-related mechanisms responsible for the relationships observed in my dissertation. For example MR spectroscopy can be used to identify the density of GABA and glutamate neurotransmitter receptors within the motor cortices. Identifying age-differences in the density and availability of these neurotransmitter receptors in the aging motor cortex will provide a more direct explanation of the mechanisms underlying the age differences in interhemispheric facilitation and inhibition reported in my dissertation.

There are also limitations related to the force production tasks utilized in my dissertation. The goal of my dissertation is to leverage the current results in a more applied sense to improve function on activities of daily living. The force production tasks, specifically the bimanual independent task, may not be ideal for such an extrapolation. While my previous work (Fling et al., 2011b) and the work comprising my dissertation report similar relationships between callosal microstructure and motor performance, the choice of motor tasks are quite different (discrete finger tapping versus continuous force production in the current investigation). The tapping tasks I have previously used are an example of event timing, where individual are making discrete movements that are temporally coupled in some fashion (Zelaznik & Rosenbaum, 2010). Conversely the force production paradigm used in this dissertation is not temporally coupled; i.e. during the bimanual independent task the two hands do not share a mutual goal, each hand has its own distinct task goal. Future studies using these same force production tasks may benefit from integrating visual feedback into a single display, such as a Lissajous plot (Kovacs et al., 2009). Previous work has shown that moving the two limbs in a cyclical fashion 90° out of phase with each other is quite difficult, but performance can be improved if the limb trajectories are plotted in real time on a single angle-angle, or Lissajous plot, resulting in a circular trajectory (cf. Verschueren et al., 1997; Lee et al., 1995; Swinnen et al., 1991, 1996). Recent work by Kovacs and colleagues (2009) has shown that a variety of difficult out-of-phase bimanual actions can be performed with ease if participants are prevented from viewing the two hands moving and instead only view a single, integrated perceptual goal for the task (i.e., an angle-angle plot of the two moving limbs). I hypothesize that presenting task goals and movement

feedback as a single integrated perceptual goal could reduce the IHI demands of bimanual control and result in improved performance for both young and older adults.

An additional limitation pertinent to Chapters 3 and 4 is the attentional demand required to perform two tasks synchronously, particularly during the bimanual independent force production task. It is well established that performing two tasks simultaneously often degrades performance of one or both tasks, potentially due to competition for shared attentional resources (Hiraga et al. 2009). In the current studies performance of the dominant hand became more variable as the involvement of the non-dominant hand's task increased for both young and older adults. Therefore, while the increase in dominant hand variability may be due to interhemispheric M1 interactions, it is also quite possible that the dual-task nature of the bimanual condition played a significant role. Previous work has shown that older adults benefit from bihemispheric processing across all levels of task complexity on a divided visual field letter-matching task, whereas young adults only demonstrate similar benefits on the most complex tasks (Reuter-Lorenz et al., 1999). Taken together these results suggest that older adults benefit from bilateral cortical cooperation (decreased IHI) across tasks of all complexity, whereas young adults only benefit from such cooperation during independent bimanual tasks.

Implications and future directions

The current studies have important applied implications for understanding and counteracting age deficits in motor function, as well as theoretical importance for determining the neural bases of bimanual control. These studies have provided an

integrated view of relationships between callosal structure, physiology, and functional motor behavior extending our current understanding of neuromotor control. Moreover, the results from these studies have the potential to extend work productivity and prolong independent living for older adults.

Future studies would benefit from exploring interhemispheric resting state functional connectivity (e.g. Langan et al., 2010; Jelsone-Swain et al., 2011), along with DTI to further our understanding of the interaction of these different measures, along with potential age-related differences. Furthermore, incorporating MR spectroscopy to assess neurotransmitter concentration and density would be beneficial to answering questions raised by the current dissertation. It is possible that there is a selective decrease in the concentration of GABA, as compared to glutamate, with aging. Furthermore, by altering stimulation parameters, TMS can be used to assess interhemispheric excitation as well as IHI (Chen et al., 2003). It would be beneficial to assess each of these metrics in the same older adult individuals to determine if there is a shift in the balance of interhemispheric communication as compared to young adults.

These studies also have the potential to provide a greater understanding of clinical populations exhibiting altered interhemispheric interactions such as individuals with multiple sclerosis and those living with a stroke. Individuals with multiple sclerosis demonstrate declines in motor control as well as decreased fiber tract microstructure between primary motor cortices (Bonzano et al., 2008; Wahl et al., 2010) and decreased IHI compared to neurologically healthy controls (Wahl et al., 2010). These declines may be similar to those observed in older adults, however this has yet to be investigated. It is quite possible that both healthy older adults and those living with multiple sclerosis

would benefit from training interventions designed to facilitate independent bimanual control.

Increased IHI from the less affected hemisphere to the more affected hemisphere has been shown to be a significant contributor to post-stroke motor deficits (Hummel & Cohen, 2006; Murase et al., 2004). This effect reduces the potential for neural plasticity and recovery in the more affected hemisphere due to the increased suppressive effect. Recent rehabilitation studies have demonstrated that through extrinsic constraints (constraint-induced therapy; Liepert et al., 2004) as well as non-invasive brain stimulation interventions (Harris-Love et al., 2011; Liepert et al., 2004), the balance of interhemispheric communication can be restored, although not to pre- neurological insult levels. I am interested in combining metrics of structural sensorimotor network connectivity (assessed with DTI as in the current dissertation) with non-invasive stimulation protocols. It is quite possible that interhemispheric structural (DTI) and functional (fcMRI) connectivity strength may serve as excellent predictors of the potential for neurophysiologic plasticity in individuals with chronic unilateral hemispheric stroke.

Conclusions

The current dissertation provides a comprehensive description of interhemispheric sensorimotor structural connectivity and neurophysiologic function in young and older adults. By combinatorial approaches of behavior, MRI, DTI, and TMS I have shown the following: **I)** a strong, positive relationship between strength of interhemispheric

inhibition and microstructure of interhemispheric fibers specific to tracts connecting the primary motor cortices in young adults. **II)** Young adults with greater IHI capacity demonstrate reduced mirror EMG activity in the left hand during unimanual right hand contraction; however, these same individuals demonstrate the poorest performance during the bimanual independent force production task. **III)** Finally, better microstructure of callosal tracts connecting the two primary motor cortices was positively related to bimanual task performance in older adults, but negatively related to performance in young adults. Further, increased IHI was related to poorer bimanual task performance in older adults across all unimanual and bimanual tasks, whereas this relationship was only observed in young adults for the independent bimanual task. I report a fundamental shift with age in the relationship between callosal fiber tract microstructure and inhibitory function. These studies provide an integrated view of relationships between callosal structure, physiology, and functional motor behavior extending our current understanding of neuromotor control.

References

- Alexander DC, Barker GJ, Arridge SR (2002): Detection and modeling of non-Gaussian apparent diffusion coefficient profiles in human brain data. *Magn Reson Med* 48:331-340.
- Basser PJ, Mattiello J, LeBihan D (1994a): Estimation of the effective self-diffusion tensor from the NMR spin echo. *J Magn Reson B* 103:247-254.
- Basser PJ, Mattiello J, LeBihan D (1994b): MR diffusion tensor spectroscopy and imaging. *Biophys J* 66:259-267.
- Behrens TE, Johansen-Berg H, Jbabdi S, Rushworth MF, Woolrich MW (2007): Probabilistic diffusion tractography with multiple fibre orientations: What can we gain? *NeuroImage* 34:144-155.
- Bonzano L, Tacchino A, Roccatagliata L, Abbruzzese G, Mancardi GL, Bove M. (2008): Callosal contributions to simultaneous bimanual finger movements. *J Neurosci* 28(12):3227-33.
- Bonzano L, Tacchino A, Roccatagliata L, Mancardi GL, Abbruzzese G, Bove M. (2011): Structural integrity of callosal midbody influences intermanual transfer in a motor reaction-time task. *Hum Br Map* 32(2):218-228.
- Chen R, Yung D, Li JY (2003) Organization of ipsilateral excitatory and inhibitory pathways in the human motor cortex. *J Neurophysiol* 89:1256-1264.
- Dancause N, Barbay S, Frost SB, Mahnken JD, Nudo RJ. (2007): Interhemispheric connections of the ventral premotor cortex in a new world primate. *J Comp Neurol* 505(6):701-15.
- Davis SW, Dennis NA, Buchler NG, White LE, Madden DJ, Cabeza R (2009) Assessing the effects of age on long white matter tracts using diffusion tensor tractography. *Neuroimage* 46:530-541.
- Fang PC, Stepniewska I, Kaas JH. (2008): Corpus callosum connections of subdivisions of motor and premotor cortex, and frontal eye field in a prosimian primate, *Otolemur garnetti*. *J Comp Neurol* 508(4):565-78.
- Fling BW, Chapekis M, Reuter-Lorenz PA, Anguera J, Bo J, Langan J, Welsh RC, Seidler RD (2011a): Age differences in callosal contributions to cognitive and motor performance. *Neuropsychologia*.
- Fling BW, Walsh CM, Bangert AS, Reuter-Lorenz PA, Welsh RC, Seidler RD (2011b): Differential Callosal Contributions to Bimanual Control in Young and Older Adults. *J Cogn Neurosci*.
- Frank LR (2001): Anisotropy in high angular resolution diffusionweighted MRI. *Magn Reson Med* 45:935-939.
- Frank LR (2002): Characterization of anisotropy in high angular resolution diffusion-weighted MRI. *Magn Reson Med* 47:1083-1099.
- Fujiyama H, Garry MI, Levin O, Swinnen SP, and Summers JJ (2009): Age-related differences in inhibitory processes during interlimb coordination. *Brain Res* 1262: 38-47.

- Giovannelli F, Borgheresi A, Balestrieri F, Zaccara G, Viggiano MP, Cincotta M, Ziemann U. (2009): Modulation of interhemispheric inhibition by volitional motor activity: an ipsilateral silent period study. *J Physiol* 587(Pt 22):5393-410.
- Gulani, V., Webb, A. G., Duncan, I. D., & Lauterbur, P. C. (2001). Apparent diffusion tensor measurements in myelin-deficient rat spinal cords. *Magn Reson Med*, 45(2), 191-195.
- Harrie-Love ML, Morton SM, Perez MA, and Cohen LG. Mechanisms of short-term training-induced reaching improvement in severely hemiparetic stroke patients: A TMS study. *Neurorehabil Neural Repair* Epub ahead of print 2011 Feb 22.
- Hiraga CY, Garry MI, Carson RG, and Summers JJ. Dual-task interference: attentional and neurophysiological influences. *Behav Br Res* 205: 10-18, 2009.
- Hofer S, Frahm J. (2006): Topography of the human corpus callosum revisited--comprehensive fiber tractography using diffusion tensor magnetic resonance imaging. *Neuroimage* 32(3):989-94.
- Hummel FC, and Cohen LG (2006). Non-invasive brain stimulation: a new strategy to improve neurorehabilitation after stroke? *Lancet Neurol* 5(8):708-12.
- Jelsone-Swain L, Fling BW, Seidler RD, Horvatter R, Gruis K, Welsh RC (2010). Interhemispheric motor cortex connectivity changes in those with amyotrophic lateral sclerosis. *Frontiers in Systems Neuroscience*. 4:158.
- Johansen-Berg H, Della-Maggiore V, Behrens TE, Smith SM, Paus T (2007): Integrity of white matter in the corpus callosum correlates with bimanual co-ordination skills. *Neuroimage* 36 Suppl 2:T16-21.
- Koerte I, Heinen F, Fuchs T, Laubender RP, Pomschar A, Stahl R, Berweck S, Winkler P, Hufschmidt A, Reiser MF and others. (2009): Anisotropy of callosal motor fibers in combination with transcranial magnetic stimulation in the course of motor development. *Invest Radiol* 44(5):279-84.
- Kovacs, A.J., Buchanan, J.J., & Shea, C.H., Bimanual 1:1 with 90 degree continuous relative phase: difficult or easy! *Exp Br Res*, 2009. 193(1): p. 129-136.
- Langan J, Peltier SJ, Bo J, Fling BW, Welsh RC, Seidler RD Functional implications of age differences in motor system connectivity. *Front Syst Neurosci* 4:17.
- Lee TD, Verschueren S (1995): Relative Phase Alterations During Bimanual Skill Acquisition. *J Mot Behav* 27(3): p. 263-274.
- Liepert J, Hamzei F, and Weller C. Lesion-induced and training-induced brain reorganization. *Restor Neurol Neurosci* 22(3-5):269-77.
- Murase N, Duque J, Mazzocchio R, and Cohen LG (2004) Influence of interhemispheric interactions on motor function in chronic stroke. *Ann Neurol* 55(3):400-9.
- Pandya DN, Vignolo LA. (1968): Interhemispheric neocortical projections of somatosensory areas I and II in the rhesus monkey. *Brain Res* 7(2):300-3.
- Pierpaoli C, Barnett A, Pajevic S, Chen R, Penix LR, Virta A, Bassar PJ (2001): Water diffusion changes in Wallerian degeneration and their dependence on white matter architecture. *NeuroImage* 13:1174-1185.

- Reuter-Lorenz, PA, Stanczak L, Miller A (1999): Neural recruitment and cognitive aging: Two hemispheres are better than one especially as you age. *Psychological Science* 10, 494-500.
- Rouiller EM, Babalian A, Kazennikov O, Moret V, Yu XH, Wiesendanger M. (1994): Transcallosal connections of the distal forelimb representations of the primary and supplementary motor cortical areas in macaque monkeys. *Exp Brain Res* 102(2):227-43.
- Stinear JW, and Byblow WD. (2002): Disinhibition in the human motor cortex is enhanced by synchronous upper limb movements. *J Physiol* 543: 307-316.
- Swinnen SP, Meulenbroek R (1996): Between-limb asynchronies during bimanual coordination: effects of manual dominance and attentional cueing. *Neuropsychologia* 34(12): 1203-1213.
- Swinnen SP, Walter CB, Serrien DJ (1991): Control of asymmetrical bimanual movements. *Exp Brain Res* 85(1): 163-173.
- Sullivan EV, Rohlfing T, Pfefferbaum A. (2010): Longitudinal study of callosal microstructure in the normal adult aging brain using quantitative DTI fiber tracking. *Dev Neuropsychol* 35(3):233-56.
- Tuch DS, Reese TG, Wiegell MR, Makris N, Belliveau JW, Wedeen VJ (2002): High angular resolution diffusion imaging reveals intravoxel white matter fiber heterogeneity. *Magn Reson Med* 48:577–582.
- Vercauteren K, Pleysier T, Van Belle L, Swinnen SP, and Wenderoth N (2008): Unimanual muscle activation increases interhemispheric inhibition from the active to the resting hemisphere. *Neurosci Lett* 445: 209-213.
- Verschueren SM, Dom R, De Weerd W (1997): Interlimb coordination in patients with Parkinson's disease: motor learning deficits and the importance of augmented information feedback. *Exp Brain Res* 113(3):497-508.
- Wahl M, Hubers A, Lauterbach-Soon B, Hattingen E, Jung P, Cohen LG, and Ziemann U (2011): Motor callosal disconnection in early relapsing-remitting multiple sclerosis. *Hum Brain Mapp* 32(6):846-55.
- Werhahn KJ, Kunesch E, Noachtar S, Benecke R, Classen J. (1999): Differential effects on motorcortical inhibition induced by blockade of GABA uptake in humans. *J Physiol* 517 (Pt 2):591-7.
- Zelaznik HN, Rosenbaum DA (2010): Timing processes are correlated when tasks share a salient event. *J Exp Psychol Hum Percept Perform* 36(6):1565-75.

APPENDIX

APPENDIX A – TMS Safety Screening Questionnaire

Screening Procedure to Identify Contraindications for TMS

Name: _____
Date of Birth: _____

Date: _____

In order to rule out risk factors and contraindications for transcranial magnetic stimulation, I need to ask you a few questions. It is important that you consider each question carefully and give an honest answer. If you are unsure about anything, please let me know.

1. Do you currently have a serious medical condition?
YES _____ NO _____
2. Have you ever had a seizure of any sort?
YES _____ NO _____
3. Has anyone in your family ever had epilepsy or experienced seizures?
YES _____ NO _____
4. Have you had active depression in the past 6 months?
YES _____ NO _____
5. Have you had attention deficit or learning disorder?
YES _____ NO _____
6. Do you take any epileptogenic medications?
YES _____ NO _____
7. Have you ever had a neurological disorder?
YES _____ NO _____
 - 7a. Ever had a serious head trauma?
YES _____ NO _____
 - 7b. Ever have a stroke?
YES _____ NO _____
 - 7c. Ever had any form of brain surgery?
YES _____ NO _____
8. Do you have a history of migraine or other types of severe or frequent headaches?
YES _____ NO _____

9. Do you have any metal implants in your head, including in your mouth?
YES _____ NO _____
10. Do you have permanent eye liner or any tattoos above the neck?
YES _____ NO _____
11. Do you have a pacemaker or any implanted medical devices?
YES _____ NO _____
12. Are you pregnant or is there any possibility that you may be?
YES _____ NO _____
13. Do you have high blood pressure that is not currently controlled by medication?
YES _____ NO _____
- 13a. If you are on medication for high blood pressure has it changed in the past 6 months?
YES _____ NO _____
14. Do you have any hearing loss or hearing impairments?
YES _____ NO _____
15. Do you consume more than two alcoholic drinks per day?
YES _____ NO _____
16. Have you ever been treated for alcoholism?
YES _____ NO _____