Functional and Neurophysiological correlates of Corticospinal Function in Human Aging

Travis Davidson
B.Sc.HK, University of Ottawa, 2009

Thesis presented to the Faculty of Graduate and Postdoctoral Studies
Submitted as a requirement for the degree
of Master of Science in Human Kinetics

School of Human Kinetics
Faculty of Health Sciences
University of Ottawa
June 2011

Acknowledgments

First and farmost, I would like to thank my thesis supervisor Dr. François Tremblay for his time and guidance throughout my research project. Thanks to him I was not only able successfully complete my project, but also have the opportunity to develop as a researcher by participating at various conferences.

I extend my gratitude to Sabah Master for her help in data collection as well as her company, guidance and suggestions throughout my whole research project. I would also like to acknowledge Marielle Young-Bernier help with data collection.

Thanks to Dr Nicole Paquet and Dr Erin Cressman for their suggestions as members of my thesis committee.

Finally, I would like to thank the Élizabeth Bruyère Research Institute and the University of Ottawa for their financial support. They provided a master's graduate study scholarship and a research trainee fellowship respectively, towards the completion and presentation of this project.

List of Abbreviations

AMT	active motor threshold
ANOVA	analysis of variance
ANCOVA	analysis of covariance
cm	centimetre
CM	corticomotor
cSP	contralateral silent period
CST	corticospinal tract
DTI	duration of transcallosal inhibition
EMG	electromyogram
FA	fractional anisotropy
FDI	first dorsal interosseous
FTT	simple finger tapping test
GABA	gamma-aminobutyric acid
GPT	grooved pegboard test
HAROLD	hemispheric asymmetry reduction in older adults
IHI	interhemispheric inhibition
ISI	inter-stimulus interval
iSP	ipsilateral silent period
iSParea	area under the curve during the ipsilateral silent period
kg	kilogram
$Latency_{fac}$	Latency facilitated during active contraction
$Latency_{120}$	MEP latency at 120% RMT

LTI	latency of transcallosal inhibition
MEP	motor evoked potential
MEP_{fac}	facilitated motor evoked potential amplitude
MEP_{120}	MEP elicited at 120% RMT
ms	milliseconds
MovT	reaction/movement time
MT	motor threshold
mV	millivolt
MVC	maximal voluntary contraction
M1	primary motor cortex
PFC	prefontral cortex
RC	recruitment curve
RMT	resting motor threshold
sqrtRC	Squareroot transformed slope of the recruitment curve
s	second
SRT	simple reaction time
TES	transcranial electric stimulation
TMS	transcranial magnetic stimulation
µV	microvolt

Summary

Healthy normal aging is characterized by a series of progressive changes observed throughout the body, such as those at the neurological and musculoskeletal level. However, few studies have examined the link that exists between age-related alteration in neurophysiology and hand function. In this study, we used transcranial magnetic stimulation (TMS) to investigate age-related effects on intracortical excitability and interhemispheric inhibition, including how changes in these measures could predict hand function. Participants consisted of young (n=13) and senior (n=17) healthy, right-handed individuals. Participants underwent a series of stimulations to determine their intracortical excitability and interhemispheric inhibition of each hemisphere. The former was evaluated by measuring the resting motor threshold (RMT), recruitment curve (RC) and contralateral silent period (cSP), while the latter was determined by measuring the ipsilateral silent period (iSP). Each participant also underwent behavioral testing bilaterally consisting of the grooved pegboard test (GPT), simple finger tapping test (FTT), simple reaction time (SRT), reaction/movement time (MovT) and pinch strength. Our results indicate an age-related slowing observable throughout most functional measures, with both age groups performing significantly better with their dominant hand. SRT was the only behavioral measure that was not affected by either age or handedness. Our neurophysiological measures obtained through TMS indicated an age-related decline in both intracortical excitability and interhemispheric inhibition. Only the senior participants demonstrated any interhemispheric asymmetries, which appeared in their RMT favoring the hemisphere controlling their dominant hand. When both age groups were combined, it was found that increases in both excitability and inhibition were found

to correlate with preserved hand function. For example, larger facilitated MEP amplitude was related to increased dexterity. Interestingly, intracortical measures taken during the active state were found to be better predictors of hand function than similar measures taken during the resting state. Additionally, the left hemisphere/right hand relationships were found to be stronger than those observed for the right hemisphere/left hand. Our results indicate that normative data for hand function and neurophysiology change with age, which could be helpful in the early diagnosis of conditions that could lead to pathological aging.

Table of contents

General introduction

The control of human movement is made possible by the intricate interplay that exists between the muskuloskelatal system, the nervous system and the environment where the movement is taking place. Voluntary movement in any part of the body is first iniated in the motor areas situated in the cortex. Following the generation of motor commands a neural signal is sent via the descending tracts to activate the alpha motor neurons. The primary interaction between the muscles and nervous system comes through these alpha motor neurons which provide the neural excitation that drives muscle contractions. This neuromuscular coupling, as well as each independent system, must be functionally optimal functional in order to allow the movements necessary for a good quality of life.

Small deficiencies that occur with age may lead to difficulty in performing fine manipulative actions (e.g., buttoning one's shirt). This decline in hand function has been associated with various changes affecting the nervous system both centrally in the brain and in the periphery (loss of touch receptors), as well as physical alterations in the muscular system (sarcopenia). Although it is widely accepted that functional ability of the hand deteriorates with age, the extent to which healthy aging affects neurophysiology has yet to be reliably quantified.

The current work seeks to identify and describe the effects of healthy aging on neurological functions that are involved in the control of manual dexterity with the overall goal of establishing relationships between age-related changes in neural functions and behaviour.

Chapter I: Litterature review

1. Neurophysiology of human motor control

Motor control can be defined as "the systematic transmission of nerve impulses from the motor cortex to motor units, resulting in coordinated contractions of muscles" (Mosby, 2009). Hence, motor control is a general definition that encompasses all motor areas, descending pathways and effectors. The central nervous system (CNS) of the human body is extremely complex. The forebrain alone is comprised of approximately 22 billion neurons with an estimated 157 trillion synapses (Saver, 2006). In addition, Shumway-Cook and Woollacott (2007) proposed that motor control involves not only internal processes related to CNS function but also the interactions with the individual and the environment in the context of task performance. The following sections provide an overview of the processes involve in motor control of the hand. The first section deals with the corticospinal system. The second examines methods to assess hand function. The last section deals with the neurophysiological basis of aging and its impact on hand function.

1.1 Cortical projections and connectivity

The human primary motor cortex (M1), which is located in the precentral gyrus, is the area associated with the execution of motor commands allowing movement in the human body. Fritz and Hitzig were the first to stimulate the cortex in order to map motor function in the dog in 1870. In the 1950s, Wilder Penfield helped to establish that the M1 had a somatotopic organization of body representation which is often referred to as the Penfield's motor homunculus (Penfield, & Rasmussen, 1952). To map motor responses,

Penfield applied direct stimulation of the precentral gyrus in patients undergoing open brain surgery for epilepsy.

Several descending pathways contribute to the transmission of the motor commands to spinal motoneurones to the effectors. The grouping of these descending pathways depends on their termination within the spinal gray matter (Kuypers & Brinkman, 1970). The three major descending pathways are the ventromedial brainstem pathway, the dorsolateral brainstem pathway and the corticospinal and corticobular pathways. Each one of these pathways possesses its own anatomy and functions which define them. The corticospinal pathway is considered the most functionally important in primates for its role in generation of discrete voluntary movements. In the primate's brain, the corticospinal tract (CST) originate from multiple areas in the frontal and parietal lobes, including the primary motor cortex (M1), the dorsal and ventral premotor cortices, the supplementary motor area, and cingulated motor areas, the primary somatosensory cortex, the posterior parietal cortex, and the parietal operculum (see Dum & Strick 2005). Corticomotor (CM) fibres project through the anterior and posterior limb of the internal capsule and descend in the cerebral peduncules. CM refers to the CST fibres that make direct, monosynaptic excitatory conections with motoneurons (Lemon & Griffiths, 2005). At the level of the lower medulla, ~85% of the fibers decussate and project down the contralateral dorsolateral funiculus to form the lateral CST. The remaining 15% of the fibers do not cross and remain ispsilateral and form the ventral CST (Lemon, 2008). Depending on their cortical origin, corticospinal neurones will make excitatory connections with spinal neurons in the dorsal, the intermediate or the ventral horn. In humans, most corticospinal neurons originating from M1 establish strong and

secure connections with spinal motoneurones in the ventral horn innervating limb muscles (Bernhard & Bohm, 1954).

The classical view of the CST is that it acts as the main motor pathway for the control of voluntary movement; however, recent studies have confirmed that it has a multitude of functions, each of which are similar in the fact that there is a cortical modulation of spinal cord activity (Lemon & Griffiths, 2005). Some known functions of the CST include the descending control of afferent inputs (Wall & Lidierth, 1997), gain control of spinal reflexes (Evarts & Tanji, 1976), excitation and inhibition of motoneurons (Maier, Illert, Kirkwood, Nielsen, & Lemon, 1998), autonomic control (Bacon & Smith, 1993) and plasticity (Wolpaw, 1997). The multitude of possible functions accord with the aforementioned fact that the CST originates from a variety of different cortical areas (Lemon & Griffiths, 2005).

Following a lesion to the CST, there will be initial deficits that reflect the loss of corticospinal connections to the spinal segments controlling the limb (Nishimura et al. 2007). Sasaki et al. (2004) found an absence of the excitatory postsynaptic potentials in the fast CM that are normally evoked in most hand motoneurons. Although some motor deficits are permanent, these impairments are often ameliorated over time; the extent of recovery seems to be related to the amount of CST fiber remaining. The recovery of the grasping function (Freund et al., 2006; Sasaki et al., 2004) or of locomotor function (Courtine et al., 2007; Nishimura et al., 2007) after corticospinal lesions at the spinal level most likely reflects the plastic changes occurring elsewhere in the central nervous system, for instance there is significant generation of these fibers above the lesion (Bareyre et al., 2004).

1.1.1 Animal studies

The motor systems of all mammals are composed of similar building blocks; all mammalian species possess the CST that links the cerebrum to the spinal cord (Nudo & Masterton, 1988, 1990). Hans Kuypers (1970) first showed that there are large differences in the functional organization of the CM system across different mammalian species. A number of studies have confirmed that the CM system is unique to primates; there are no functional CM connections in the cat (Illert, Lundberg, & Tanaka, 1976), rat (Yang & Lemon, 2003), raccoon (Gugino, Rowinski, & Stoney, 1990), or mouse (Alstermark, Ogawa, & Isa, 2004). The development of the CM system varies depending on the primate species (Lemon & Griffiths, 2005), for example it is well developed in the capuchin monkey and the macaque with great apes possessing generally more CM connections. In 2006, Rathelot and Strick created a technique using transneural labeling with the rabies virus to identify anatomically the cells of origin of the CM projection to hand muscles in the macaque monkey. The area of M1 that encompasses the CM cells innervating an individual muscle was found to overlap heavily with representations of other hand muscles (Rathelot & Strick, 2006). As stressed recently by Lemon (2009), these findings finally settle the long-running debate that the M1 has a fine, nonoverlapping, somatatotopic mapping of the hand muscles (Lemon, 1988; Phillips, 1975).

1.1.2 Human Studies

The CST is a critical motor pathway in humans and is more expanded than in any other mammalian species. Heffner & Masterton (1983) established the relationship across

species between the extent of development on the CST projections and the index of dexterity, with humans surpassing every other mammal in both dexterity and extent of CST projections. Therefore, it was postulated that the well developed CST affords humans superior dexterity; however, as a result lesions to this descending tract have more devastating effects than in any other mammals (Vilensky, 1987). Lesions to the CST will have irrevocable effects on motor function, despite some slow but substantial recovery (Ropper, Fisher, & Kleinman, 1979). Empirical data suggests that CM monosynaptic projections exist in motoneurons in humans with its strongest projections innervating distal limb muscles such as the intrinsic hand muscles (Baldissera & Cavallari, 1993; de Noordhout et al., 1999; Nielsen, Petersen, & Ballegaard, 1995). Additionally, the current research suggests that the CM system is a recently evolved feature that allows new aspects of motor behavior, including voluntary control of independent fingers (Lemon, 2008).

1.2 Stimulation techniques to investigate CST functions

In 1980, Merton and Morton created a procedure coined transcranial electrical simulation (TES) which allowed a non-invasive method to stimulate the cerebral cortex transcranially. They developed a device that produced a single high-voltage capacitative discharge capable of flowing through the scalp to stimulate the brain structure lying beneath. It was then shown that TES over the M1 could produce a motor response in associated muscles, known as a motor evoked potential (MEP), and that a stimulus over the visual cortex could produce phosphenes (Terao & Ugawa, 2002). However, this technique has a few drawbacks; the most significant being the pain accompanying

stimulation which is strong enough to prevent it from being adopted for widespread clinical use.

In 1985, Barker et al. developed a method called transcranial magnetic stimulation (TMS) in order to magnetically stimulate the human cerebrum in a non-invasive and practically painless manner. This technique creates a magnetic field that can penetrate the cranium virtually unimpeded. The changing magnetic fields in the cortex engender the creation of an eddy current that can depolarize cerebral neurons thereby generating a neural response that can be either excitatory or inhibitory (Terao & Ugawa, 2002). The introduction of this technique significantly advanced the neurophysiologic investigation of the cerebral cortex, especially of the motor cortex, which had been practically confined to animal studies. In fact, the number of published papers per year using TMS almost doubled from 1999-2003 to 2003-2008 (Rossi, Hallett, Rossini, & Pascual-Leone, 2009).

Despite its overwhelming success, practicality and safety, TMS cannot fully replace TES as a tool for studying neurophysiology. One advantage to using TES is its ability to stimulate the motor cortex neurons directly to produce short latency direct wave (D-wave) by activating corticospinal axons directly. In comparison, TMS primarily stimulates corticospinal neurons transynaptically via interneurons prompting the creation of indirect waves (I-waves) which occur approximately 1.5 ms sequentially following a D-wave (Chen, 2000; Reis et al., 2008). However, at higher intensities TES can produce I-waves and TMS can produce D-waves, yet it is this fundamental difference between these techniques that warrants the use of TES (Day et al., 1989).

When TMS was first developed it could only be applied in single monophasic pulses with a circular coil (Barker, Jalinous, & Freeston, 1985). Today's stimulators

either produce monophasic or biphasic waveforms. Biphasic waveforms are more powerful than monophasic ones when the stimulation energy is normalized to the square root of the maximal energy stored (Kammer, Beck, Thielscher, Laubis-Herrmann, & Topka, 2001). Although the circular coil is very useful as a general purpose coil, its site of stimulation is not very well defined. For this reason, traditional circular coils have generally been replaced with the figure-of-eight coil (also termed butterfly or double coil). This shape allows a focused stimulation of superficial cortical regions by inducing a current under the junction region of the eight that is roughly twice as large as that under the two wings (Rothwell, 1997). Finally, the new stimulators allow for repetitive stimulation which has led to the development of different protocols; the most popular being paired pulse TMS and theta burst stimulation. All these protocols involve trains of repetitive stimuli to elicit excitatory or inhibitory responses in the stimulated region. There is a multitude of applications of these techniques, however the following will focus on the use of single pulse TMS to obtain reliable neurophysiological measures.

1.2.1 Single-pulse TMS measures

Motor Threshold (MT) is defined as the minimum stimulation intensity capable of eliciting MEPs of 50 to 100 μV in about 50% of a series of consecutive stimulations (Rossini et al., 1994). This can be measured at rest (ie., resting motor threshold, RMT) or with some underlying tonic contraction (ie. Active motor threshold, AMT). RMT is a principal measure of cortical excitability and reflects the local density of a central core of excitatory interneurons and corticospinal neurons (Rossini & Rossi, 2007). AMT is a measure that conveys approximately the same physiologic information and possesses

more variability than RMT. In theory AMT would be more reliable since it is less sensitive to fluctuations in synaptic excitability; nonetheless, the presence of background electromyographic (EMG) activity increases the difficulty of reliably quantifying this measure (Talelli, Greenwood, & Rothwell, 2006).

The most common measure of corticospinal excitability has traditionally been the MEP amplitude. This peak-to-peak amplitude is the EMG response following a single TMS pulse at a given intensity relative to the person's RMT (Talelli et al., 2006). The amplitude of MEPs is an important measure because it provides a direct measure of the intrinsic and extrinsic excitability of cortical and spinal motoneurons (Taube et al., 2006).

The time between the delivery of the TMS pulse and the onset of the evoked motor response, known as the MEP latency, is affected by neural fibre diameter, myelin sheath thickness and the number of synapses crossed. It has been used to estimate conduction velocities in the fast descending spinal tracts (Rossini, Rosinni & Ferreri, 2010). It is pivotal in the measurement of central conduction time, which has been considered to be the most useful clinical parameter (Rossini & Rossi, 2007)

A recruitment curve (RC; also known as input-output or stimulus-response curve) can be done by examining the MEP amplitude increase with increasing TMS intensities. This is done to determine the progressive recruitment of less excitable or adjacent neurons that aren't localized directly on the hot spot, which is the optimal stimulation area for achieving a response from a muscle (Chen, 2000, Darling, Wolf, & Butler, 2006). Overall, RC provides an index of the strength of corticospinal projections and can detect changes in cortical motor maps (Ridding & Rothwell, 1997).

TMS can also be used to investigate the excitability of cortical inhibitory circuits. For instance, when a TMS pulse is delivered during a tonic contraction of the corresponding muscle a period of no EMG activity is induced, called the contralateral silent period (cSP). The first part of this inhibitory period is thought to be due primarily to spinal mechanisms whereas the later part is thought to be caused by cortical mechanisms (Chen, Lozano, & Ashby, 1999; Fuhr, Agostino, & Hallett, 1991). Additionally, the entirety of the cSP is thought to be of cortical origin, being specifically generated in the M1 (Roick, von Giesen, & Benecke, 1993; Schnitzler & Benecke, 1994). This measure of corticospinal inhibition is thought to be partially mediated by $GABA_B$-ergic cortical interneurons (Werhahn, Kunesch, Noachtar, Benecke, & Classen, 1999).

Inter-hemispheric inhibition can be assessed using single pulse via the ipsilateral silent period (iSP). This measure is characterized by a short attenuation of interruption of ongoing EMG activity in the contracting muscle ipsilateral to the stimulated hemisphere (Wassermann, Fuhr, Cohen, & Hallett, 1991). The iSP is thought to reflect hemispheric interactions through transcallosal inhibition mediated by the posterior half of the corpus callosum (Meyer, Roricht, Grafin von Einsiedel, Kruggel, & Weindl, 1995). The iSP can be used to assess transcallosal inhibition, which can be used to evaluate inter-hemispheric conduction time and strength (Rossini & Rossi, 2007). Furthermore, Chen et al (2003) found that iSP duration was strongly correlated with paired-pulse inter-hemispheric inhibition (IHI) with an interstimulus interval (ISI) of 40 ms while it was not correlated with an ISI of 8 ms. They concluded that IHI_{40} and iSP may be mediated by similar neuronal populations (Chen, Yung, & Li, 2003). Modulation of the activity in this common pathway was found to be a mechanism that regulates the amount and functional

role of the ipsilateral M1 activation during the execution of a simple grip task (Talelli, Ewas, Waddingham, Rothwell, & Ward, 2008).

1.3 Laterality effects on neurophysiology

It has been demonstrated that there exists functional and structural differences in M1's physiology depending on the extent of handedness laterality of the subject (Amunts et al., 1996; Halsey, Blauenstein, Wilson, & Wills, 1979). The extent to which laterality affects single-pulse TMS measures is a controversial subject among researchers. It is reported that there are lower MTs (Macdonell et al., 1991; Triggs, Calvanio, & Levine, 1997), more inhibition (Cicinelli et al., 2000; Priori et al., 1999) and larger cortical maps controlling the dominant hand than the non-dominant hand for two intrinsic hand muscles for both left and right handers (Triggs, Subramanium, & Rossi, 1999); however, these findings were not replicated in similar studies (Cicinelli, Traversa, Bassi, Scivoletto, & Rossini, 1997; Inghilleri, Berardelli, Cruccu, & Manfredi, 1993; Wilson, Thickbroom, & Mastaglia, 1993). More studies are needed to validate these past studies in order to determine if and to what extent hand preference affects TMS measures.

2. Hand function

The ability to control ones hand is one of the major factors that has allowed humans to evolve in building tools and for communication through gestures. It is suggested that skilled forelimb movements originate from feeding behaviours of early mammals (Iwaniuk & Whishaw, 2000). Over the course of evolution, the human hand has undergone multiple modifications and alterations leading to its unique anatomy and

functions which allow the exceptional skilled hand movements exhibited in everyday human life (Wilson, 1998).

2.1 Anatomy

Despite its relatively small size compared to other parts of the body; control of the human hand involves a very large proportion of the M1 (Penfield, & Rasmussen, 1952). This allows the hand to intricately control all of the 11 intrinsic hand muscles and 15 extrinsic hand muscles. The grouping of these muscles on the lateral and medial aspects of the hand form the thenar and hypothenar eminences respectively. The thumb, 5^{th} digit and to a lower extent the 2^{nd} digit (index finger) all possess a plethora of muscles controlling them allowing for a variety of movements including flexion, extension, adduction, abduction and opposition (Moore & Daller, 2006). The expert combination of these movements allow for incredible level of sophistication in terms of possible configurations and manipulative abilities, including the ability to form power grasps, precision handling and pinching.

2.2 Assessment of Hand Function

The hand is highly specialized with respect to its sensory and motor capacities which have long been recognized to present unique properties (Jones, 1994). To adequately assess hand function, several aspects have to be taken into consideration individually (Jones, 1989). The subdivision of hand function into sensory and motor components is done in order to properly quantify these measures individually.

2.2.1 Sensory assessement

Vibration threshold. Vibration is among the many sensations to which the cutaneous mechanoreceptors respond. While other mechanoreceptors are more sensitive to edges (Merkel discs) or motion (Meissner and Ruffini corpusles), the fast afferent Pacinian corpusles located deeper in the cutaneous tissue are the mechanoreceptors responsible for sensing vibration (Johnson, 2001). Impairments in the sense of vibration may be a sign of peripheral nerve dysfunction, especially if the disfunction is found in distal parts of the limb such as the hand (Martina, van Koningsveld, Schmitz, van der Meche, & van Doorn, 1998; Pestronk et al., 2004). In clinical settings, vibration testing with Rydel-Seiffer tuning forks is often done in order to quickly and reliably screen for the presence of neuropathies (Martina, van Koningsveld, Schmitz, van der Meche, & van Doorn, 1998; Pestronk et al., 2004).

Tactile acuity threshold. This is a measure of the integrity and density of the mechanoreceptors at the fingertip (Peters, Hackeman, & Goldreich, 2009) as well as the central processing of tactile information (Tremblay et al., 2003). This tactile information is vital for the accomplishment of daily tasks that require proper prehension of various objects to prevent slipping and dropping. In the eventuality of mistakenly dropping an object, a person must quickly analyze the event and react in order to quickly adapt to the situation.

2.2.2 Motor assessment

Grip strength. Grip strength has traditionally been used as a test for gross motor power in order to evaluate the muskoletal health of the hand (Jones, 1989). Based on the eight most common grips types, handgrip strength tests are used to measure total body

strength, the power in specific hand grips and even declining muscle strength in aging (Sollerman & Ejeskar, 1995). Additionally, grip strength tests have proved to be a useful tool in prediction of functional limitations and disabilities (Giampaoli et al., 1999).

Dexterity. A variety of tests have been created in order to assess manual dexterity and its relation to overall functional ability. For instance, the grooved pegboard test (GPT) is considered to be a measure of manual dexterity and complex motor coordination; moreover, recent literature has found that the results of this test correlate to neuropsychological and cognitive measurements (Ashendorf, Vanderslice-Barr, & McCaffrey, 2009). Furthermore, there are reports that GPT results correlate with spatial resolution thresholds at the fingertip (Tremblay, Wong, Sanderson, & Cote, 2003).

Reaction time. This measure is defined as the interval of time between the perception and evaluation of a stimulus and the required response (Zajdel & Nowak, 2007). Since the 19th century, reaction time has been a widely used measure of functional ability (Merkel, 1885). The time required in decision making during a reaction time test is influenced by the stimulus registration time, choice-reaction time and a decision time to consider the proper movement. While short movement simple reaction times have been known to be quite fast, approaching a minimum of 100ms (Reynolds & Day, 2007), reaction times tend to increase when coupled with a longer movement time. Therefore, a simple reaction time test would be useful to assess the integrity of the coupling between stimulus perception and speed of corticospinal signal propagation. A reaction time combined with a set movement goal would be a better indicator of an individual's ability to quickly process information to accurately control the given limb, which is further

complicated by the trade-off that exists between speed and accuracy (See Bogacz, Wagenmakers, Forstmann, & Nieuwenhuis, 2010 for review).

Simple Finger Tap. This measure of musculoskeletal and neuromuscular function is considered to be a valid measure of motor function (Ashendorf et al., 2009). Although finger tapping could seem somewhat trivial because of its simplicity, it is one of the most widely used neuropsychological tests (Rabin, Barr, & Burton, 2005) in reason of its ability to quickly produce an indication of the hands motor ability.

Bimanual tap test. All aforementioned tests are unimanual to simplify their interpretation, for it is known that bimanual task are noticeably more difficult (Wiesendanger, Kaluzny, Kazennikov, Palmeri, & Perrig, 1994), especially in elderly subjects (Bangert, Reuter-Lorenz, Walsh, Schachter, & Seidler, 2010). This is caused by the interhemispheric coordination of movements that must occur in order to accomplish the task. The final manual test that will be discussed will be the dual asynchronous finger tap test. Unlike the simple finger tap test, this test's purpose is not limited to assessing motor capabilities of the hand, its main purpose is to observe the subject's coordination mediated transcallosal mechanisms. Throughout all of these tests, it is important to note that the dominant hand will generally perform better than the non-dominant hand, with more variability in left-handed subjects. This lateralization is an important marker of overall manual ability, for the accomplishment of daily tasks often requires the use of both hands.

3. Aging

Aging is defined as "The process of becoming older, a process that is genetically determined and environmentally modulated."(Mosby, 2009) This process is experienced

by every living being and is generally defined as a slowing of all metabolic processes which leads to a multitude of different effects. The following will discuss how aging will affect manual abilities and neural health.

3.1 Physiological and Behavioural changes

Given the aging demographic, it is important to understand the physiological basis for the decline in functional motor capacity as people advance in age. Aging is associated with the progressive degenerative loss of skeletal muscle mass and strength, known as sarcopenia. A recent study has estimated that the healthcare costs due to sarcopenia in the United States in the year 2000 exceeded $18.5 billon. The loss of strength during the course of aging is a well documented phenomenon (Harris, 1997) which has a deleterious effect on the aging population by diminishing their functional ability (Wiacek & Zubrzcki, 2010). Furthermore, the loss of strength and functional ability which is partially due to sarcopenia increases the risk of hospitalization (Cawthon et al., 2009). Luckily, the decrease in muscle mass in the hand muscle groups is not as prominent as other skeletal muscle groups (Carmeli, Patish, & Coleman, 2003). Manipulative skills are a critical component of upper extremity function, allowing us to perform a variety of tasks through interactions with tools and objects around us. The ability to perform fine manipulative actions deteriorates gradually from 60 years of age (Shiffman, 1992; Smith et al., 1999). This decline is manifested in the difficulty experienced by older adults in skills requiring fine motor control (e.g., picking up small objects, buttoning actions). Such a decline has been linked with observations of reduced grip strength in older persons (Ranganathan et al, 2001) along with difficulty in finely modulating grip force

when manipulating objects (Cole 2001, 2002). The important interplay between sensation and action is altered in aging, owing to a reduction in cutaneous mechanoreceptors and the resulting decline in tactile sensibility. Investigations in this field have revealed substantial decline in touch sensation in older persons with a doubling and even a tripling in sensory thresholds for touch detection and in spatial acuity (Tremblay et al 2003, Tremblay et al 2005). These studies also showed that the degree of tactile loss was closely associated with impaired manual dexterity levels, as measured in standardized tests (Tremblay et al 2003). While aging inevitably leads to a decline in sensory and motor function, there are also wide variations at the individual level, though certain factors, like gender, seem to be important in the aging process. For instance, manual dexterity appears to decline at a faster rate in aged women than in aged men (Ranganathan et al, 2001).

3.2 Neurophysiological changes

Many studies have been conducted to examine the effects of aging on the neurological system. Age is associated with a degradation of multiple neuronal tracts; two of which is the corpus callusom and cortical fibers that connect frontal regions to more posterior regions (Perry et al., 2009). Recent results revealed a differential pattern of effects on major cortical, subcortical, callosal and cerebellar fiber tracts, whereas age effects on the tracts were more substantial on anterior than posterior, inferior than superior, and association than projection fiber tracts (Madden et al., 2009; Sullivan, Adalsteinsson, & Pfefferbaum, 2006). However, the CST seems to be resistant to the effects of age (Perry et al., 2009). Age is associated with a reduction in global and

regional white and gray matter in the cerebral cortex (Good et al., 2001; Seidler et al., 2010; Walhovd et al., 2005), with frontal white matter particularly affected (O'Sullivan et al., 2001; Pfefferbaum, Adalsteinsson, & Sullivan, 2005; Sullivan et al., 2006). Nevertheless, M1 appears to be fairly resistant to age related neural loss (Haug & Eggers, 1991).

Recent studies using TMS have revealed several age-related changes in the excitability of corticospinal projections controlling hand muscles. For example, the amplitude of motor evoked potentials (MEP) is reduced, indicating a possible loss in the number of functional projections or a reduction in fast conducting fibers (Rossini et al, 2008). In support of this, Pitcher, Ogston and Miles (2003) found that elderly subjects needed a higher TMS intensity in order to produce MEPs similar those of young subjects during the construction of an RC. The excitability of inhibitory circuits has also been explored with TMS. In general, these studies have revealed a decrease in inhibitory control with age (Kossev, Schrader, Dauper, Dengler & Rollnik, 2002; Wassermann, 2002; Sale & Semmler, 2005). Right-left asymmetries in corticospinal excitability have also been described in older adults, as shown by Sale & Semmler (2005). They found that the motor cortex controlling the dominant hand of right-handers had greater excitability and more efficient inhibition than the contralateral motor cortex controlling the left hand. Such an asymmetry was not observed in younger subjects. However, there is a disparity between these findings and those of other studies which found no neurophysiological differences in laterality caused by aging. One such study found no RMT and AMT asymmetries between hemispheres in elderly subjects whilst the younger subjects had lower MTs in their dominant hemisphere (Matsunaga, Uozumi, Tsuji, & Murai, 1998).

This result could be influenced by the large inherent variability of MTs (Wassermann, 2002). Knowing that are is associated with a reduction in both white and gray matter in the cerebral cortex (Seidler et al., 2010) and that RMT increases with the distance between the coil and the M1 (McConnell et al., 2001), it would seem logical that MT would increase with age. In accordance with this logic, some studies have found an association between healthy aging and increased motor thresholds (Peinemann, Lehner, Conrad, & Siebner, 2001; Rossini, Desiato, & Caramia, 1992). Unfortunately, many TMS studies have not found significant differences in MTs of the M1 between young and elderly (Oliviero et al., 2006; Pepin, Bogacz, de Pasqua, & Delwaide, 1999; Pitcher, Ogston, & Miles, 2003; Rossi et al., 2004). These discrepancies likely originate from technical and experimental differences as well as the high variability of MT.

The results of these neurophysiological tests must be analyzed with caution since they are biased towards large fast-conducting neurons, so the contribution of the much more numerous small CM neurons have likely been seriously overlooked (Maier, Illert, Kirkwood, Nielsen, & Lemon, 1998). Furthermore, these important large mylienated nerve fibres were found to be more susceptible to injury (Quencer et al., 1992) and to decline in number and density with age (Mittal & Logmani, 1987). These limitations among others explain our lack of knowledge concerning the changes that occur in the human CST.

Overall, these results suggest that neurophysiological alterations occur with age, yet it remains unclear as to what extent such alterations affect progressive degeneration at the behavioural level. Few neurophysiological studies have examined this issue, especially in the context of aging (Rossini et al, 2008).

3.3 Correlation between neurophysiology and behaviour

Current evidence supports that there is an age-related disruption in white matter integrity (Seidler et al., 2010) and these deteriorations seem to be concomitant with a multitude of motor deficits ranging from simple motor tasks such as repetitive finger tapping (Shimoyama, Ninchoji, & Uemura, 1990), to more demanding timed tasks (Smith et al., 1999), steadiness tasks (Cole, 2001) and dexterity tasks (Cole, Cook, Hynes, & Darling, 2009). Despite the seemingly linear relationship that exist between these physiological and behavioural measures; there have been very few studies relating these two measures.

The first to establish a strong correlation between markers of corticospinal excitability using TMS and motor performance were Triggs, Calvanio and Levine (1997). Their results indicated that MT was strongly correlated with finger tapping as well as scores on a Purdue pegboard. Therefore, these finding indicate that a person's MT would be a strong predictor of functional manual performance. However, these results were not repeated in other similar studies. Sale and Semmler (2005) compared an array of manual performance tasks with a series of neurophysiological TMS measures in young and old subjects. They found that there was only a weak relationship between cSP and scores on the Purdue pegboard task. They did not find a strong relationship between the age-related changes in TMS neurophysiological measures and the aging effects on hand function. The authors concluded that the chosen tests were not sensitive enough to establish strong associations between TMS measures and measures of motor performance. Another study conducted by Brouwer, Sale and Nordstrom (2001) found no significant correlation between MEP asymmetry and any asymmetry in motor function test.

Lindberg, Feydy and Maier in 2010 used magnetic resonance diffusion tensor imaging to determine if there was a significant correlation between accuracy of grip force control (which was used as a measure of dexterity) and fractional anisotropy in the cervical spine (FA). FA reflects the structural characteristics of white matter and is used as a quantitative measure of white matter integrity. FA was found to correlate with age, meaning that there is an age-related degradation in white matter (Lindberg, Feydy, & Maier, 2010). These results provided further support for the notion that associations exist between age, manual performance and neurophysiology.

We know from TMS explorations that the corticospinal system, which is a critical component for hand function, undergoes various physiological alterations with age. The loss of functional projections (McComas, Galea, & de Bruin, 1993) and reduced cortical inhibition seem to be of primary importance. However, as indicated earlier few studies have actually attempted to relate these two streams of research in trying to establish the functional significance of alterations in corticospinal function with age. Understanding the relationship between these two variables will advance our current knowledge on the process and effects of healthy aging. Furthermore, health assessment could possibly be quickly assessed by establishing a baseline acceptable range for these variables that are correlated with healthy aging.

3.4 Objectives and purpose of present work

Ultimately, our goal is to examine the link between neurophysiology and functional behavioural with regard to human corticospinal functions. Describing this relationship could help identify potential markers of corticospinal dysfunction that can be used to predict early signs of deterioration in hand function due to aging. Such findings could be important in developing strategies for early prevention or for remediation of hand impairments in the aging population (Abbruzzese, Marchese, & Trompetto, 1997). Clinically, the establishment of a relationship between neurophysiological and functional measures could lead to a better understanding and earlier diagnosis of certain neuropathologies and movement disorders. Our current research searches to expand on the research done by Sale and Semmler (2005) and Brouwer, Sale and Nordstrom (2001) by including more hand function tests and TMS measures to be able to accurately depict which measure of corticospinal function relates with behaviour in the context of aging.

The objectives of the present work are:

(1) to examine neural and behavioural markers of aging in the human corticospinal system, especially with regard to hand function ,

(2) to determine the possible relationships between the neurophysiological markers of corticospinal aging derived from TMS measures and corresponding behavioural measures of age-related functional decline in hand function,

(3) to determine the possible contribution of factors such as gender and hand dominance in influencing markers of aging at the neurophysiological and behavioural level

Chapter II: Research Paper

Neurophysiological and Behavioral Correlates

of Corticospinal Function in Young and Old healthy adults

(in prepation for Exp Brain Research)

Travis Davidson[a,c] & François Tremblay[b,c],

[a]School of Human Kinetics,

[b] School of Rehabilitation Sciences,

and

[c] Elisabeth Bruyère Research Institute,

Running title: Neurophysiological correlates with aging

Key Words: transcranial magnetic stimulation, aging, interhemispheric inhibition, intracortical excitability, behavior

Address correspondence to François Tremblay, Ph.D.

Abstract

Transcranial magnetic stimulation (TMS) is a non-invasive technique that can be used to assess the integrity of excitatory and inhibitory neuronal circuits in the motor cortex, both at the intrahemispheric and interhemispheric level. In the present study, TMS was used to examine neurophysiological correlates of corticospinal function in the context of normal aging. Participants also underwent hand function testing to examine possible links between TMS measures of corticospinal excitability and age-related decline in manual ability. Participants consisted of healthy young (n=13) and senior (n=17) right-handed individuals. Hand function testing consisted of a battery of tests administered bilaterally, which included the grooved pegboard test (GPT), finger tapping test (FTT), pinch strength, simple reaction times (SRT) and reaction/movement time (MovT). The following TMS measures were assessed bilaterally using a Magstim Rapid^2 stimulator: resting motor threshold (RMT), the recruitment curve (RC), and silent periods of the contralateral (cSP) and ipsilateral hand (iSP). Both young and senior subjects showed significant intermanual differences in most behavioral measures, favoring their dominant right hand. Age differences were found in both intrahemispheric excitability and interhemispheric inhibition, indicating an age-related decrease in the excitability in both these motor circuits. A general trend linking specific TMS markers of corticospinal function with preserved hand function, especially in the dominant hand, was indicated over the course of aging. Intrahemispheric measures of excitability during an active state were better predictors than measures performed in the resting state. Our results indicate that neurophysiological markers can be fair to moderate predictors of behavior, which could in turn provide an early diagnosis of pathological aging.

Introduction

Given the aging demographic, it is important to understand the physiological basis for the decline in functional motor capacity as people advance in age. Manipulative skills are a critical component of upper extremity function, allowing us to perform a variety of tasks through interactions with tools and objects around us. The ability to perform fine manipulative actions deteriorates gradually after 60 years of age (Shiffman, 1992; Smith et al., 1999). At the functional level, such a decline has been linked with observations of reduced grip strength (Ranganathan et al, 2001) and dexterity (Cole, Cook, Hynes, & Darling, 2009; Tremblay, Wong, Sanderson, & Cote, 2003), along with difficulty in finely modulating grip force when manipulating objects (Cole & Rotella, 2001, 2002). The important interplay between sensation and action is altered in aging, owing to a reduction in cutaneous mechanoreceptors and the resulting decline in tactile sensibility (Carmeli, Patish, & Coleman, 2003). Investigations in this field have revealed substantial decline in touch sensation in older persons with a doubling and even a tripling in sensory thresholds for touch detection and in tactile acuity (Tremblay et al 2003; Tremblay et al 2005). Besides declines in force and sensation, hand function is also affected by the general decline in processing speed affecting both motor performance and cognitive processes (Birren & Fisher, 1995). At the behavioral level, this slowing is demonstrated by age-related increases in reaction times (Cerella, 1985) as well as a decreased performance in dexterity and finger tapping tasks (Aoki & Kukuoka, 2010; Ashendorf, Vanderslice-Barr, & McCaffrey, 2009). While the age-related decline in hand function has been well characterized in the aging population, the physiological basis of this decline at the neurophysiological level remains largely unexplored.

The integrity and functional state of the corticospinal tract (CST) can be evaluated using a non-invasive cortical stimulation technique called transcranial magnetic stimulation (TMS). When applied to the primary motor cortex at an appropriate intensity, TMS can depolarize neurons leading to transynaptic activation of large pyramidal cells. The projections of these pyramidal cells form the corticospinal tract and their activation leads to descending volleys that will excite spinal motor neurons thereby generating a muscle response known as motor evoked potential (MEP) that can be recorded via surface electrodes (Terao & Ugawa, 2002). Measures of intrahemispheric excitability include the resting motor threshold (RMT), the MEP amplitude, the MEP latency, the recruitment curve (RC) and the contralateral silent period (cSP). Each one of these measures is thought to reflect the integrity and excitability of corticospinal projection neurons. The RMT is defined as the minimum stimulation intensity capable of eliciting an MEP in the corresponding muscle of at least 50μV in about 50% of a series of consecutive stimulations in a resting muscle. RMT is thought to depend on multiple factors, including the axonal threshold of motor cortical interneurons, the excitability of synapses at the cortical level between excitatory inputs and corticospinal cells, and the synapses at the spinal cord between corticospinal terminals and motoneurons (Talelli, Greenwood, & Rothwell, 2006). The peak-to-peak amplitude of the MEPs is thought to provide a direct measure of the intrinsic and extrinsic excitability of cortical and spinal motoneurons (Taube et al., 2006). The time between the delivery of the TMS pulse and the onset of the evoked motor response, known as the MEP latency, is affected by neural fiber diameter, myelin sheath thickness, and the number of synapses crossed. It has been used to estimate conduction velocities in the fast descending spinal tracts (Rossini,

Rosinni & Ferreri, 2010). A slight contraction in the target muscle will significantly shorten the onset of the MEP latency as well as increase corticospinal excitability demonstrated by a lower motor threshold and increased MEP amplitude (Kawakita et al., 1991). A prominent MEP derivation is the RC, which is determined by examining the concurrent increases in MEP amplitude and stimulation intensities. RC provides an index of the strength of corticospinal projections and can detect changes in cortical motor maps (Ridding & Rothwell, 1997). The cSP is defined as the suppression of voluntary electromyographical activity following a TMS pulse. The early part of this inhibitory period (<50 ms) is thought to be due primarily to spinal mechanisms whereas the later part is thought to be caused by cortical mechanisms (Chen, Lozano, & Ashby, 1999; Fuhr, Agostino, & Hallett, 1991). This measure of corticospinal inhibition is thought to be partially mediated by $GABA_B$-ergic cortical interneurons (Werhahn, Kunesch, Noachtar, Benecke, & Classen, 1999).

Inter-hemispheric inhibition can be assessed using single TMS pulse via the ipsilateral silent period (iSP). This measure is characterized by a short attenuation of interruption of ongoing EMG activity in the contracting muscle ipsilateral to the stimulated hemisphere (Wassermann, Fuhr, Cohen, & Hallett, 1991). The iSP is thought to reflect hemispheric interactions through transcallosal inhibition mediated by the posterior half of the corpus callosum (Meyer, Roricht, Grafin von Einsiedel, Kruggel, & Weindl, 1995). The iSP can be used to assess transcallosal inhibition, which can be used to evaluate inter-hemispheric conduction time and strength (Rossini & Rossi, 2007). Furthermore, Chen et al (2003) found that iSP duration was strongly correlated with paired-pulse inter-hemispheric inhibition (IHI) with an interstimulus interval (ISI) of 40

ms while it was not correlated with an ISI of 8 ms. They concluded that IHI_{40} and iSP may be mediated by similar neuronal populations (Chen, Yung, & Li, 2003). Modulation of the activity in this common pathway was found to be a mechanism that regulates the amount and functional role of the ipsilateral M1 activation during the execution of a simple grip task (Talelli, Ewas, Waddingham, Rothwell, & Ward, 2008).

Generally, the aforementioned intrahemispheric measures of excitability (RMT, MEP amplitude, RC, cSP) have been found to decrease with age. Some studies have found an association between ages and increased motor thresholds (Peinemann, Lehner, Conrad, & Siebner, 2001; Rossini, Desiato, & Caramia, 1992). However, such age differences in MT have not been found in other studies (Oliviero et al., 2006; Pepin, Bogacz, de Pasqua, & Delwaide, 1999; Pitcher, Ogston, & Miles, 2003; Rossi et al., 2004). These discrepancies likely originate from technical and experimental differences as well as in the inherent variability of MT measurements (Wassermann, 2002). In contrast, most TMS studies have reported a consistent reduction in MEP amplitude with age, indicating a possible loss in the number of functional projections or a reduction in fast conducting fibers (Rossini et al, 2008). In support of this, Pitcher, Ogston and Miles (2003) found that elderly subjects needed a higher TMS intensity in order to produce MEPs similar those of young subjects during the construction of an RC. Studies examining the excitability of motor inhibitory circuits, as determined by cSP, have revealed a decrease in inhibitory control with age (Kossev, Schrader, Dauper, Dengler & Rollnik, 2002; Wassermann, 2002; Sale & Semmler, 2005).

Right-left asymmetries in corticospinal excitability have also been described in older adults, as shown by Sale & Semmler (2005). They found that the motor cortex

controlling the dominant hand of right-handers had greater excitability and more efficient inhibition than the contralateral motor cortex controlling the left hand. Such an asymmetry was not observed in younger subjects. However, there is a again controversy regarding the presence of asymmetries as other studies have failed to find differences in laterality with aging (Matsunaga, Uozumi, Tsuji, & Murai, 1998). The paired-pulse technique using TMS have found significant age-related attenuation in interhemispheric inhibition with age during the active condition (Talelli, Waddingham, Ewas, Rothwell, & Ward, 2008); however, there is still very limited information with regard to changes in with age especially concerning age difference in iSP.

Given the evidence of alterations in corticospinal excitability measures with age, few studies have examined how these physiological alterations could be related to actual deficits in hand function (Rossini et al, 2008). Triggs, Calvanio and Levine (1997) looked for a link between indices of corticospinal excitability using TMS and motor performance. Their results showed that RMT was strongly correlated with finger tapping performance, as well as dexterity scores on a Purdue pegboard test. Such findings indicated that a RMT measures could be used to predict manual performance. However, these results were not supported in subsequent studies. Sale and Semmler (2005) compared a battery of manual performance tasks with a series of neurophysiological TMS measures in young and old subjects. They found that there was only a weak relationship between cSP duration and scores on the Purdue pegboard task. Their different TMS measures largely failed to predict age-related changes in hand function. The authors concluded that the behavioural tests were likely not sensitive enough to reveal associations between TMS measures of excitability and motor performance. In the

same vein, another study conducted by Brouwer, Sale and Nordstrom (2001) found no significant correlation between MEP asymmetry across hemispheres and corresponding asymmetries in motor function test.

In the present study, we sought to determine whether neurophysiological measures of corticospinal function derived from TMS could be used to predict performance in hand function tests in the context of normal human aging. To examine the relationships between TMS measures and behavioral performance, young and senior participants underwent a battery of tests to assess dexterity, strength and speed of motor performance in both the dominant and non dominant hand. Subsequently, participants were subject to TMS in the both the resting and active states to measure several markers of corticospinal facilitation and inhibition both within (intrahemispheric) and between hemispheres (interhemispheric). The ultimate goal was to determine whether specific TMS measures could be identified as valid markers of age-related decline in hand function.

Methods

The Institutional Review Ethics Board approved the study procedure in accordance with the principles of the Declaration of Helsinki and informed consent was obtained before the experimental session. All assessments were performed in a controlled laboratory environment. Each participant received a small honorarium for his or her participation.

Participants

A total of 13 young adults (5 female, 13 male) and 17 seniors (11 females, 6 males) were recruited from the population in the Ottawa area. All subjects were right-handed, as determined by the Edinburg Handedness Inventory (Oldfield, 1971). Prior to the experimental session, all participants completed a medical questionnaire to determine their general health, to ensure that there were no contra-indications to TMS and that no antecedents of conditions likely to affect their performance in the tests. The height and weight of the subjects were collected in this questionnaire as well. In addition, sensory function of the hand was assessed using a Rydel-Seiffer tuning fork to determine the vibration extinction threshold and compare it with available norms. This simple test consists of applying the fork over the ulnar styloid process and asking the subject to report when they no longer perceive vibration. The threshold is determined by inspecting visual markers on the fork. If a potential subject exhibited values outside the norms, suggestive of a sensory deficit (Hesselmann et al., 2001), they were excluded from the

study and invited to consult with a physician. The demographic characteristics of the participants are listed in Table 1 along vibration thresholds.

Hand Function tests

For the hand function assessment, participants were comfortably seated in front of a table. All tests were performed in a controlled laboratory environment by the same experimenter. The order of the tests was the same for all participants. All subsequent manual performance tests were applied to both hands. To prevent a contralateral practice effect, each hand used to complete the test first was chosen at random.

a. Grooved Pegboard Test (GPT)

The GPT (Lafayette Instrument Co.) consists of a board that contains 25 slotted holes in a 5 by 5 array. The objective of the task is to fit the pegs into the holes in the specified order as fast as possible. Timing began when the first peg is touched. The test differs from the more traditional Purdue pegboard test because it requires complex visuo-sensori-motor integration since pegs have to be rotated to match the hole before they can be inserted (Tremblay, Mireault, Letourneau, Pierrat, & Bourrassa, 2002).

b. Simple reaction time (SRT) and reaction time/movement time (MovT)

A MOART™ panel (Lafayette Instruments Co.) was used to measure simple reaction times, reaction time/movement time and the finger tapping speed. A period of familiarization with practice trials was given before the application of any of these tests. Simple reaction times required the participants to place their index finger on the designated button until the designated light stimulus is given, at which point they lifted

their finger. The time interval between the activation of the light and the removal of the finger from the button was designated as the simple reaction time. Removing the finger from the button instead of pressing the button is a reliable method of measuring reaction time according to previous guidelines (Crabtree & Antrim, 1988) and it was chosen in order to be comparable to the reaction time/movement time test (MovT). MovT involved moving the finger from one specified button to another one 20cm away when prompted by a light cue. Speed was the focus of this test to properly assess the coupling between reaction time and movement speed. Accuracy was noted, but not taken into account for further analysis. Ten trials were completed for each reaction time test.

c. Finger tapping test (FTT)

The finger tapping test consisted of tapping a specified button as quickly as possible with the index finger for a period of 15 seconds on the MOART™ panel. The total number of taps in this time period was noted as a measure of motor function. Two trials were done for the FTT. The average of the trials was taken for analysis.

d. Pinch strength

The final test consisted of determining grip force using a small pinch dynamometer (B&L pinch gauge) where the subjects performed a key pinch with maximal strength. Three trials were applied for each hand. The average of these three trials was considered the maximal voluntary contraction (MVC) for the first dorsal interosseous muscles (FDI). This test was conducted last because it was deemed to be the most strenuous and capable

of inducing fatigue in the hand muscles. Therefore, it was only given after all other manual tests to assure that fatigue was not a factor affecting reaction times or dexterity.

EMG recording and TMS

Electromyographic (EMG) activity was recorded using small auto-adhesive surface electrodes (10 mm diameter, Ag-AgCl) placed over the first dorsal interosseous (FDI) muscles of the right and left hand. EMG signals were amplified (100 μV/div) and filtered (bandwidth, 16 Hz to 1 kHz) with a polygraph amplifier (RMP-6004, Nihon-Kohden Corp.). Signals were digitized at a 2 kHz sampling rate using custom software on a PC running under Microsoft® Windows® XP equipped with a digital/analogue acquisition card (BNC-2090, National Instrument Corp.).

TMS was administered with participants comfortably seated in a recording chair. Magnetic stimulation was delivered with a SuperRapid^2 stimulator (Magstim Co. Dyfed, UK) connected to a figure-eight coil (90 mm outer loop diameter). To determine the optimal site to evoke MEP's in the contralateral hand muscles, participants were fitted with a Waveguard TMS compatible cap. A U-shaped neck cushion was used to restrain head movements and prevent neck fatigue. With the coil held ~45° in the mid-sagittal plane, the approximate location of the hand motor area on the left hemisphere was explored in 1 cm steps until reliable MEP's could be evoked in the target muscle. This site was then marked with a red dot to ensure consistent coil positioning. After determination of this stimulation "hotspot", the coil was held in place manually by one of the experimenters. The experimenter frequently reassessed the coil position to ensure that it remained over the optimal stimulation site throughout the experiment. All testing took

place between 9am and 4pm to avoid any variability in corticospinal excitability which could be influenced by wakefulness (Doeltgen & Ridding, 2010).

From the TMS assessment, we derived the following excitability measures on each hemisphere: RMT, MEP amplitude at rest, RC, cSP and iSP.

a. Resting motor threshold (RMT)

The RMT was determined using a procedure described by Mills and Nithi (1997) to obtain the minimal stimulation intensity required to evoke reliable MEP's in the target muscle while the subject is at rest. This method showed good reliability and suggested that it might be superior to other possible algorithms to calculate RMT (Tranulis et al., 2006). First the stimulus intensity was gradually decreased in 1% steps until there were no motor responses in 10 consecutive trials (lower threshold). Intensity was then increased in 1% increments to find the minimal intensity that would produce reliable peak-to-peak amplitude MEPs of at least 50 μV 10 consecutive trials (upper threshold). The RMT was defined for each participant as the median intensity between the upper and lower threshold values. EMG was continuously monitored on an oscilloscope, at high gain, to ensure the absence of any muscle activity during the test.

b. Recruitment curve (RC)

For RC measurement, the stimulator intensity was initially set at 90% of the previously determined RMT value. Ten MEPs are then recorded at this intensity in order to obtain a reliable MEP amplitude (Christie, Fling, Crews, Mulwitz, & Kamen, 2007). From this point, the stimulator output is increased gradually by 10% increments of their

RMT with 10 MEPs being recorded for each subsequent increase reaching a maximum of 130% RMT.

c. Contralateral silent period (cSP)

The cSP was calculated with the stimulator output intensity adjusted to 120% of RMT in order to achieve reliable measures (Thomas, Enoka, Gandevia, McComas, & Stuart, 1995). Ten pulses were administered while the subject held the pinch dynamometer with a contraction corresponding to 25% of their MVC.

d. Ipsilateral silent period (iSP).

To obtain a reliable iSP, the motor cortex was stimulated at an intensity of 120% of RMT while a minimal contraction was maintained in the contralateral hand and the ipsilateral hand is performing a key pinch at maximal strength (Giovannelli et al., 2009). Five pulses were given to the ipsilateral cortex to determine the average duration of the iSP.

Analysis of MEP data and background EMG

All EMG data were stored for offline analysis. MEP amplitude (peak-to-peak) and latency were measured for each trial and then averaged to derive mean individual values for each task condition. RCs were obtained by plotting the increases in MEP amplitude against corresponding increases in TMS intensity. As suggested by Ray et al. (2002), we used simple linear regression analyses to compute the slope of each RC. However, recent studies have found that an RC done with a wide range of intensities until a plateau is

reached follows the non-linear Boltzmann equation (Devanne, Lavoie, & Capaday, 1997). To adjust for this, we used a more limited range of intensities between 90% and 130% of RMT which has been found to exhibit a nearly linear relationship (Lewis, Polych, & Byblow, 2004). The slope summarizing the strength of the RC provided a single parameter for statistical comparisons.

MEP traces were also analyzed off-line to determine the duration of the cSP, which was calculated as the time interval from the onset of the MEP to the return of at least 50% of the mean pre-stimulus background EMG activity. For iSP measures, three parameters were measured by inspecting trials individually. First, the onset latency of transcallosal inhibition (LTI) was determined as the time from the stimulus onset till the 1st sign of significant decline (>25%) in background EMG activity. The second parameters consisted of determining the duration of transcallosal inhibition (DTI) by measuring the time in ms from the onset of TI till the 1st sign of recovery in the background EMG (Bushnell, Duncan, & Tremblay, 1993). Thirdly, the area under the curve during the DTI was taken into account (iSParea).

Statistical analysis

The positively skewed MEP amplitudes were not normally distributed therefore individual mean values were squareroot transformed to compute slopes for the RC. The transformed MEP values significantly improved the goodness of fit of the linear slope of the RC when compared to the raw MEP data (right hand $t(28)=5.542$, $p < .001$; left hand

$t(28)=2.312$, $p < .05$). Grubb's tests were done for each variable to identify and remove any significant outliers. A total of 12 outliers were removed in total.

Repeated measures ANOVAs were used to determine the impact of within- and between-subjects factors on the dependant variables. In all analyses, the reapeated factors was "hand" (right vs. left) and the between factors consisted of age group (young vs. senior). Post—hoc planned comparisons were performed to examined right-left differences between hands using paired t-tests. The age-group*hand interactions were examined to determine if intermanual or interhemispheric asymmetries differed between age groups. An Analysis of Covariance (ANCOVA) was performed to examine certain covariates (e.g. height) known to influence MEP characteristics. Pearson's correlations were used to examine the relationships between selected neurophysiological measures and performance in the hand function tests. All tests were performed using SPSS software version 17.0 for Windows® (Chicago, IL, USA). Figures were prepared using GraphPad Prism version 5.00 for Windows (GraphPad Software, San Diego California USA, www.graphpad.com).

Results

All participants successfully completed all the testing with little to no discomfort. As shown in Table 1, tuning fork measures were all within the norms for each age group.

Comparison of Behavioral Measures of right and left hand function

Mean values for hand function measure for the two age groups are shown in Table 2. Young subjects performed significantly better with their dominant hand on every test ($p<.01$), except for SRT which tended towards better performance in the right hand but it did not reach statistical significance ($t(12)=1.99$, $p=.07$). Senior subjects mirrored the young subjects and performed significantly better with their dominant hand ($p<.05$) on most hand function measures. However, unlike their younger counterparts, seniors had significantly faster reaction times with their dominant hand ($t(14)=2.34$, $p=.035$). Furthermore, no age-group*hand interactions was detected ($F<2.89$, $p>.10$) on any functional tests, indicating that right-left differences observed in seniors were similar to those observed in young subjects.

Right-left differences in Neurophysiology measures

In general, only small differences were observed between right and left TMS measures of corticomotor excitability in both age groups. The fact that no age-group*hand interactions ($F<2.34$, $p>.14$) were detected in the ANOVAs indicated that interhemispheric differences were not influenced by age. Individual examples of right-left variations in MEP amplitude at increasing TMS intensities are shown in Figure 1 for

young and senior subjects. The results indicate an increase in MEP amplitude with higher stimulation intensity was relatively comparable in the two hemispheres for both subjects. Similarly, Figure 2 shows that inter and intrahemispheric measures of cortical inhibition, as reflected in the duration of the iSP and cSP respectively, were largely comparable in both hemispheres in both the young and senior subject. The average right and left intra and interhemispheric measures of excitability are shown in Table 3 for all participants in the two age groups. Both young and senior participants exhibited only small variations between measures for the right and left hemispheres. In fact, apart from the difference in resting MT found in senior ($t(16)= 2.89$, $p=.011$); none of the intra or interhemispheric measures of excitability differed significantly between the right and left hemispheres.

Age differences in measures of intrahemispheric motor excitability and interhemispheric inhibition

As shown in Table 3, significant age differences were found for measures of intrahemispheric excitability and interhemispheric inhibition in both the right and left hemispheres. However, the age difference in MEP latency at 120% MT in the resting state ($Latency_{120}$) was not significant ($F(1,27)= 3.42$, $p=.075$), but this was accounted for by the fact that younger subject were significantly taller than seniors ($p=.04$). When height was entered into as a co-variate in an ANCOVA, significant age-related differences in MEP latencies were found ($F(1,26)= 15.55$, $p<.001$). Therefore, only the ANCOVAs were taken for further analysis for all latency measures.

Relationship between TMS measures of corticospinal function and hand performance in the two age groups.

Preliminary analysis of the relationships between neurophysiological measures and behavioral measures indicated a stronger association between specific set of variables. Therefore, the correlative analysis was performed only on this subset of selected variables. Correlation coefficients between the selected TMS markers of corticospinal excitability in the right hemisphere and behavioral measures of left hand function are given in Table 4 and Table 5 contains relationship data for the right hand and left hemisphere. As seen in Table 4 and 5, all significant correlations pointed to TMS markers of increased excitability, shorter latencies or greater inhibition as better predictors of performance in the tests. Examples of such relationships can be found in Figure 3. Intrahemispheric measures of excitability in the resting state correlated only infrequently with hand function (i.e., 2 in the left hand and 3 in the right hand). In contrast, similar measures performed in the active state provided stronger and more frequent correlations with behavior (4 in the left hand and 5 in the right hand). Likewise, measures of interhemispheric inhibition correlated well with manual performance in both the left hand and the right hand. Thus, in general, our analysis revealed that TMS measures performed during active contraction and involving the dominant right hand provided correlated better with behavioral performance as opposed to measures performed at rest or involving the non dominant left hand.

Discussion

In the present study, we investigated the relationships between neurophysiological measures of corticospinal excitability obtained with TMS and behavioural measures of hand function in young and senior individuals. We also sought to determine if a lifetime of preferential use would alter intermanual and interhemispheric asymmetries; favoring the dominant hand and hemisphere. Three main results emerge. First, we found that most neurophysiological and behavioral measures observed were significantly affected by age. Second, our results indicate that right versus left intermanual or interhemispheric asymmetries are not significantly altered by age, with the dominant right hand outperforming the left hand in almost all tests. Third, there is an overall trend suggesting that specific TMS measures of intrahemispheric excitability and corresponding measures of interhemispheric inhibition provide valid markers of age-dependant change in manual performance.

Age differences in hand function and in TMS measures

As expected, we found significant age-related declines in hand function with both the right and left hand. The effect of age on manual slowing, sarcopenia, sensory deterioration and functional ability is well documented (Agrawal et al., 2009; Mutha & Sainburg, 2009; Rosenthal, Roche-Kelly, Husain, & Kennard, 2009). Consistent with previous studies, we found significant age differences on GPT scores (Fathi et al., 2010), reaction times (Agrawal, Vats, Wallace, Salhan, & Mittal, 2008; Basu et al., 2006), finger tapping (Aoki & Fukuoka, 2010) and grip strength (Bhattacharya, Mittal, Bhansali, Radotra, & Behera, 2006). We also found that age had no major effect on SRT, a finding

consistent with other studies (Sharma, Kumar, Mittal, Misra, & Dadhwal, 2005). Cerella & Halle (1994) suggested that processes involved in SRT were relatively well preserved with healthy aging, and thus, excessively prolonged SRT in older individuals could be indicative of perceptual, motor or cognitive deficits.

Our comparison of TMS measures at rest in young and senior subjects reveal a decrease in corticospinal excitability with age both in the resting and in the active state. This was manifested in the increased RMT combined with reduced MEP amplitude at rest and during contraction found in senior individuals. Age effects on MEP latency was found only during active conditions and not during rest, when height was not considered as a covariate, but this could be due to the decreased variability in MEP properties with active contraction (Wassermann, 2002). Previous studies have provided conflicting evidence concerning the effects of age on baseline measures of excitability, some studies finding significant age-related differences on RMT (Levin et al., 2011; Peinemann et al., 2001; Rossini et al., 1992) and MEP amplitude (Oliviero et al., 2006; Pitcher et al., 2003) while others found no changes with age in RMT(Cirillo, Rogasch, & Semmler, 2010; Pepin et al., 1999; Pitcher et al., 2003; Rossi et al., 2004) of MEP amplitude (Fathi et al., 2010; Levin et al., 2011; Rogasch, Dartnall, Cirillo, Nordstrom, & Semmler, 2009). These inconsistencies in results likely reflect differences in methodological approaches and stimulation paradigms. For instance, in the present study, we used biphasic pulses instead of the monophasic pulses that were used in most other TMS studies. These different stimulus waveforms have been found to have a significant effect on cortical activation, biphasic pulses being more effective at activating cortical neurons than monophasic pulses for the same energy of the capacitor (Kammer, Beck, Thielscher,

Laubis-Herrmann, & Topka, 2001). Furthermore, TMS waveforms were found to have profound effects on RMT, MEP area and cSP duration measurements (Di Lazzaro et al., 2001; Orth & Rothwell, 2004; Sommer et al., 2006). Another source of discrepancy between studies is the inherent large variability that exists both within and between subjects when determining primary measures of excitability such as RMT. This variability limits the potential of detecting functional differences both in healthy individuals and in clinical populations (Tranulis et al., 2006; Wassermann, 2002).

The decrease in basic measures of corticospinal excitability with age could reflect different alterations affecting the corticospinal system. An increase in RMT could reflect structural age-related alteration such as those affecting white matter integrity (Klöppel et al., 2008) or a decreased excitability of cortico-cortical connections or in corticospinal synapses (Talelli et al., 2006). Changes in RMT could also be caused by age-related cortical thinning, which alters the scalp-cortex distance (Kozel et al., 2000; McConnell et al., 2001) and is known to be strongly positively correlated to threshold values (Klöppel et al., 2008; Stokes et al., 2007). The reduced MEP amplitude both at rest and with contraction is considered a strong marker of the age-related reduction in the strength of corticospinal projections (Rossi, Babiloni, & Polich, 2007). This reduction is thought to be caused by a decrease in the number of corticospinal projections being activated with each stimulus along with a reduction in the synchronous activation of the spinal motor neurons (Rossini, Rossi, Babiloni, & Polich, 2007). Increased MEP latency with age likely reflects alterations in central conduction affecting temporal synchrony in corticospinal fibers combined with delayed conduction at the peripheral level such as increased internode distance with age (Levine, Elgert, & Mittal, 2003).

In parallel with age-related changes in basic measures of excitability, we also found significant decreases in measures of cortical inhibition, as reflected in shorter cSP and iSP durations measured in seniors. Previous studies support our results, indicating a shorter silent period with age (Oliviero et al., 2006; Sale & Semmler, 2005). This reduction in cSP suggests a reduction in the strength of the corticospinal projections as well as impaired GABAergic transmission with a reduced inhibition mediated by $GABA_B$ receptor subtype (Chen et al., 2008). As for the iSP, this study is one of the first to report a decrease in this variable reflecting efficiency of transcallosal inhibition between motor cortices. The decreased transcallosal inhibition with age could reflect alteration in the integrity of the white matter in the corpus callosum, as suggested in a recent review by Seidler et al. (2010). Such an interpretation is further supported by the increased latency of transcallosal inhibition we found in seniors, which could also be affected by alterations in the quantity and quality of motor callosal connections with age (Michielse et al., 2010). On the other hand, given that iSP-derived measures such as DTI, iSParea and LTI are influenced by stimulation intensity (Chen et al., 2003; Meyer et al., 1995), there is a possibility that age-related differences in iSP parameters could have been affected by the increased RMT found in the older age-group. Similar observations were found by Pitcher et al. (2003), where higher stimulus intensities were needed in the older age group to achieve the results of the young subjects. It remains that the present observations on TMS measures of inhibition are consistent with other TMS reports in supporting the notion that the excitability of intracortical circuits mediating inhibition is reduced in the motor cortex with age (Fling, Peltier, Bo, Welsh, & Seidler, 2011; Peinemann et al., 2001; Sale & Semmler, 2005).

Right-left asymmetries

In accordance with the HAROLD (hemispheric asymmetry reduction in older adults) model for aging (Singh, Sachan, Devi, Pandey, & Mittal, 2008), we did not find evidence for greater right-left asymmetries in either our measures of hand function or our measures of corticospinal excitability. At the behavioral level, senior individuals exhibited the same advantage for performance with the right hand as was observed in younger subjects**.** However, this functional right-lateralized asymmetry in hand function, was not reflected at the neurophysiological level since TMS measures of excitability were highly comparable between the two motor cortices in both young and old subjects. Right-left differences in hand performance reflect a multitude of factors acting both at the central (e.g. sensorimotor representation, motor planning and programming) and peripheral level (e.g. muscle strength, joint flexibility, proprioception; Seidler et al., 2010), whereas TMS-derived measures reflect only one major, albeit critical, component of hand function associated with the corticospinal control of fine execution. It is therefore expected that TMS measures cannot account for all the complex interactions that underlie age-related changes in asymmetry at the functional level (Brouwer, Sale, & Nordstrom, 2001; Sale & Semmler, 2005). This issue will be further addressed bellow in the section examining correlations between TMS measures and function.

Going back to the HAROLD model, this model is largely concerned with the reduced left-lateralized activation observed in the prefontral cortex (PFC) of older individuals when they are engaged in verbal memory or executive control tasks (Singh, Sachan, Goel, & Mittal, 2008). Recent diffusion tensor imaging evidence provides further support for no greater asymmetries in diffusivity and cerebral volume with age; except in

the dorsal cingulum (Michielse et al., 2010). The present observation that senior exhibited no evident hemispheric asymmetries in the various TMS measures of corticospinal excitability is more concordant with the HAROLD model than the classical right hemi-aging model. The latter model proposes that cognitive function attributed to the right hemisphere decreases in function notably quicker than the dominant left hemisphere function, especially in right handed subject. Although this model was initially supported by observed changes in verbal processing (Brown & Jaffe, 1975; Goldstein & Shelly, 1981); the inability to replicate and generalize the results to other tests evaluating spatial and verbal components have left many to favor the HAROLD model (Dolcos, Rice, & Cabeza, 2002).

While older individuals tend to see themselves as strongly lateralized when assessed using various handedness inventory tests (Fleminger, Dalton, & Standage, 1977), this perception does not seem to be reflected at the behavioral level, unlike in younger subjects (Kalisch, Wilimzig, Kleibel, Tegenthoff, & Dinse, 2006). In fact, our group of seniors was as much as right-lateralized as our group of young subjects, an observation consistent with recent reports indicating similar perception of laterality in hand function with age (Francis & Spirduso, 2000; Kalisch et al., 2006; Przybyla, Haaland, Bagesteiro, & Sainburg, 2011).The observation that right hand dominance does not becomes stronger with age, in spite of many years of preferential use, could be due to the increased use of the non-dominant hand in daily life activities as people age (Kalisch et al., 2006). This implies an important reliance on bimanual actions with advancing age. This may be related to increasing occurrences of impairments in the right hand(Carmeli et al., 2003), forcing individuals to use the left hand in a greater extent in everyday tasks. This

increased reliance on the non-dominant hand could drive experience-dependent plastic changes in the motor system, which is known to affect both intracortical excitability and interhemispheric inhibition (Avanzino, Bassolino, Pozzo, & Bove, 2011; Caramia, Scalise, Gordon, Michalewski, & Starr, 2000; Rosenkranz, Williamon, & Rothwell, 2007). In this connection, the suggestion that older people tend to rely more on bimanual control than young may explain the absence of strong asymmetries at the corticomotor level with age, as we found in the present study.

Relationship between neurophysiological measures and hand function

One of the major goals of the present study was to examine possible relationships between TMS-derived measures of corticospinal excitability and behavioral measures of hand function in young and old subjects. From the correlative analyses, we found that some key measures of corticospinal excitability provided better predictors of hand function and its change with age. In general, intrahemispheric TMS measures of resting excitability, such as RMT and resting MEP amplitude, proved to be only poor to fair predictors of hand function. In fact, RMT was found to be a very poor predictor of hand function; for it was not significantly correlated with any measure of hand function in either the right or left hand. The RC at rest, on the other hand, was a better predictor of hand function. This supports the notion that the RC provides a good index of the strength of corticospinal projections and is relatively independent of the RMT (Ray, McNamara, & Boniface, 2002). In fact, RC was found to be the best predictor among all the other TMS resting measures of intrahemispheric excitability.

The poor predictive power of RMT and MEP amplitude is surprising given that these measures have been largely used in other studies that have attempted to relate hand function to TMS markers of corticospinal excitability (Sale & Semmler, 2005; Triggs, Calvanio, & Levine, 1997; Triggs, Subramanium, & Rossi, 1999). Their weak predicting power could partially explain the conflicting results found in previous reports. For example, finger tapping has been found to either correlate strongly or weakly with TMS measures of corticospinal excitability (Brouwer et al., 2001; Garvey et al., 2003; Sale & Semmler, 2005; Triggs et al., 1997). Despite these conflicting results, most TMS studies have found that improved manual performance is generally associated with enhanced corticospinal excitability (Brouwer et al., 2001; Garvey et al., 2003; Sale & Semmler, 2005; Triggs et al., 1997).

Intrahemispheric measures in the active state, such as MEP_{fac}, proved to be far better predictors of hand function than similar measures performed at rest. Such findings possibly reflect the fact that MEP amplitude during contraction provides better estimates of the "true" excitability of the corticospinal projections than MEP amplitude at rest (Talelli et al., 2006). This, in turns, probably reflects attenuated fluctuations in synaptic excitability, thereby providing a more secure excitation of corticospinal neurons, as demonstrated by the reduced variability of MEP amplitude when elicited during a low submaximal contraction compared to rest (Darling, Wolf, & Butler, 2006). Further, this reduced variability in MEP amplitude could be of great importance, especially in the seniors, where increased variability is typically seen at the behavioral and cognitive level (Hultsch, MacDonald, & Dixon, 2002; Morse, 1993). Besides, given that measurements in hand function reflect performance in the active state, it makes sense that TMS should

also be performed in an active, to assess excitability of the system in the same behavioral state.

Our results also show that more significant correlations are found between the left hemisphere and the right hand than in the corresponding relationship between the compared to the right hemisphere and the left hand. This observation could reflect the more unpredictable nature of measurements performed both on the right motor cortex and with the left hand, where greater variability was observed both at the intra and inter-individual levels. This could also reflect adaptations at the functional and neurophysiological level caused by the relative use of the two hands in daily activities (Avanzino et al., 2011) or in sports (Pearce, Thickbroom, Byrnes, & Mastaglia, 2000) and leading to a stronger and a more stable corticomotor representation of the right dominant hand strengthening in the left hemisphere (Cirillo et al., 2010). Recent literature has put forward the hypothesis that the left hemisphere plays a dominant role in the execution and planning of skilled movements (Frey, 2008; Haaland, Harrington, & Knight, 2000; Janssen, Meulenbroek, & Steenbergen, 2011) and thus this might explain why correlations with hand function were more frequent and stronger in the left motor cortex than with the right motor cortex. Future research with left-handers will need to be performed to determine whether the excitability-function relationships between one hemisphere and the dominant hand is related to preferential use or is an inherent specialization of the left hemisphere.

Interhemispheric inhibition measures provided fair to good correlations with hand function, with the largest correlations being found for the left to right interhemisphere inhibition and right hand function. Interhemispheric inhibition is critical for independent

coordination of each hand during bimanual actions. Individuals who have underwent callosotomy to alleviate severe epilepsy show hand coordination deficits in temporal coupling tasks (Kennerley, Diedrichsen, Hazeltine, Semjen, & Ivry, 2002). Furthermore, iSP were found to correlate with improved performance during bimanual activation (Giovannelli et al., 2009). Hence, although iSP measurements were found to be correlated to unimanual hand function tests in the present study, they may be better suited to predict behavior at bimanual tasks.

Our observations on the importance of iSP in predicting hand performance are in line with recent reports (Lindberg, Feydy, & Maier, 2010; Sullivan, Rohlfing, & Pfefferbaum, 2010) examining age-associated changes in white matter using fractional anisotropy (FA) based on diffusion tensor imaging. FA reflects the structural characteristics of white matter and is used as a quantitative measure of white matter integrity. Variations in FA were found to correlate with age and also with better hand performance, suggesting that axonal and myelin integrity are critical factors in influencing manual dexterity (Budde et al., 2007); this is similar to what we can infer from the present results on neurophysiological correlates of short cortico-cortical (iSP) and long descending corticospinal projections (RC, MEPfac, cSP) from the TMS measures. In this respect, our results could be used as possible building blocks for the development of normative data on neurophysiological markers of hand function to reflect normal changes when one goes from young to old age. Such a database could provide critical information to distinguish between alterations due to normal aging and those linked with pathological processes caused by undiagnosed neuropathies, movement disorders or musculoskeletal injuries (Chen et al., 2008).

Conclusion

Healthy human aging leads to changes in hand functional ability and these changes are reflected to a large extent in TMS measures performed in the active state and reflecting either intrahemispheric excitability or interhemispheric inhibition. Our findings highlight in particular the fact that the behavior-TMS relationships were more frequent and stronger for the right hand/left hemisphere couple than for the left hand/right hemisphere couple in our sample of young and senior subjects. These results provide a basis to develop normative data that could be used for the early diagnosis of age-related impairments affecting hand function in seniors.

Acknowledgments

The authors wish to thank all participants for their time and patience during testing. Travis Davidson received a research trainee fellowship by the Elisabeth Bruyere Research Institute towards the completion of this project. Part of this project was supported by a discovery grant to Francois Tremblay.

References

Agrawal, T., Vats, V., Wallace, P. K., Salhan, S., & Mittal, A. (2008). Role of cervical dendritic cell subsets, co-stimulatory molecules, cytokine secretion profile and beta-estradiol in development of sequalae to Chlamydia trachomatis infection. *Reprod Biol Endocrinol, 6*, 46.

Agrawal, T., Vats, V., Wallace, P. K., Singh, A., Salhan, S., & Mittal, A. (2009). Recruitment of myeloid and plasmacytoid dendritic cells in cervical mucosa during Chlamydia trachomatis infection. *Clin Microbiol Infect, 15*(1), 50-59.

Avanzino, L., Bassolino, M., Pozzo, T., & Bove, M. (2011). Use-dependent hemispheric balance. *J Neurosci, 31*(9), 3423-3428.

Basu, P., Sarkar, S., Mukherjee, S., Ghoshal, M., Mittal, S., Biswas, S., et al. (2006). Women's perceptions and social barriers determine compliance to cervical screening: results from a population based study in India. *Cancer Detect Prev, 30*(4), 369-374.

Bhattacharya, A., Mittal, B. R., Bhansali, A., Radotra, B. D., & Behera, A. (2006). Cervical paraganglioma mimicking a parathyroid adenoma on Tc-99m sestamibi scintigraphy. *Clin Nucl Med, 31*(4), 234-236.

Birren, J. E., & Fisher, L. M. (1995). Aging and speed of behavior: possible consequences for psychological functioning. *Annu Rev Psychol, 46*, 329-353.

Brouwer, B., Sale, M. V., & Nordstrom, M. A. (2001). Asymmetry of motor cortex excitability during a simple motor task: relationships with handedness and manual performance. *Exp Brain Res, 138*(4), 467-476.

Brown, J. W., & Jaffe, J. (1975). Hypothesis on cerebral dominance. *Neuropsychologia, 13*(1), 107-110.

Budde, M. D., Kim, J. H., Liang, H. F., Schmidt, R. E., Russell, J. H., Cross, A. H., et al. (2007). Toward accurate diagnosis of white matter pathology using diffusion tensor imaging. *Magn Reson Med, 57*(4), 688-695.

Bushnell, M. C., Duncan, G. H., & Tremblay, N. (1993). Thalamic VPM nucleus in the behaving monkey. I. Multimodal and discriminative properties of thermosensitive neurons. *J Neurophysiol, 69*(3), 739-752.

Caramia, M. D., Scalise, A., Gordon, R., Michalewski, H. J., & Starr, A. (2000). Delayed facilitation of motor cortical excitability following repetitive finger movements. *Clin Neurophysiol, 111*(9), 1654-1660.

Carmeli, E., Patish, H., & Coleman, R. (2003). The aging hand. *J Gerontol A Biol Sci Med Sci, 58*(2), 146-152.

Cerella, J. (1985). Information processing rates in the elderly. *Psychol Bull, 98*(1), 67-83.

Chen, R., Cros, D., Curra, A., Di Lazzaro, V., Lefaucheur, J. P., Magistris, M. R., et al. (2008). The clinical diagnostic utility of transcranial magnetic stimulation: report of an IFCN committee. *Clin Neurophysiol, 119*(3), 504-532.

Chen, R., Lozano, A. M., & Ashby, P. (1999). Mechanism of the silent period following transcranial magnetic stimulation. Evidence from epidural recordings. *Exp Brain Res, 128*(4), 539-542.

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.

Christie, A., Fling, B., Crews, R. T., Mulwitz, L. A., & Kamen, G. (2007). Reliability of motor-evoked potentials in the ADM muscle of older adults. *J Neurosci Methods, 164*(2), 320-324.

Cirillo, J., Rogasch, N. C., & Semmler, J. G. (2010). Hemispheric differences in use-dependent corticomotor plasticity in young and old adults. *Exp Brain Res, 205*(1), 57-68.

Cole, K. J., Cook, K. M., Hynes, S. M., & Darling, W. G. (2009). Slowing of dexterous manipulation in old age: force and kinematic findings from the 'nut-and-rod' task. *Exp Brain Res*.

Cole, K. J., & Rotella, D. L. (2001). Old age affects fingertip forces when restraining an unpredictably loaded object. *Exp Brain Res, 136*(4), 535-542.

Cole, K. J., & Rotella, D. L. (2002). Old age impairs the use of arbitrary visual cues for predictive control of fingertip forces during grasp. *Exp Brain Res, 143*(1), 35-41.

Crabtree, D. A., & Antrim, L. R. (1988). Guidelines for measuring reaction time. *Percept Mot Skills, 66*(2), 363-370.

Darling, W. G., Wolf, S. L., & Butler, A. J. (2006). Variability of motor potentials evoked by transcranial magnetic stimulation depends on muscle activation. *Exp Brain Res, 174*(2), 376-385.

Devanne, H., Lavoie, B. A., & Capaday, C. (1997). Input-output properties and gain changes in the human corticospinal pathway. *Exp Brain Res, 114*(2), 329-338.

Di Lazzaro, V., Oliviero, A., Mazzone, P., Insola, A., Pilato, F., Saturno, E., et al. (2001). Comparison of descending volleys evoked by monophasic and biphasic magnetic stimulation of the motor cortex in conscious humans. *Exp Brain Res, 141*(1), 121-127.

Doeltgen, S. H., & Ridding, M. C. (2010). Behavioural exposure and sleep do not modify corticospinal and intracortical excitability in the human motor system. *Clin Neurophysiol, 121*(3), 448-452.

Dolcos, F., Rice, H. J., & Cabeza, R. (2002). Hemispheric asymmetry and aging: right hemisphere decline or asymmetry reduction. *Neurosci Biobehav Rev, 26*(7), 819-825.

Fathi, D., Ueki, Y., Mima, T., Koganemaru, S., Nagamine, T., Tawfik, A., et al. (2010). Effects of aging on the human motor cortical plasticity studied by paired associative stimulation. *Clin Neurophysiol, 121*(1), 90-93.

Fleminger, J. J., Dalton, R., & Standage, K. F. (1977). Age as a factor in the handedness of adults. *Neuropsychologia, 15*(3), 471-473.

Fling, B. W., Peltier, S., Bo, J., Welsh, R. C., & Seidler, R. D. (2011). Age Differences in Interhemispheric Interactions: Callosal Structure, Physiological Function, and Behavior. [Focused Review]. *Frontiers in Neuroscience, 5*.

Francis, K. L., & Spirduso, W. W. (2000). Age differences in the expression of manual asymmetry. *Exp Aging Res, 26*(2), 169-180.

Frey, S. H. (2008). Tool use, communicative gesture and cerebral asymmetries in the modern human brain. *Philos Trans R Soc Lond B Biol Sci, 363*(1499), 1951-1957.

Fuhr, P., Agostino, R., & Hallett, M. (1991). Spinal motor neuron excitability during the silent period after cortical stimulation. *Electroencephalography & Clinical Neurophysiology, 81*(4), 257-262.

Garvey, M. A., Ziemann, U., Bartko, J. J., Denckla, M. B., Barker, C. A., & Wassermann, E. M. (2003). Cortical correlates of neuromotor development in healthy children. *Clin Neurophysiol, 114*(9), 1662-1670.

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. *The Journal of Physiology, 587*(22), 5393-5410.

Goldstein, G., & Shelly, C. (1981). Does the right hemisphere age more rapidly than the left? *Journal of Clinical Neuropsychology, 3*(1), 65 - 78.

Haaland, K. Y., Harrington, D. L., & Knight, R. T. (2000). Neural representations of skilled movement. *Brain, 123 (Pt 11)*, 2306-2313.

Hesselmann, V., Zaro Weber, O., Wedekind, C., Krings, T., Schulte, O., Kugel, H., et al. (2001). Age related signal decrease in functional magnetic resonance imaging during motor stimulation in humans. *Neurosci Lett, 308*(3), 141-144.

Hultsch, D. F., MacDonald, S. W., & Dixon, R. A. (2002). Variability in reaction time performance of younger and older adults. *J Gerontol B Psychol Sci Soc Sci, 57*(2), P101-115.

Janssen, L., Meulenbroek, R. G., & Steenbergen, B. (2011). Behavioral evidence for left-hemisphere specialization of motor planning. *Exp Brain Res, 209*(1), 65-72.

Kalisch, T., Wilimzig, C., Kleibel, N., Tegenthoff, M., & Dinse, H. R. (2006). Age-related attenuation of dominant hand superiority. *PLoS One, 1*, e90.

Kammer, T., Beck, S., Thielscher, A., Laubis-Herrmann, U., & Topka, H. (2001). Motor thresholds in humans: a transcranial magnetic stimulation study comparing different pulse waveforms, current directions and stimulator types. *Clin Neurophysiol, 112*(2), 250-258.

Kawakita, H., Kameyama, O., Ogawa, R., Hayes, K. C., Wolfe, D. L., & Allatt, R. D. (1991). Reinforcement of motor evoked potentials by remote muscle contraction. *J Electromyogr Kinesiol, 1*(2), 96-106.

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.

Klöppel, S., Bäumer, T., Kroeger, J., Koch, M. A., Büchel, C., Münchau, A., et al. (2008). The cortical motor threshold reflects microstructural properties of cerebral white matter. *NeuroImage, 40*(4), 1782-1791.

Kozel, F. A., Nahas, Z., deBrux, C., Molloy, M., Lorberbaum, J. P., Bohning, D., et al. (2000). How coil-cortex distance relates to age, motor threshold, and antidepressant response to repetitive transcranial magnetic stimulation. *J Neuropsychiatry Clin Neurosci, 12*(3), 376-384.

Levin, O., Cuypers, K., Netz, Y., Thijs, H., Nuttin, B., Helsen, W. F., et al. (2011). Age-related differences in human corticospinal excitability during simple reaction time. *Neurosci Lett, 487*(1), 53-57.

Levine, P. H., Elgert, P. A., & Mittal, K. (2003). False-positive squamous cell carcinoma in cervical smears: cytologic-histologic correlation in 19 cases. *Diagn Cytopathol, 28*(1), 23-27.

Lewis, G. N., Polych, M. A., & Byblow, W. D. (2004). Proposed cortical and sub-cortical contributions to the long-latency stretch reflex in the forearm. *Exp Brain Res, 156*(1), 72-79.

Lindberg, P. G., Feydy, A., & Maier, M. A. (2010). White matter organization in cervical spinal cord relates differently to age and control of grip force in healthy subjects. *J Neurosci, 30*(11), 4102-4109.

Manning, H., & Tremblay, F. (2006). Age differences in tactile pattern recognition at the fingertip. *Somatosens Mot Res, 23*(3-4), 147-155.

Matsunaga, K., Uozumi, T., Tsuji, S., & Murai, Y. (1998). Age-dependent changes in physiological threshold asymmetries for the motor evoked potential and silent period following transcranial magnetic stimulation. *Electroencephalogr Clin Neurophysiol, 109*(6), 502-507.

McConnell, K. A., Nahas, Z., Shastri, A., Lorberbaum, J. P., Kozel, F. A., Bohning, D. E., et al. (2001). The transcranial magnetic stimulation motor threshold depends on the distance from coil to underlying cortex: a replication in healthy adults comparing two methods of assessing the distance to cortex. *Biol Psychiatry, 49*(5), 454-459.

Meyer, B. U., Roricht, S., Grafin von Einsiedel, H., Kruggel, F., & Weindl, A. (1995). Inhibitory and excitatory interhemispheric transfers between motor cortical areas in normal human and patients with abonormalities of the corpus callosum. *Brain, 118*(2), 429-440.

Michielse, S., Coupland, N., Camicioli, R., Carter, R., Seres, P., Sabino, J., et al. (2010). Selective effects of aging on brain white matter microstructure: a diffusion tensor imaging tractography study. *NeuroImage, 52*(4), 1190-1201.

Morse, C. K. (1993). Does variability increase with age? An archival study of cognitive measures. *Psychol Aging, 8*(2), 156-164.

Mutha, P. K., & Sainburg, R. L. (2009). Shared Bimanual Tasks Elicit Bimanual Reflexes During Movement. *J Neurophysiol, 102*(6), 3142-3155.

Oliviero, A., Profice, P., Tonali, P. A., Pilato, F., Saturno, E., Dileone, M., et al. (2006). Effects of aging on motor cortex excitability. *Neuroscience Research, 55*(1), 74-77.

Orth, M., & Rothwell, J. C. (2004). The cortical silent period: intrinsic variability and relation to the waveform of the transcranial magnetic stimulation pulse. *Clinical Neurophysiology, 115*(5), 1076-1082.

Pearce, A. J., Thickbroom, G. W., Byrnes, M. L., & Mastaglia, F. L. (2000). Functional reorganisation of the corticomotor projection to the hand in skilled racquet players. *Exp Brain Res, 130*(2), 238-243.

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.

Pepin, J. L., Bogacz, D., de Pasqua, V., & Delwaide, P. J. (1999). Motor cortex inhibition is not impaired in patients with Alzheimer's disease: evidence from paired transcranial magnetic stimulation. *J Neurol Sci, 170*(2), 119-123.

Pitcher, J. B., Ogston, K. M., & Miles, T. S. (2003). Age and sex differences in human motor cortex input-output characteristics. *J Physiol (Lond), 546*(2), 605-613.

Przybyla, A., Haaland, K. Y., Bagesteiro, L. B., & Sainburg, R. L. (2011). Motor asymmetry reduction in older adults. *Neurosci Lett, 489*(2), 99-104.

Ray, J., McNamara, B., & Boniface, S. (2002). Acquisition and expression of proximal and distal upper limb stimulus-response curves to transcranial magnetic stimulation. *Muscle Nerve, 25*(2), 202-206.

Ridding, M. C., & Rothwell, J. C. (1997). Stimulus/response curves as a method of measuring motor cortical excitability in man. *Electroencephalogr Clin Neurophysiol, 105*(5), 340-344.

Rogasch, N. C., Dartnall, T. J., Cirillo, J., Nordstrom, M. A., & Semmler, J. G. (2009). Corticomotor plasticity and learning of a ballistic thumb training task are diminished in older adults. *J Appl Physiol, 107*(6), 1874-1883.

Rosenkranz, K., Williamon, A., & Rothwell, J. C. (2007). Motorcortical Excitability and Synaptic Plasticity Is Enhanced in Professional Musicians. *J. Neurosci., 27*(19), 5200-5206.

Rosenthal, C. R., Roche-Kelly, E. E., Husain, M., & Kennard, C. (2009). Response-Dependent Contributions of Human Primary Motor Cortex and Angular Gyrus to Manual and Perceptual Sequence Learning. *J. Neurosci., 29*(48), 15115-15125.

Rossi, S., Miniussi, C., Pasqualetti, P., Babiloni, C., Rossini, P. M., & Cappa, S. F. (2004). Age-Related Functional Changes of Prefrontal Cortex in Long-Term Memory: A Repetitive Transcranial Magnetic Stimulation Study. *J. Neurosci., 24*(36), 7939-7944.

Rossini, P. M., Desiato, M. T., & Caramia, M. D. (1992). Age-related changes of motor evoked potentials in healthy humans: non- invasive evaluation of central and peripheral motor tracts excitability and conductivity. *Brain Res, 593*(1), 14-19.

Rossini, P. M., & Rossi, S. (2007). Transcranial magnetic stimulation: Diagnostic, therapeutic, and research potential. *Neurology, 68*(7), 484-488.

Rossini, P. M., Rossi, S., Babiloni, C., & Polich, J. (2007). Clinical neurophysiology of aging brain: From normal aging to neurodegeneration. *Progress in Neurobiology, 83*(6), 375-400.

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.

Sharma, Y., Kumar, S., Mittal, S., Misra, R., & Dadhwal, V. (2005). Evaluation of glyceryl trinitrate, misoprostol, and prostaglandin E2 gel for preinduction cervical ripening in term pregnancy. *J Obstet Gynaecol Res, 31*(3), 210-215.

Shiffman, L. M. (1992). Effects of aging on adult hand function. *Am J Occup Ther, 46*(9), 785-792.

Singh, H., Sachan, R., Devi, S., Pandey, S. N., & Mittal, B. (2008). Association of GSTM1, GSTT1, and GSTM3 gene polymorphisms and susceptibility to cervical cancer in a North Indian population. *Am J Obstet Gynecol, 198*(3), 303 e301-306.

Singh, H., Sachan, R., Goel, H., & Mittal, B. (2008). Genetic variants of interleukin-1RN and interleukin-1beta genes and risk of cervical cancer. *BJOG, 115*(5), 633-638.

Smith, C. D., Umberger, G. H., Manning, E. L., Slevin, J. T., Wekstein, D. R., Schmitt, F. A., et al. (1999). Critical decline in fine motor hand movements in human aging. *Neurology, 53*(7), 1458-1461.

Sommer, M., Alfaro, A., Rummel, M., Speck, S., Lang, N., Tings, T., et al. (2006). Half sine, monophasic and biphasic transcranial magnetic stimulation of the human motor cortex. *Clin Neurophysiol, 117*(4), 838-844.

Stokes, M. G., Chambers, C. D., Gould, I. C., English, T., McNaught, E., McDonald, O., et al. (2007). Distance-adjusted motor threshold for transcranial magnetic stimulation. *Clinical Neurophysiology, 118*(7), 1617-1625.

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.

Talelli, P., Ewas, A., Waddingham, W., Rothwell, J. C., & Ward, N. S. (2008). Neural correlates of age-related changes in cortical neurophysiology. *NeuroImage, 40*(4), 1772-1781.

Talelli, P., Greenwood, R. J., & Rothwell, J. C. (2006). Arm function after stroke: Neurophysiological correlates and recovery mechanisms assessed by transcranial magnetic stimulation. *Clinical Neurophysiology, 117*(8), 1641-1659.

Talelli, P., Waddingham, W., Ewas, A., Rothwell, J. C., & Ward, N. S. (2008). The effect of age on task-related modulation of interhemispheric balance. *Experimental Brain Research, 186*(1), 59-66.

Taube, W., Schubert, M., Gruber, M., Beck, S., Faist, M., & Gollhofer, A. (2006). Direct corticospinal pathways contribute to neuromuscular control of perturbed stance. *J Appl Physiol, 101*(2), 420-429.

Terao, Y., & Ugawa, Y. (2002). Basic mechanisms of TMS. *J Clin Neurophysiol, 19*(4), 322-343.

Thomas, C. K., Enoka, R. M., Gandevia, S. C., McComas, A. J., & Stuart, D. G. (1995). The scientific contributions of Brenda Bigland-Ritchie. *Adv Exp Med Biol, 384*, 11-25.

Tranulis, C., Gueguen, B., Pham-Scottez, A., Vacheron, M. N., Cabelguen, G., Costantini, A., et al. (2006). Motor threshold in transcranial magnetic stimulation: comparison of three estimation methods. *Neurophysiologie Clinique/Clinical Neurophysiology, 36*(1), 1-7.

Tremblay, F., Mireault, A. C., Letourneau, J., Pierrat, A., & Bourrassa, S. (2002). Tactile perception and manual dexterity in computer users. *Somatosens Mot Res, 19*(2), 101-108.

Tremblay, F., Wong, K., Sanderson, R., & Cote, L. (2003). Tactile spatial acuity in elderly persons: assessment with grating domes and relationship with manual dexterity. *Somatosens Mot Res, 20*(2), 127-132.

Triggs, W. J., Calvanio, R., & Levine, M. (1997). Transcranial magnetic stimulation reveals a hemispheric asymmetry correlate of intermanual differences in motor performance. *Neuropsychologia, 35*(10), 1355-1363.

Triggs, W. J., Subramanium, B., & Rossi, F. (1999). Hand preference and transcranial magnetic stimulation asymmetry of cortical motor representation. *Brain Res, 835*(2), 324-329.

Wassermann, E. M. (2002). Variation in the response to transcranial magnetic brain stimulation in the general population. *Clin Neurophysiol, 113*(7), 1165-1171.

Wassermann, E. M., Fuhr, P., Cohen, L. G., & Hallett, M. (1991). Effects of transcranial magnetic stimulation on ipsilateral muscles. *Neurology, 41*(11), 1795-1799.

Werhahn, K. J., 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)*, 591-597.

Tables

Table 1. Demographic characteristics of the participants

		Age (years)	Height (cm)	Weight (kg)	BMI	Tuning fork score
Young						
	Males (n = 8)	23.5 ± 3.0	182.1 ± 7.1	76.4 ± 7.2	23.0 ± 1.8	7.6 ± 0.4
	Females (n = 5)	20.6 ± 2.3	160.9 ± 4.7	54.9 ± 4.8	21.2 ± 1.5	7.9 ± 0.2
Senior						
	Males (n = 6)	72.3 ± 5.9	173.9 ± 4.1	77.6 ± 15.1	25.6 ± 4.6	7.7 ± 0.4
	Females (n = 11)	73.4 ± 8.7	161.2 ± 7.7	64.4 ± 8.9	24.8 ± 3.0	7.6 ± 0.4

Table 2. Bilateral manual performance in hand function tests in the two age groups

	Young (n=13)		Senior (n=17)	
Test	Right Hand	Left Hand	Right Hand	Left Hand
GPT (s) ††	55.5 ± 4.9 ***	67.5 ± 6.9	88.5 ± 33.6 ***	100.3 ± 38.9
SRT (ms)	202.8 ± 14.7	211.8 ± 17.4	217.5 ± 22.6 *	224.1 ± 23.9
MovT (ms) †††	461.8 ± 47.0 **	510.7 ± 58.6	636.6 ± 155.3 *	672.3 ± 188.6
FTT (# taps) †††	100.2 ± 9.5 ***	89.8 ± 7.4	81.1 ± 10.6 ***	75.1 ± 12.0
MVC (kg) †††	10.1 ± 2.5 **	9.2 ± 2.4	7.2 ± 1.7 **	6.7 ± 1.6

Values for right and left hands are means ± standard deviation. Only the means of the absolute differences between right and left are present for the Δdiff. GPT – Grooved Pegboard Time; SRT – Simple Reaction Time; MovT – Reaction and Movement Time; FTT – Finger Tap test; MVC – Maximum voluntary contraction.

† Significant young-senior difference from ANOVA († $p<.05$; †† $p<.01$; ††† $p<.001$).

* Significant right-left difference, as determined with paired t-test (* $p<.05$; ** $p<.01$; *** $p<.001$).

Table 3. Bilateral measures (Mean ±SD) of hemispheric motor excitability in the two age groups

	Young		Senior	
TMS measures	Right Hemisphere	Left Hemisphere	Right Hemisphere	Left Hemisphere
Intrahemispheric				
Resting state				
RMT (% output) †	61.0 ± 11.3	57.6 ± 8.3	71.9 ± 12.5*	67.7 ± 13.0
MEP_{120} (mV) ††	1.0 ± 0.75	0.99 ± .77	0.44 ± 0.35	0.45 ± 0.33
$Latency_{120}$ (ms) ††	22.9 ± 1.3	22.8 ± 1.4	24 ± 2.1	24.0 ± 1.9
sqrtRC ††	1.0 ± 0.4	1.0 ± 0.4	0.5 ± 0.3	0.7 ± 0.3
Active state				
MEP_{fac}(mV) †††	4.3 ± 1.4	4.1 ± 0.9	2.6 ± 1.2	2.9 ± 1.2
$Latency_{fac}$ (ms) †††	20.5 ± 1.7	20.3 ± 1.3	22.2 ± 2.2	21.8 ± 2.0
cSP (ms) ††	137.8 ± 24.5	131.6 ± 21.1	107.6 ± 20.2	111.8 ± 22.6
Interhemispheric				
(Active state)				
DTI (ms) †††	14.9 ± 4.4	16.7 ± 4.8	10.4 ± 2.1	11.2 ± 2.3
LTI (ms) †††	34.1 ± 2.8	33.2 ± 2.8	39.9 ± 3.4	38.4 ± 3.8
iSParea †††	3.3 ± 1.6	4.0 ± 1.5	1.4 ± 0.4	1.7 ± 0.9

RMT: Resting Motor Threshold; MEP_{120}: MEP eat 120% RMT; $Latency_{120}$: MEP latency at 120% RMT; sqrtRC: Squareroot transformed slope of the recruitment curve; $MEP_{fac:}$: MEP elicited durin active contraction; $Latency_{fa:}$ MEP latency during active contraction; cSP : Contralateral silent period; DTI – Duration of transcallosal inhibition; LTI – Latency of transcallosal inhibition; iSParea

Symbols as in Table 2.

Table 4. Associations between selected TMS measures and manual performance of the left hand

TMS measures for right hemisphere		GPT	SRT	MovT	FTT	MVC
Intrahemispheric excitability						
Resting state						
RMT	*r*=	.24	.17	.06	-.10	-.33
MEP_{120}	*r*=	-.18	.05	-.12	.19	.50**
sqrtRC	*r*=	-.22	.12	-.14	.13	.41*
Active state						
MEP_{fac}	*r*=	-.34	-.05	-.24	.33	.48**
cSP	*r*=	-.29	-.24	-.45*	.39*	.39*
Interhemispheric inhibition						
(Active state)						
DTI	*r*=	-.32	-.09	-.29	.34	.44*
LTI	*r*=	.45*	.09	.11	-.32	-.33

Values represent the Pearson's r coefficient.

Abbreviations as in Table 2 and Table 3.

*p<.05; **p<.01

Table 5. Associations between selected TMS measures and manual performance of the the right hand

TMS measures for left hemisphere		GPT	SRT	MovT	FTT	MVC
Intrahemispheric excitability						
Resting state						
RMT	*r*=	.36	.26	.33	-.24	-.34
MEP_{120}	*r*=	-.37	-.33	-.32	.35	.34
sqrtRC	*r*=	-.38*	-.39*	-.43*	.27	.32
Active state						
MEP_{fac}	*r*=	-.53**	-.36	-.50**	.45*	.21
cSP	*r*=	-.43*	-.26	-.39*	.21	.21
Interhemispheric Inhibition						
(Active state)						
DTI	*r*=	-.25	-.08	-.25	.31	.32
LTI	*r*=	.52**	.17	.39*	-.45*	-.37*

Values represent the Pearson's r coefficient.

Abbreviations as in Table 2 and Table 3.

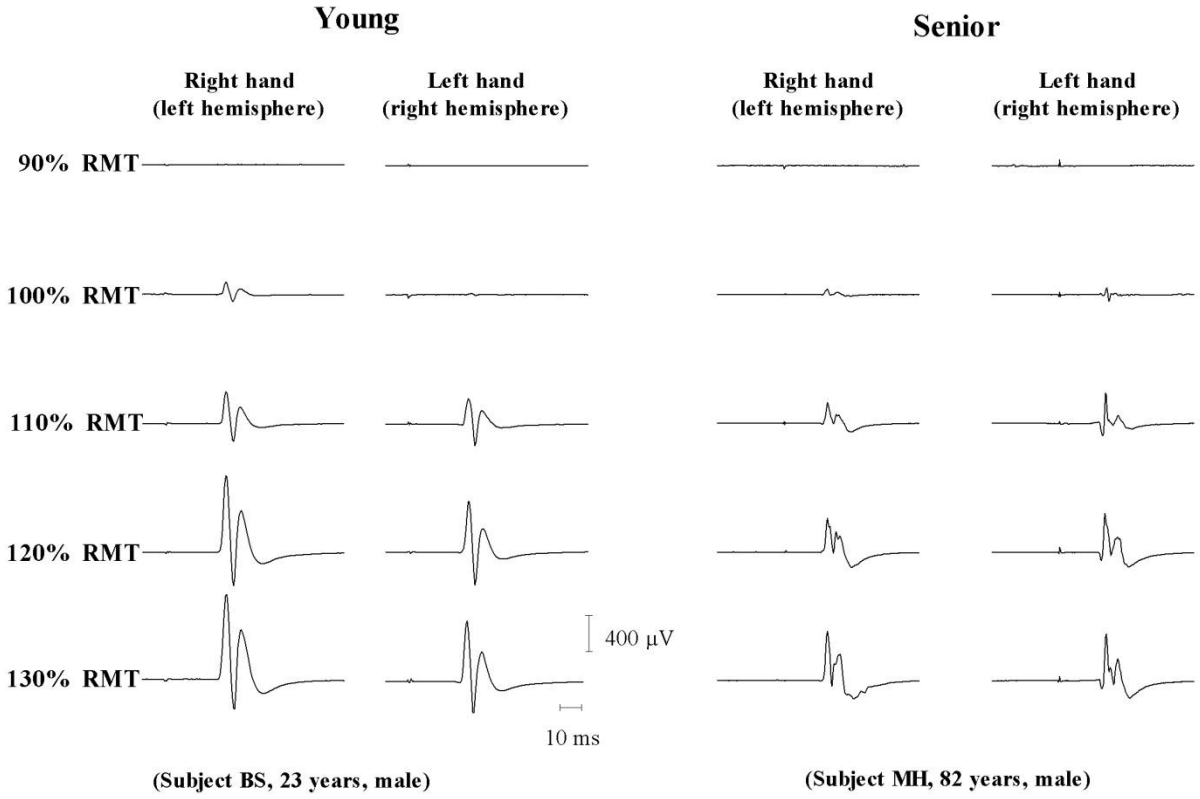
*p<.05; **p<.01

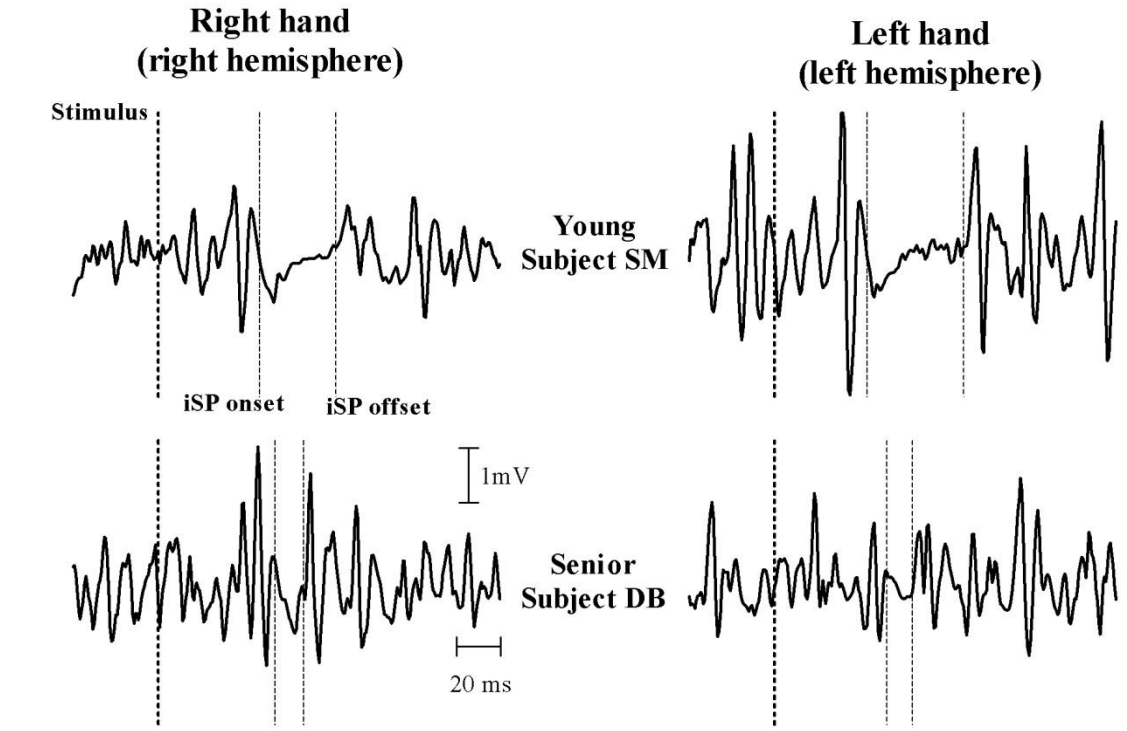
Figure Legends:

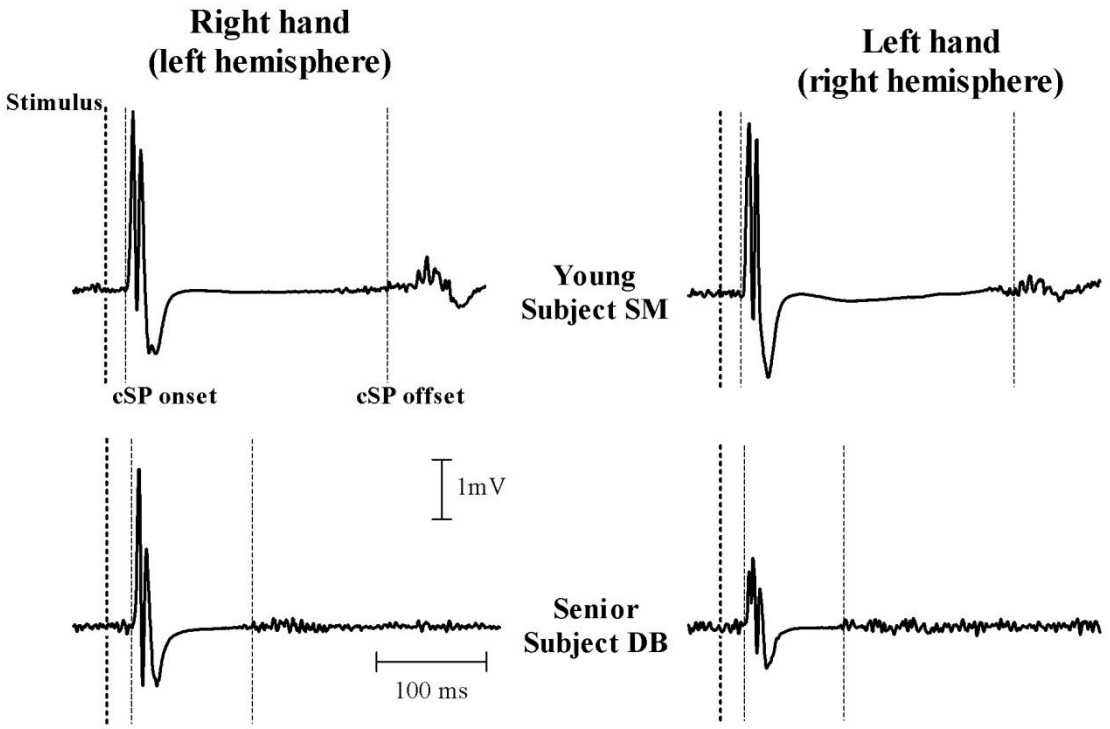
Figure 1. Examples of bilateral MEP data recorded at increasing TMS intensities in a young and a senior subject. Note the increase in MEP amplitude with higher intensities, which provides the basis for determination of the recruitment curve. Note also that MEP responses are highly comparable between the two hands in each subject and the relative reduction in amplitude observed in the senior.

Figure 2. Individual examples of ipsilateral and contralateral silent period measured in a young and a senior subject. Note the relative decrease in the duration of the iSP and cSP in the senior subject.

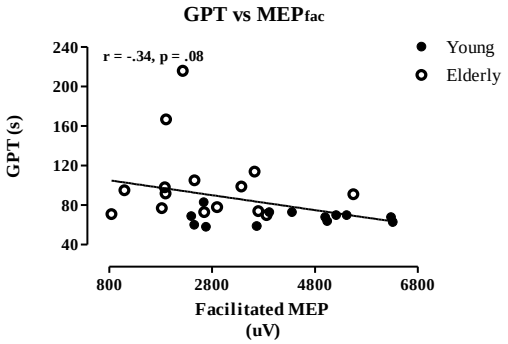
Figure 3. Scatterplots illustrating the relationships between selected TMS markers and performance in the manual dexterity test. Note the stronger associations found for the right hand/left hemisphere couple as opposed to the left hand/right hemisphere couple.

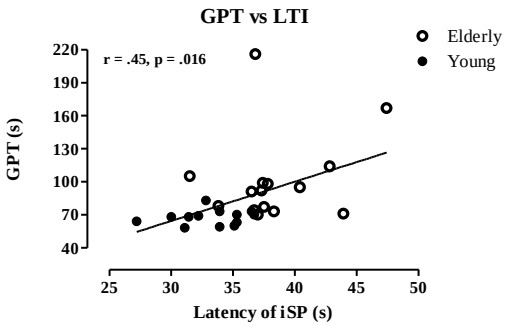

Young
Senior
Right hand
(left hemisphere)
Left hand
(right hemisphere)
Right hand
(left hemisphere)
Left hand
(right hemisphere)
90% RMT
100% RMT
110% RMT
120% RMT
130% RMT
400 µV
10 ms
(Subject BS, 23 years, male)
(Subject MH, 82 years, male)


Ipsilateral silent period
Right hand
(right hemisphere)
Left hand
(left hemisphere)
Stimulus
Young
Subject SM
iSP onset
iSP offset
1mV
Senior
Subject DB
20 ms

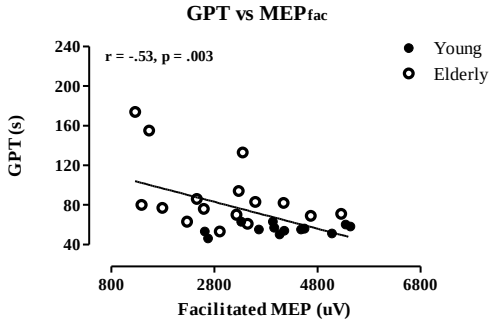

Contralateral silent period
Right hand
(left hemisphere)
Left hand
(right hemisphere)
Stimulus
Young
Subject SM
cSP onset
cSP offset
1mV
Senior
Subject DB
100 ms

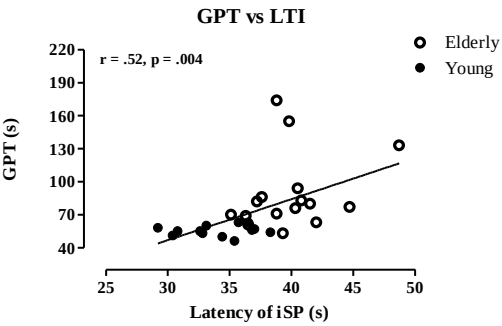
Left hand & Right hemisphere





Right hand & Left hemisphere





General discussion and conclusion

In conclusion, we determined that a lifetime of preferential use of the right hand did not significantly alter the existing functional and neurophysiological asymmetries. This indicates a maintenance of laterality with age.

We noted a significant age-related impairment of hand function, intrahemispheric excitability and interhemispheric inhibition. These changes reflect alterations in corticospinal excitability, transcallosal connectivity and signal propagation, which could all have an effect on the age-related degradation of hand function we observed.

Most importantly, we were able to successfully describe the relationships that exist between neurophysiological markers obtained through TMS and hand function. Measures of intracortical excitability taken during the active condition were found to be better predictors of hand function than either the similar measures taken during the resting condition, or measures of interhemispheric inhibition. Furthermore, we found the behavior-TMS relationships were more frequent and stronger for the dominant right hand/left hemisphere couple, at least in our subset of right-handed individuals. Therefore, TMS markers of corticospinal excitability taken during the active state in the dominant hand could be used as tool for early prognosis of pathological aging.

References cited in thesis

Abbruzzese, G., Marchese, R., & Trompetto, C. (1997). Sensory and motor evoked potentials in multiple system atrophy: a comparative study with Parkinson's disease. *Mov Disord, 12*(3), 315-321.

Agrawal, T., Vats, V., Wallace, P. K., Salhan, S., & Mittal, A. (2008). Role of cervical dendritic cell subsets, co-stimulatory molecules, cytokine secretion profile and beta-estradiol in development of sequalae to Chlamydia trachomatis infection. *Reprod Biol Endocrinol, 6*, 46.

Agrawal, T., Vats, V., Wallace, P. K., Singh, A., Salhan, S., & Mittal, A. (2009). Recruitment of myeloid and plasmacytoid dendritic cells in cervical mucosa during Chlamydia trachomatis infection. *Clin Microbiol Infect, 15*(1), 50-59.

Alstermark, B., Ogawa, J., & Isa, T. (2004). Lack of monosynaptic corticomotoneuronal EPSPs in rats: disynaptic EPSPs mediated via reticulospinal neurons and polysynaptic EPSPs via segmental interneurons. *J Neurophysiol, 91*(4), 1832-1839.

Amunts, K., Schlaug, G., Schleicher, A., Steinmetz, H., Dabringhaus, A., Roland, P. E., et al. (1996). Asymmetry in the human motor cortex and handedness. *Neuroimage, 4*(3 Pt 1), 216-222.

Ashendorf, L., Vanderslice-Barr, J. L., & McCaffrey, R. J. (2009). Motor tests and cognition in healthy older adults. *Appl Neuropsychol, 16*(3), 171-176.

Avanzino, L., Bassolino, M., Pozzo, T., & Bove, M. (2011). Use-dependent hemispheric balance. *J Neurosci, 31*(9), 3423-3428

Bacon, S. J., & Smith, A. D. (1993). A monosynaptic pathway from an identified vasomotor centre in the medial prefrontal cortex to an autonomic area in the thoracic spinal cord. *Neuroscience, 54*(3), 719-728.

Baldissera, F., & Cavallari, P. (1993). Short-latency subliminal effects of transcranial magnetic stimulation on forearm motoneurones. *Exp Brain Res, 96*(3), 513-518.

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.

Bareyre, F. M., Kerschensteiner, M., Raineteau, O., Mettenleiter, T. C., Weinmann, O., & Schwab, M. E. (2004). The injured spinal cord spontaneously forms a new intraspinal circuit in adult rats. *Nat Neurosci, 7*(3), 269-277.

Barker, A. T., Freeston, I. L., Jalinous, R., & Jarratt, J. A. (1987). Magnetic stimulation of the human brain and peripheral nervous system: an introduction and the results of an initial clinical evaluation. *Neurosurgery, 20*(1), 100-109.

Barker, A. T., Jalinous, R., & Freeston, I. L. (1985). Non-invasive magnetic stimulation of human motor cortex. *Lancet, 1*(8437), 1106-1107.

Basu, P., Sarkar, S., Mukherjee, S., Ghoshal, M., Mittal, S., Biswas, S., et al. (2006). Women's perceptions and social barriers determine compliance to cervical screening: results from a population based study in India. *Cancer Detect Prev, 30*(4), 369-374.

Bernhard, C. G., & Bohm, E. (1954). Cortical representation and functional significance of the corticomotoneuronal system. *AMA Arch Neurol Psychiatry, 72*(4), 473-502.

Bhattacharya, A., Mittal, B. R., Bhansali, A., Radotra, B. D., & Behera, A. (2006). Cervical paraganglioma mimicking a parathyroid adenoma on Tc-99m sestamibi scintigraphy. *Clin Nucl Med, 31*(4), 234-236.

Birren, J. E., & Fisher, L. M. (1995). Aging and speed of behavior: possible consequences for psychological functioning. *Annu Rev Psychol, 46*, 329-353

Bogacz, R., Wagenmakers, E. J., Forstmann, B. U., & Nieuwenhuis, S. (2010). The neural basis of the speed-accuracy tradeoff. *Trends Neurosci, 33*(1), 10-16.

Braun, A. R., Balkin, T. J., Wesenten, N. J., Carson, R. E., Varga, M., Baldwin, P., et al. (1997). Regional cerebral blood flow throughout the sleep-wake cycle. An H2(15)O PET study. *Brain, 120* (7), 1173-1197.

Brouwer, B., Sale, M. V., & Nordstrom, M. A. (2001). Asymmetry of motor cortex excitability during a simple motor task: relationships with handedness and manual performance. Exp Brain Res, 138(4), 467-476.

Brown, J. W., & Jaffe, J. (1975). Hypothesis on cerebral dominance. *Neuropsychologia, 13*(1), 107-110.

Budde, M. D., Kim, J. H., Liang, H. F., Schmidt, R. E., Russell, J. H., Cross, A. H., et al. (2007). Toward accurate diagnosis of white matter pathology using diffusion tensor imaging. *Magn Reson Med, 57*(4), 688-695.

Bushnell, M. C., Duncan, G. H., & Tremblay, N. (1993). Thalamic VPM nucleus in the behaving monkey. I. Multimodal and discriminative properties of thermosensitive neurons. *J Neurophysiol, 69*(3), 739-752.

Craig, J.C. (1999). Grating orientation as a measure of tactile spatial acuity. Somatosens Mot Res 16(3), 197–206.

Caramia, M. D., Scalise, A., Gordon, R., Michalewski, H. J., & Starr, A. (2000). Delayed facilitation of motor cortical excitability following repetitive finger movements. *Clin Neurophysiol, 111*(9), 1654-1660.

Carmeli, E., Patish, H., & Coleman, R. (2003). The aging hand. *J Gerontol A Biol Sci Med Sci, 58*(2), 146-152.

Cawthon, P. M., Fox, K. M., Gandra, S. R., Delmonico, M. J., Chiou, C. F., Anthony, M. S., et al. (2009). Do muscle mass, muscle density, strength, and physical function similarly influence risk of hospitalization in older adults? *J Am Geriatr Soc, 57*(8), 1411-1419.

Cerella, J. (1985). Information processing rates in the elderly. *Psychol Bull, 98*(1), 67-83.

Chen, R. (2000). Studies of human motor physiology with transcranial magnetic stimulation. *Muscle Nerve Suppl, 9*, S26-32.

Chen, R., Cros, D., Curra, A., Di Lazzaro, V., Lefaucheur, J. P., Magistris, M. R., et al. (2008). The clinical diagnostic utility of transcranial magnetic stimulation: report of an IFCN committee. *Clin Neurophysiol, 119*(3), 504-532.

Chen, R., Lozano, A. M., & Ashby, P. (1999). Mechanism of the silent period following transcranial magnetic stimulation. Evidence from epidural recordings. *Exp Brain Res, 128*(4), 539-542.

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.

Christie, A., Fling, B., Crews, R. T., Mulwitz, L. A., & Kamen, G. (2007). Reliability of motor-evoked potentials in the ADM muscle of older adults. *J Neurosci Methods, 164*(2), 320-324.

Cicinelli, P., Traversa, R., Bassi, A., Scivoletto, G., & Rossini, P. M. (1997). Interhemispheric differences of hand muscle representation in human motor cortex. *Muscle and Nerve, 20*(5), 535-542.

Cicinelli, P., Traversa, R., Oliveri, M., Palmieri, M. G., Filippi, M. M., Pasqualetti, P., et al. (2000). Intracortical excitatory and inhibitory phenomena to paired transcranial magnetic stimulation in healthy human subjects: differences between the right and left hemisphere. *Neurosci Lett, 288*(3), 171-174.

Cirillo, J., Rogasch, N. C., & Semmler, J. G. (2010). Hemispheric differences in use-dependent corticomotor plasticity in young and old adults. *Exp Brain Res, 205*(1), 57-68.

Cole, K. J., Cook, K. M., Hynes, S. M., & Darling, W. G. (2009). Slowing of dexterous manipulation in old age: force and kinematic findings from the 'nut-and-rod' task. *Exp Brain Res, 201*(2):239-47.

Cole, K.J., & Rotella, D.L. (2001). Old age affects fingertip forces when restraining an unpredictably loaded object. *Exp Brain Res, 136*(4), 535-542.

Cole, K.J., Rotella, D.L. (2002). Old age impairs the use of arbitrary visual cues for predictive control of fingertip forces during grasp. *Exp Brain Res, 143*, 35-41.

Courtine, G., Bunge, M. B., Fawcett, J. W., Grossman, R. G., Kaas, J. H., Lemon, R., et al. (2007). Can experiments in nonhuman primates expedite the translation of treatments for spinal cord injury in humans? *Nat Med, 13*(5), 561-566.

Crabtree, D. A., & Antrim, L. R. (1988). Guidelines for measuring reaction time. *Percept Mot Skills, 66*(2), 363-370.

Darling, W. G., Wolf, S. L., & Butler, A. J. (2006). Variability of motor potentials evoked by transcranial magnetic stimulation depends on muscle activation. *Exp Brain Res, 174*(2), 376-385.

Day, B. L., Dressler, D., Maertens de Noordhout, A., Marsden, C. D., Nakashima, K., Rothwell, J. C., et al. (1989). Electric and magnetic stimulation of human motor cortex: surface EMG and single motor unit responses. *J Physiol, 412*, 449-473.

de Noordhout, A. M., Rapisarda, G., Bogacz, D., Gerard, P., De Pasqua, V., Pennisi, G., et al. (1999). Corticomotoneuronal synaptic connections in normal man: an electrophysiological study. *Brain, 122 (Pt 7)*, 1327-1340.

Devanne, H., Lavoie, B. A., & Capaday, C. (1997). Input-output properties and gain changes in the human corticospinal pathway. *Exp Brain Res, 114*(2), 329-338.

Di Lazzaro, V., Oliviero, A., Mazzone, P., Insola, A., Pilato, F., Saturno, E., et al. (2001). Comparison of descending volleys evoked by monophasic and biphasic magnetic stimulation of the motor cortex in conscious humans. *Exp Brain Res, 141*(1), 121-127.

Doeltgen, S. H., & Ridding, M. C. (2010). Behavioural exposure and sleep do not modify corticospinal and intracortical excitability in the human motor system. *Clin Neurophysiol, 121*(3), 448-452.

Dolcos, F., Rice, H. J., & Cabeza, R. (2002). Hemispheric asymmetry and aging: right hemisphere decline or asymmetry reduction. *Neurosci Biobehav Rev, 26*(7), 819-825.

Dum, R. P., & Strick, P. L. (2005). Frontal lobe inputs to the digit representations of the motor areas on the lateral surface of the hemisphere. *J Neurosci, 25*(6), 1375-1386.

Evarts, E. V., & Tanji, J. (1976). Reflex and intended responses in motor cortex pyramidal tract neurons of monkey. *J Neurophysiol, 39*(5), 1069-1080.

Fathi, D., Ueki, Y., Mima, T., Koganemaru, S., Nagamine, T., Tawfik, A., et al. (2010). Effects of aging on the human motor cortical plasticity studied by paired associative stimulation. *Clin Neurophysiol, 121*(1), 90-93.

Fleminger, J. J., Dalton, R., & Standage, K. F. (1977). Age as a factor in the handedness of adults. *Neuropsychologia, 15*(3), 471-473.

Fling, B. W., Peltier, S., Bo, J., Welsh, R. C., & Seidler, R. D. (2011). Age Differences in Interhemispheric Interactions: Callosal Structure, Physiological Function, and Behavior. [Focused Review]. *Frontiers in Neuroscience, 5*.

Francis, K. L., & Spirduso, W. W. (2000). Age differences in the expression of manual asymmetry. *Exp Aging Res, 26*(2), 169-180.

Freund, P., Schmidlin, E., Wannier, T., Bloch, J., Mir, A., Schwab, M. E., et al. (2006). Nogo-A-specific antibody treatment enhances sprouting and functional recovery after cervical lesion in adult primates. *Nat Med, 12*(7), 790-792.

Frey, S. H. (2008). Tool use, communicative gesture and cerebral asymmetries in the modern human brain. *Philos Trans R Soc Lond B Biol Sci, 363*(1499), 1951-1957.

Fuhr, P., Agostino, R., & Hallett, M. (1991). Spinal motor neuron excitability during the silent period after cortical stimulation. *Electroencephalography & Clinical Neurophysiology, 81*(4), 257-262.

Garvey, M. A., Ziemann, U., Bartko, J. J., Denckla, M. B., Barker, C. A., & Wassermann, E. M. (2003). Cortical correlates of neuromotor development in healthy children. *Clin Neurophysiol, 114*(9), 1662-1670.

Garvey, M. A., Barker, C. A., Bartko, J. J., Denckla, M. B., Wassermann, E. M., Castellanos, F. X., et al. (2005). The ipsilateral silent period in boys with attention-deficit/hyperactivity disorder. *Clin Neurophysiol, 116*(8), 1889-1896.

Giampaoli, S., Ferrucci, L., Cecchi, F., Lo Noce, C., Poce, A., Dima, F., et al. (1999). Hand-grip strength predicts incident disability in non-disabled older men. *Age Ageing, 28*(3), 283-288.

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. *The Journal of Physiology, 587*(22), 5393-5410.

Goldstein, G., & Shelly, C. (1981). Does the right hemisphere age more rapidly than the left? *Journal of Clinical Neuropsychology, 3*(1), 65 - 78.

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.

Gugino, L. D., Rowinski, M. J., & Stoney, S. D., Jr. (1990). Motor outflow to cervical motoneurons from raccoon motorsensory cortex. *Brain Res Bull, 24*(6), 833-837.

Haaland, K. Y., Harrington, D. L., & Knight, R. T. (2000). Neural representations of skilled movement. *Brain, 123 (Pt 11)*, 2306-2313.

Halsey, J. H., Jr., Blauenstein, U. W., Wilson, E. M., & Wills, E. H. (1979). Regional cerebral blood flow comparison of right and left hand movement. *Neurology, 29*(1), 21-28.

Hammond, G. (2002). Correlates of human handedness in primary motor cortex: a review and hypothesis. *Neurosci Biobehav Rev, 26*(3), 285-292.

Harris, T. (1997). Muscle mass and strength: relation to function in population studies. *J Nutr, 127*(5 Suppl), 1004S-1006S.

Haug, H., & Eggers, R. (1991). Morphometry of the human cortex cerebri and corpus striatum during aging. *Neurobiol Aging, 12*(4), 336-338; discussion 352-335.

Hesselmann, V., Zaro Weber, O., Wedekind, C., Krings, T., Schulte, O., Kugel, H., et al. (2001). Age related signal decrease in functional magnetic resonance imaging during motor stimulation in humans. *Neurosci Lett, 308*(3), 141-144.

Hultsch, D. F., MacDonald, S. W., & Dixon, R. A. (2002). Variability in reaction time performance of younger and older adults. *J Gerontol B Psychol Sci Soc Sci, 57*(2), P101-115.

Janssen, L., Meulenbroek, R. G., & Steenbergen, B. (2011). Behavioral evidence for left-hemisphere specialization of motor planning. *Exp Brain Res, 209*(1), 65-72.

Illert, M., Lundberg, A., & Tanaka, R. (1976). Integration in descending motor pathways controlling the forelimb in the cat. 1. Pyramidal effects on motoneurones. *Exp Brain Res, 26*(5), 509-519.

Inghilleri, M., Berardelli, A., Cruccu, G., & Manfredi, M. (1993). Silent period evoked by transcranial stimulation of the human cortex and cervicomedullary junction. *Journal of Physiology, 466*, 521-534.

Iwaniuk, A. N., & Whishaw, I. Q. (2000). On the origin of skilled forelimb movements. *Trends Neurosci, 23*(8), 372-376.

Johnson, K. O. (2001). The roles and functions of cutaneous mechanoreceptors. *Curr Opin Neurobiol, 11*(4), 455-461.

Johnson, K.O., Van Boven, R.W., & Hsiao, S.S. (1994). The perception of two points is not the spatial resolution threshold. In *Touch, Temperature and Pain in Health and Disease: Mechanisms and Assessments*. J. Boivie, P. Hansson, & U. Lindblom (Eds.), Vol. 3, pp. 389–404, IASP Press, Seattle.

Jones, L.A. (1994). Introduction I. Peripheral Mechapnism of Touch and Proprioception. *Can J Physiol Phamacol, 72*(5), 484 -487.

Jones, L.A. (1989). The assessment of hand function: a critical review of techniques. *J Hand Surg Am, 14*(2 Pt 1), 221-228.

Kalisch, T., Wilimzig, C., Kleibel, N., Tegenthoff, M., & Dinse, H. R. (2006). Age-related attenuation of dominant hand superiority. *PLoS One, 1*, e90.

Kammer, T., Beck, S., Thielscher, A., Laubis-Herrmann, U., & Topka, H. (2001). Motor thresholds in humans: a transcranial magnetic stimulation study comparing different pulse waveforms, current directions and stimulator types. *Clin Neurophysiol, 112*(2), 250-258.

Kawakita, H., Kameyama, O., Ogawa, R., Hayes, K. C., Wolfe, D. L., & Allatt, R. D. (1991). Reinforcement of motor evoked potentials by remote muscle contraction. *J Electromyogr Kinesiol, 1*(2), 96-106.

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.

Kimberley, T. J., Borich, M. R., Prochaska, K. D., Mundfrom, S. L., Perkins, A. E., & Poepping, J. M. (2009). Establishing the definition and inter-rater reliability of cortical silent period calculation in subjects with focal hand dystonia and healthy controls. *Neuroscience Letters, 464*(2), 84-87.

Klöppel, S., Bäumer, T., Kroeger, J., Koch, M. A., Büchel, C., Münchau, A., et al. (2008). The cortical motor threshold reflects microstructural properties of cerebral white matter. *NeuroImage, 40*(4), 1782-1791.

Kossev, A. R., Schrader, C., Dauper, J., Dengler, R., & Rollnik, J. D. (2002). Increased intracortical inhibition in middle-aged humans; a study using paired-pulse transcranial magnetic stimulation. *Neurosci Lett, 333*(2), 83-86.

Kozel, F. A., Nahas, Z., deBrux, C., Molloy, M., Lorberbaum, J. P., Bohning, D., et al. (2000). How coil-cortex distance relates to age, motor threshold, and antidepressant response to repetitive transcranial magnetic stimulation. *J Neuropsychiatry Clin Neurosci, 12*(3), 376-384.

Kuypers, H. G., & Brinkman, J. (1970). Precentral projections to different parts of the spinal intermediate zone in therhesus monkey. *Brain Res, 24*(1), 29-48.

Lemon, R. N. (1988). The output map of the primate motor cortex. *Trends Neurosci, 11*(11), 501-506.

Lemon, R. N., & Griffiths, J. (2005). Comparing the function of the corticospinal system in different species: Organizational differences for motor specialization? *Muscle & Nerve, 32*(3), 261-279.

Lemon, R. N. (2008). Descending pathways in motor control. *Annu Rev Neurosci, 31*, 195-218.

Leonard, G., & Tremblay, F. (2007). Corticomotor facilitation associated with observation, imagery and imitation of hand actions: a comparative study in young and old adults. Exp Brain Res, 177(2), 167-175.

Levin, O., Cuypers, K., Netz, Y., Thijs, H., Nuttin, B., Helsen, W. F., et al. (2011). Age-related differences in human corticospinal excitability during simple reaction time. *Neurosci Lett, 487*(1), 53-57.

Levine, P. H., Elgert, P. A., & Mittal, K. (2003). False-positive squamous cell carcinoma in cervical smears: cytologic-histologic correlation in 19 cases. *Diagn Cytopathol, 28*(1), 23-27.

Lewis, G. N., Polych, M. A., & Byblow, W. D. (2004). Proposed cortical and sub-cortical contributions to the long-latency stretch reflex in the forearm. *Exp Brain Res, 156*(1), 72-79.

Lindberg, P. G., Feydy, A., & Maier, M. A. (2010). White matter organization in cervical spinal cord relates differently to age and control of grip force in healthy subjects. *J Neurosci, 30*(11), 4102-4109.

Macdonell, R. A., Shapiro, B. E., Chiappa, K. H., Helmers, S. L., Cros, D., Day, B. J., et al. (1991). Hemispheric threshold differences for motor evoked potentials produced by magnetic coil stimulation. *Neurology, 41*(9), 1441-1444.

Madden, D. J., Spaniol, J., Costello, M. C., Bucur, B., White, L. E., Cabeza, R., et al. (2009). Cerebral white matter integrity mediates adult age differences in cognitive performance. *J Cogn Neurosci, 21*(2), 289-302.

Maier, M. A., Illert, M., Kirkwood, P. A., Nielsen, J., & Lemon, R. N. (1998). Does a C3-C4 propriospinal system transmit corticospinal excitation in the primate? An investigation in the macaque monkey. *J Physiol, 511*(Pt 1), 191-212.

Manning, H., & Tremblay, F. (2006). Age differences in tactile pattern recognition at the fingertip. *Somatosens Mot Res, 23*(3-4), 147-155.

Martina, I. S., van Koningsveld, R., Schmitz, P. I., van der Meche, F. G., & van Doorn, P. A. (1998). Measuring vibration threshold with a graduated tuning fork in normal aging and in patients with polyneuropathy. European Inflammatory Neuropathy Cause and Treatment (INCAT) group. *J Neurol Neurosurg Psychiatry, 65*(5), 743-747.

Matsunaga, K., Uozumi, T., Tsuji, S., & Murai, Y. (1998). Age-dependent changes in physiological threshold asymmetries for the motor evoked potential and silent period following transcranial magnetic stimulation. *Electroencephalogr Clin Neurophysiol, 109*(6), 502-507.

McComas, A. J., Galea, V., & de Bruin, H. (1993). Motor unit populations in healthy and diseased muscles. *Phys Ther, 73*(12), 868-877.

McConnell, K. A., Nahas, Z., Shastri, A., Lorberbaum, J. P., Kozel, F. A., Bohning, D. E., et al. (2001). The transcranial magnetic stimulation motor threshold depends on the distance from coil to underlying cortex: a replication in healthy adults comparing two methods of assessing the distance to cortex. *Biol Psychiatry, 49*(5), 454-459.

Merkel, J. (1885). Die zeitlichen Verhältnisse der Willensthähigkeit. *Philosophische Studien, 2*(9), 73-127.

Merton, P. A., & Morton, H. B. (1980). Stimulation of the cerebral cortex in the intact human subject. *Nature, 285*(5762), 227.

Meyer, B. U., Roricht, S., Grafin von Einsiedel, H., Kruggel, F., & Weindl, A. (1995). Inhibitory and excitatory interhemispheric transfers between motor cortical areas in normal human and patients with abonormalities of the corpus callosum. *Brain, 118*(2), 429-440.

Michielse, S., Coupland, N., Camicioli, R., Carter, R., Seres, P., Sabino, J., et al. (2010). Selective effects of aging on brain white matter microstructure: a diffusion tensor imaging tractography study. *NeuroImage, 52*(4), 1190-1201.

Mills, K. R., & Nithi, K. A. (1997). Corticomotor threshold to magnetic stimulation: normal values and repeatability. *Muscle Nerve, 20*(5), 570-576.

Mittal, K. R., & Logmani, F. H. (1987). Age-related reduction in 8th cervical ventral nerve root myelinated fiber diameters and numbers in man. *J Gerontol, 42*(1), 8-10.

Moore, K. L., & Daller, A.F. (2006). Clinically Oriented Anatomy. (5th ed.). Philadelphia (PA), Lippincott Williams & Wilkins.

Morse, C. K. (1993). Does variability increase with age? An archival study of cognitive measures. *Psychol Aging, 8*(2), 156-164.

Mosby. (2009). *Mosby's Medical Dictionary*. (8th ed.). Elsevier.

Mutha, P. K., & Sainburg, R. L. (2009). Shared Bimanual Tasks Elicit Bimanual Reflexes During Movement. *J Neurophysiol, 102*(6), 3142-3155.

Nishimura, Y., Onoe, H., Morichika, Y., Perfiliev, S., Tsukada, H., & Isa, T. (2007). Time-dependent central compensatory mechanisms of finger dexterity after spinal cord injury. *Science, 318*(5853), 1150-1155.

Nudo, R. J., & Masterton, R. B. (1988). Descending pathways to the spinal cord: a comparative study of 22 mammals. *J Comp Neurol, 277*(1), 53-79.

Nudo, R. J., & Masterton, R. B. (1990). Descending pathways to the spinal cord, III: Sites of origin of the corticospinal tract. *J Comp Neurol, 296*(4), 559-583.

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.

Oldfield, R. C. (1971). The assessment and analysis of handedness: the Edinburgh inventory. *Neuropsychologia, 9*(1), 97-113.

Oliviero, A., Profice, P., Tonali, P. A., Pilato, F., Saturno, E., Dileone, M., et al. (2006). Effects of aging on motor cortex excitability. *Neuroscience Research, 55*(1), 74-77.

Orth, M., & Rothwell, J. C. (2004). The cortical silent period: intrinsic variability and relation to the waveform of the transcranial magnetic stimulation pulse. *Clinical Neurophysiology, 115*(5), 1076-1082.

Pearce, A. J., Thickbroom, G. W., Byrnes, M. L., & Mastaglia, F. L. (2000). Functional reorganisation of the corticomotor projection to the hand in skilled racquet players. *Exp Brain Res, 130*(2), 238-243.

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.

Penfield, W., & Rasmussen T. (1952). *The Cerebral Cortex of Man*. Macmillan, New York.

Pepin, J. L., Bogacz, D., de Pasqua, V., & Delwaide, P. J. (1999). Motor cortex inhibition is not impaired in patients with Alzheimer's disease: evidence from paired transcranial magnetic stimulation. *J Neurol Sci, 170*(2), 119-123.

Perry, M. E., McDonald, C. R., Hagler, D. J., Jr., Gharapetian, L., Kuperman, J. M., Koyama, A. K., et al. (2009). White matter tracts associated with set-shifting in healthy aging. *Neuropsychologia, 47*(13), 2835-2842.

Pestronk, A., Florence, J., Levine, T., Al-Lozi, M. T., Lopate, G., Miller, T., et al. (2004). Sensory exam with a quantitative tuning fork: rapid, sensitive and predictive of SNAP amplitude. *Neurology, 62*(3), 461-464.

Peters, R. M., Hackeman, E., & Goldreich, D. (2009). Diminutive digits discern delicate details: fingertip size and the sex difference in tactile spatial acuity. *J Neurosci, 29*(50), 15756-15761.

Pfefferbaum, A., Adalsteinsson, E., & Sullivan, E. V. (2005). Frontal circuitry degradation marks healthy adult aging: Evidence from diffusion tensor imaging. *Neuroimage, 26*(3), 891-899.

Phillips, C. G. (1975). Laying the ghost of 'muscles versus movements'. *Can J Neurol Sci, 2*(3), 209-218.

Pitcher, J. B., Ogston, K. M., & Miles, T. S. (2003). Age and sex differences in human motor cortex input-output characteristics. *J Physiol (Lond), 546*(2), 605-613.

Priori, A., Oliviero, A., Donati, E., Callea, L., Bertolasi, L., & Rothwell, J. C. (1999). Human handedness and asymmetry of the motor cortical silent period. *Exp Brain Res, 128*(3), 390-396.

Przybyla, A., Haaland, K. Y., Bagesteiro, L. B., & Sainburg, R. L. (2011). Motor asymmetry reduction in older adults. *Neurosci Lett, 489*(2), 99-104.

Quencer, R. M., Bunge, R. P., Egnor, M., Green, B. A., Puckett, W., Naidich, T. P., et al. (1992). Acute traumatic central cord syndrome: MRI-pathological correlations. *Neuroradiology, 34*(2), 85-94.

Rabin, L. A., Barr, W. B., & Burton, L. A. (2005). Assessment practices of clinical neuropsychologists in the United States and Canada: a survey of INS, NAN, and APA Division 40 members. *Arch Clin Neuropsychol, 20*(1), 33-65.

Ranganathan, V. K., Siemionow, V., Sahgal, V., & Yue, G. H. (2001). Effects of aging on hand function. *J Am Geriatr Soc, 49*(11), 1478-1484.

Rathelot, J. A., & Strick, P. L. (2006). Muscle representation in the macaque motor cortex: an anatomical perspective. *Proc Natl Acad Sci U S A, 103*(21), 8257-8262.

Ray, J. L., McNamara, B., Priest, A., & Boniface, S. J. (2002). Measuring TMS stimulus/response characteristics from both hemispheres simultaneously for proximal and distal upper limb muscles. *J Clin Neurophysiol, 19*(4), 371-375.

Reis, J., Swayne, O. B., Vandermeeren, Y., Camus, M., Dimyan, M. A., Harris-Love, M., et al. (2008). Contribution of transcranial magnetic stimulation to the understanding of cortical mechanisms involved in motor control. *J Physiol, 586*(2), 325-351.

Reynolds, R. F., & Day, B. L. (2007). Fast visuomotor processing made faster by sound. *J Physiol, 583*(Pt 3), 1107-1115.

Ridding, M. C., & Rothwell, J. C. (1997). Stimulus/response curves as a method of measuring motor cortical excitability in man. *Electroencephalogr Clin Neurophysiol, 105*(5), 340-344.

Rogasch, N. C., Dartnall, T. J., Cirillo, J., Nordstrom, M. A., & Semmler, J. G. (2009). Corticomotor plasticity and learning of a ballistic thumb training task are diminished in older adults. *J Appl Physiol, 107*(6), 1874-1883.

Roick, H., von Giesen, H. J., & Benecke, R. (1993). On the origin of the postexcitatory inhibition seen after transcranial magnetic brain stimulation in awake human subjects. *Exp Brain Res, 94*(3), 489-498.

Ropper, A. H., Fisher, C. M., & Kleinman, G. M. (1979). Pyramidal infarction in the medulla: a cause of pure motor hemiplegia sparing the face. *Neurology, 29*(1), 91-95.

Rosenkranz, K., Williamon, A., & Rothwell, J. C. (2007). Motorcortical Excitability and Synaptic Plasticity Is Enhanced in Professional Musicians. *J. Neurosci., 27*(19), 5200-5206.

Rosenthal, C. R., Roche-Kelly, E. E., Husain, M., & Kennard, C. (2009). Response-Dependent Contributions of Human Primary Motor Cortex and Angular Gyrus to Manual and Perceptual Sequence Learning. *J. Neurosci., 29*(48), 15115-15125.

Rossi, S., Hallett, M., Rossini, P. M., & Pascual-Leone, A. (2009). Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research. *Clin Neurophysiol, 120*(12), 2008-2039.

Rossi, S., Miniussi, C., Pasqualetti, P., Babiloni, C., Rossini, P. M., & Cappa, S. F. (2004). Age-Related Functional Changes of Prefrontal Cortex in Long-Term Memory: A Repetitive Transcranial Magnetic Stimulation Study. *J. Neurosci., 24*(36), 7939-7944.

Rossini, P. M., Barker, A. T., Berardelli, A., Caramia, M. D., Caruso, G., Cracco, R. Q., et al. (1994). Non-invasive electrical and magnetic stimulation of the brain, spinal cord and roots: basic principles and procedures for routine clinical application. Report of an IFCN committee. *Electroencephalogr Clin Neurophysiol, 91*(2), 79-92.

Rossini, P. M., Desiato, M. T., & Caramia, M. D. (1992). Age-related changes of motor evoked potentials in healthy humans: non- invasive evaluation of central and peripheral motor tracts excitability and conductivity. *Brain Res, 593*(1), 14-19.

Rossini, P. M., Rosinni, L., & Ferreri, F. (2010). Brain-behavior relations: transcranial magnetic stimulation: a review. *IEEE Eng Med Biol Mag, 29*(1), 84-95

Rossini, P. M., & Rossi, S. (2007). Transcranial magnetic stimulation: Diagnostic, therapeutic, and research potential. *Neurology, 68*(7), 484-488.

Rossini, P.M., Rossi, S., Babiloni, C. & Polich, J. (2007). Clinical neurophysiology of aging brain: From normal aging to neurodegeneration. *Progress in Neurobiology, 83*(6), 375-400.

Rothwell, J. C. (1997). Techniques and mechanisms of action of transcranial stimulation of the human motor cortex. *J Neurosci Methods, 74*(2), 113-122.

Sailer, A., Dichgans, J., & Gerloff, C. (2000). The influence of normal aging on the cortical processing of a simple motor task. *Neurology, 55*(7), 979-985.

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.

Saisanen, L., Pirinen, E., Teitti, S., Kononen, M., Julkunen, P., Maatta, S., et al. (2008). Factors influencing cortical silent period: optimized stimulus location, intensity and muscle contraction. *J Neurosci Methods, 169*(1), 231-238.

Sasaki, S., Isa, T., Pettersson, L. G., Alstermark, B., Naito, K., Yoshimura, K., et al. (2004). Dexterous finger movements in primate without monosynaptic corticomotoneuronal excitation. *J Neurophysiol, 92*(5), 3142-3147.

Saver, J. L. (2006). Time is brain--quantified. *Stroke, 37*(1), 263-266.

Schmidt, S., Cichy, R. M., Kraft, A., Brocke, J., Irlbacher, K., & Brandt, S. A. (2009). An initial transient-state and reliable measures of corticospinal excitability in TMS studies. *Clinical Neurophysiology, 120*(5), 987-993.

Schmierer, K., Irlbacher, K., Grosse, P., Roricht, S., & Meyer, B.-U. (2002). Correlates of disability in multiple sclerosis detected by transcranial magnetic stimulation. *Neurology, 59*(8), 1218-1224.

Schnitzler, A., & Benecke, R. (1994). The silent period after transcranial magnetic stimulation is of exclusive cortical origin: evidence from isolated cortical ischemic lesions in man. *Neurosci Lett, 180*(1), 41-45.

Seidler, R. D., Bernard, J. A., Burutolu, T. B., Fling, B. W., Gordon, M. T., Gwin, J. T., et al. Motor control and aging: links to age-related brain structural, functional, and biochemical effects. *Neurosci Biobehav Rev, 34*(5), 721-733.

Semmler, J. G., & Nordstrom, M. A. (1998). Hemispheric Differences in Motor Cortex Excitability During a Simple Index Finger Abduction Task in Humans. *J Neurophysiol, 79*(3), 1246-1254.

Sharma, Y., Kumar, S., Mittal, S., Misra, R., & Dadhwal, V. (2005). Evaluation of glyceryl trinitrate, misoprostol, and prostaglandin E2 gel for preinduction cervical ripening in term pregnancy. *J Obstet Gynaecol Res, 31*(3), 210-215.

Shiffman, L. M. (1992). Effects of aging on adult hand function. *Am J Occup Ther, 46*(9), 785-792.

Shimoyama, I., Ninchoji, T., & Uemura, K. (1990). The finger-tapping test. A quantitative analysis. *Arch Neurol, 47*(6), 681-684.

Shumway-Cook, A., & Woollacott, M. H. (2007). *Motor Control: Translating Research into Clinical Practice.* (3rd ed.). Philadelphia (PA), Lippincott Williams & Wilkins.

Singh, H., Sachan, R., Devi, S., Pandey, S. N., & Mittal, B. (2008). Association of GSTM1, GSTT1, and GSTM3 gene polymorphisms and susceptibility to cervical cancer in a North Indian population. *Am J Obstet Gynecol, 198*(3), 303 e301-306.

Singh, H., Sachan, R., Goel, H., & Mittal, B. (2008). Genetic variants of interleukin-1RN and interleukin-1beta genes and risk of cervical cancer. *BJOG, 115*(5), 633-638.

Smith, C. D., Umberger, G. H., Manning, E. L., Slevin, J. T., Wekstein, D. R., Schmitt, F. A., et al. (1999). Critical decline in fine motor hand movements in human aging. *Neurology, 53*(7), 1458-1461.

Sollerman, C., & Ejeskar, A. (1995). Sollerman hand function test. A standardised method and its use in tetraplegic patients. *Scand J Plast Reconstr Surg Hand Surg, 29*(2), 167-176.

Sommer, M., Alfaro, A., Rummel, M., Speck, S., Lang, N., Tings, T., et al. (2006). Half sine, monophasic and biphasic transcranial magnetic stimulation of the human motor cortex. *Clin Neurophysiol, 117*(4), 838-844.

Sullivan, E. V., Adalsteinsson, E., & Pfefferbaum, A. (2006). Selective Age-related Degradation of Anterior Callosal Fiber Bundles Quantified In Vivo with Fiber Tracking. *Cereb. Cortex, 16*(7), 1030-1039.

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.

Talelli, P., Ewas, A., Waddingham, W., Rothwell, J. C., & Ward, N. S. (2008). Neural correlates of age-related changes in cortical neurophysiology. *NeuroImage, 40*(4), 1772-1781.

Talelli, P., Greenwood, R. J., & Rothwell, J. C. (2006). Arm function after stroke: Neurophysiological correlates and recovery mechanisms assessed by transcranial magnetic stimulation. *Clinical Neurophysiology, 117*(8), 1641-1659.

Talelli, P., Waddingham, W., Ewas, A., Rothwell, J. C., & Ward, N. S. (2008). The effect of age on task-related modulation of interhemispheric balance. *Experimental Brain Research, 186*(1), 59-66.

Taube, W. J., Schubert, M., Gruber, M., Beck, S., Faist, M., & Gollhofer, A. (2006). Direct corticospinal pathways contribute to neuromuscular control of perturbed stance. *J Appl Physiol, 101*(2), 420-429.

Terao, Y., & Ugawa, Y. (2002). Basic mechanisms of TMS. *J Clin Neurophysiol, 19*(4), 322-343.

Thomas, C. K., Enoka, R. M., Gandevia, S. C., McComas, A. J., & Stuart, D. G. (1995). The scientific contributions of Brenda Bigland-Ritchie. *Adv Exp Med Biol, 384*, 11-25.

Tranulis, C., Gueguen, B., Pham-Scottez, A., Vacheron, M. N., Cabelguen, G., Costantini, A., et al. (2006). Motor threshold in transcranial magnetic stimulation: comparison of three estimation methods. *Neurophysiologie Clinique/Clinical Neurophysiology, 36*(1), 1-7.

Tremblay, F., Mireault, A. C., Letourneau, J., Pierrat, A., & Bourrassa, S. (2002). Tactile perception and manual dexterity in computer users. *Somatosens Mot Res, 19*(2), 101-108.

Tremblay, F., Mireault, A.C., Dessureault, L., Manning, H., & Sveistrup, H. (2005). Postural stabilization from fingertip contact II. Relationships between age, tactile sensibility and magnitude of contact forces. *Exp Brain Res, 164*(2), 155-164.

Tremblay, F., Wong, K., Sanderson, R., & Cote, L. (2003). Tactile spatial acuity in elderly persons: assessment with grating domes and relationship with manual dexterity. *Somatosens Mot Res, 20*(2), 127-132.

Triggs, W. J., Calvanio, R., & Levine, M. (1997). Transcranial magnetic stimulation reveals a hemispheric asymmetry correlate of intermanual differences in motor performance. *Neuropsychologia, 35*(10), 1355-1363.

Triggs, W. J., Subramanium, B., & Rossi, F. (1999). Hand preference and transcranial magnetic stimulation asymmetry of cortical motor representation. *Brain Res, 835*(2), 324-329.

van Elswijk, G., Kleine, B. U., Overeem, S., & Stegeman, D. F. (2007). Expectancy induces dynamic modulation of corticospinal excitability. *J Cogn Neurosci, 19*(1), 121-131.

Vilensky, J. A. (1987). Locomotor behavior and control in human and non-human primates: comparisons with cats and dogs. *Neurosci Biobehav Rev, 11*(3), 263-274.

Walhovd, K. B., Fjell, A. M., Reinvang, I., Lundervold, A., Dale, A. M., Eilertsen, D. E., et al. (2005). Effects of age on volumes of cortex, white matter and subcortical structures. *Neurobiol Aging, 26*(9), 1261-1270; discussion 1275-1268.

Wall, P. D., & Lidierth, M. (1997). Five sources of a dorsal root potential: their interactions and origins in the superficial dorsal horn. *J Neurophysiol, 78*(2), 860-871.

Wassermann, E. M. (1998). Risk and safety of repetitive transcranial magnetic stimulation: report and suggested guidelines from the International Workshop on the Safety of Repetitive Transcranial Magnetic Stimulation, June 5-7, 1996. *Electroencephalogr Clin Neurophysiol, 108*(1), 1-16.

Wassermann, E. M. (2002). Variation in the response to transcranial magnetic brain stimulation in the general population. *Clin Neurophysiol, 113*(7), 1165-1171.

Wassermann, E. M., Fuhr, P., Cohen, L. G., & Hallett, M. (1991). Effects of transcranial magnetic stimulation on ipsilateral muscles. *Neurology, 41*(11), 1795-1799.

Werhahn, K. J., 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)*, 591-597.

Wiacek, M., & Zubrzycki, I. Z. (2010). The age-dependent divergence of strength and coordinating parameters among men and women: The cross-sectional studies. *Arch Gerontol Geriatr*.

Wiesendanger, M., Kaluzny, P., Kazennikov, O., Palmeri, A., & Perrig, S. (1994). Temporal coordination in bimanual actions. *Can J Physiol Pharmacol, 72*(5), 591-594.

Wilson, F. R. (1998). *The Hand: How Its Use Shapes the Brain, Language, and Human Culture.* New York (NY), Pantheon.

Wilson, S. A., Thickbroom, G. W., & Mastaglia, F. L. (1993). Transcranial magnetic stimulation mapping of the motor cortex in normal subjects. The representation of two intrinsic hand muscles. *J Neurol Sci, 118*(2), 134-144.

Wolpaw, J. R. (1997). The complex structure of a simple memory. *Trends Neurosci, 20*(12), 588-594.

Yang, H. W., & Lemon, R. N. (2003). An electron microscopic examination of the corticospinal projection to the cervical spinal cord in the rat: lack of evidence for cortico-motoneuronal synapses. *Exp Brain Res, 149*(4), 458-469.

Zajdel, R., & Nowak, D. (2007). Simple and complex reaction time measurement A preliminary evaluation of new approach and diagnostic tool. *Comput Biol Med, 37*(12), 1724-1730.

Ziemann, U., Ishii, K., Borgheresi, A., Yaseen, Z., Battaglia, F., Hallett, M., et al. (1999). Dissociation of the pathways mediating ipsilateral and contralateral motor-evoked potentials in human hand and arm muscles. *J Physiol, 518 (Pt 3)*, 895-906.

Appendix I
Health questionnaire

uOttawa

L'Université canadienne
Canada's university

Faculté des sciences de la santé
École des sciences de la réadaptation

Faculty of Health Sciences
School of Rehabilitation Sciences

HEALTH QUESTIONNAIRE FOR TRANSCRANIAL MAGNETIC STIMULATION APPLICATIONS

IMPORTANT NOTICE

The present study involves the use of a magnetic stimulator to induce micro-current in the brain through a coil applied on the scalp. Although the technique is known to be safe and virtually painless, we need to screen our subjects to exclude those who might be at risk. This is why we ask you to fill this health questionnaire, as a potential participant.

Part. # ____

Have you consulted a physician recently (i.e., in the last 12 months)?
- ☐ Yes
- ☐ No

If No, when was your last visit? _____ months/years

Have you ever been diagnosed with any of the following conditions?
- ☐ Epilepsy
- ☐ Migraine
- ☐ Traumatic brain injury
- ☐ Depression
- ☐ Stroke or TIA (Transient Ischemic Attack)
- ☐ Heart Conditions (angina, hearth failure)
- ☐ Hypertension (high blood pressure)
- ☐ Sciatica or disc problems
- ☐ Arthritis
- ☐ Diabetes
- ☐ Any other conditions? (e.g., Parkinson's, MS, pain, numbness, etc.)
- ☐ Yes please specify:_____
- ☐ No,

Are you presently (in the last month) taking any prescribed medication? (e.g., antidepressants, cough or cold, insulin)
- ☐ Yes please specify:_____
- ☐ No,

Do you have any metal implants in your body?
□ Yes please specify where :_____
□ No,

Do you a have a "pace-maker" for cardiac stimulation?
□ Yes
□ No,

Are you presently receiving any form of medical treatment?
□ Yes please specify the reason:_____
□ No

For women, are you pregnant or do you think you might be?
□ Yes
□ No

Do you considered yourself in good health?
□ Yes
□ No,

Do you tend to faint or have strong reactions in response to unusual situations (e.g., seeing blood, on the dentist's chair)?
□ Yes, please specify in which context:_____
□ No

Do you have any other health condition of which we should be made aware?
□ Yes please, specify:_____
□ No

I acknowledge that I have answered this questionnaire to the best of my knowledge and that my answers truly reflect my health status.

_____
Signature

_____
Date

Appendix II
Handedness questionnaire

Handedness Questionnaire

Edinburgh Handedness Inventory

Please indicate your preferences in the use of hands in the following activities by putting a check in the appropriate column. Where the preference is so strong that you would never try to use the other hand, unless absolutely forced to, put 2 checks. If in any case you are really indifferent put and a check in both columns.

Some of the activities listed below require the use of both hands. In these cases the part of the task, or object, for which hand preference is wanted is indicated in brackets.

Please try and answer all of the questions, and only leave a blank if you have no experience at all with the object or task.

	Left	Right
1. Writing	☐ ☐	☐ ☐
2. Drawing	☐ ☐	☐ ☐
3. Throwing	☐ ☐	☐ ☐
4. Scissors	☐ ☐	☐ ☐
5. Toothbrush	☐ ☐	☐ ☐
6. Knife (without fork)	☐ ☐	☐ ☐
7. Spoon	☐ ☐	☐ ☐
8. Broom (upper hand)	☐ ☐	☐ ☐
9. Striking Match (match)	☐ ☐	☐ ☐
10. Opening box (lid)	☐ ☐	☐ ☐
TOTAL(count X's in both columns)		

Scoring:
Add up the checks in both left and right columns.
Whichever number is greater, would be considered your handedness.

Appendix III
Ethics approval

SOINS CONTINUS
Bruyère
CONTINUING CARE

Bruyère pour des soins continus.
Bruyère Is Continuing Care.

April 7, 2010

Mr. Travis Davidson
M.Sc. Student
School of Human Kinetics
University of Ottawa
EBRI/Health of the Elderly

Dr. Francois Tremblay
Scientist,
EBRI

RE: Functional and Neurophysiological Correlates of Corticospinal Function in Human Aging.
(Bruyère REB Protocol # M16-10-009)

Final Approval

Dear Dr. Tremblay and Mr. Davidson,

Thank you for your response to our conditional approval, dated March 4, 2010. The revised documents were received on April 1, 2010. This study has satisfied all of the ethical requirements.

We are pleased to give ethical approval for one year (April 7, 2010 to April 7, 2011) to proceed with the above titled study.

As you know, Pledges of Confidentiality will need to be submitted by all research staff prior to initiation of recruitment.

As per our new continuing review process for studies having undergone full REB review, we now require that an Interim Status report be submitted six months after every annual approval. Your first Interim Status report will be due on October 7, 2010.

We wish you the best of luck with this study.

Sincerely,

Dr. Lisa Sweet, C. Psych.
Chair of the Research Ethics Board
Bruyère Continuing Care

Affilié à / Affiliated with
uOttawa

Appendix IV
Abstract sbumitted to Neuroscience 2011
Washington, DC

Age-related changes in motor transcallosal inhibition as reflected ispsilateral silent period correlate with declines in unimanual hand function.

T. Davidson[1,3] and F. Tremblay[1,2,3].

[1]Sch. of Human Kinetics, [2] Sch.Rehabilitation. Sciences, Univ. Ottawa, Ottawa, ON, Canada. [3] Elisabeth Buyere Research Institute, Ottawa, ON

Previous studies suggest a decrease in interhemispheric inhibition between motor cortices with age (Fling et al, Frontiers Neurosc 5, 2011). In this study, we examined this issue with transcranial magnetic simulation (TMS) using the ipsilateral silent period (iSP) as a surrogate measure of transcallosal inhibition in the motor cortex. We looked more specifically for the presence of greater right-left asymmetries with age and whether interhemispheric inhibition might be linked with declining hand function. Participants consisted of young (n=13, 19-25 years) and old (n=16, 65-83) right-handed healthy individuals. For hand function, participants were assessed with the grooved pegboard test and for pinch strength. For iSP measurements, supramaximal TMS pulses (120% RMT) were applied on the motor cortex with participants exerting a maximal voluntary contraction with the ipsilateral hand while the contralateral hand exerted a light contraction. Transcallosal inhibition between motor cortices was determined by measuring the area of the iSP. As expected, participants showed large and significant ($p<0.001$) right-left asymmetries in both dexterity scores and in grip strength. In contrast, right-left comparisons of iSP area revealed no significant difference between hemispheres in the two age groups (mean diff. young, 0.71 mV.ms; old, 0.45 mV.ms). On the other hand, young subjects showed, on average, 50% larger iSP area than older subjects in both motor cortices. Interestingly, dexterity scores in the two hands were found to be inversely correlated ($p<0.05$) with iSP area (right, $r= -0.39$; left, $r= -0.51$); suggesting a link between declining dexterity with age and reduced interhemispheric inhibition. These results highlight the lack of correspondence between the large asymmetries often found at the functional level and those found at the neurophysiological level with TMS, which can be small or absent. Our results are also in line with other TMS reports showing a reduced excitability of inhibitory cortical circuits with age, in particular, those involved in mediating transcallosal inhibition between motor cortices (Langan et al. Front Sys Neurosc 4, 2010).