Upper Limb Asymmetries of Movement Sense and Sense of Effort: The Contribution of Gender and Handedness

by

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A dissertation submitted in partial fulfillment
of the requirements for the degree of
Doctor of Philosophy
(Industrial & Operations Engineering)
in the University of Michigan
2013

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ACKNOWLEDGMENTS

It is fair to say that this research would not have been possible without the help and support of my advisors, colleagues, friends and family. So it is with the greatest pleasure that I briefly acknowledge all those who contributed along the way. I would first like to thank the members of my doctoral committee – Prof. Martin, Prof. Adamo, Prof. Armstrong and Prof. Seidler - for their time, guidance and support throughout this research process. All were truly appreciated, so thank you again.

Special thanks to the co-chairs, Prof. Martin and Prof. Adamo - to Prof. Martin, a heartfelt thank you for your seemingly endless supply of patience and kindness, guidance, willingness to share your knowledge (and humor), and financial support. And to Prof. Adamo, your insights, thoroughness and financial support were invaluable and much appreciated. It was a privilege to work with both of you and I could not have asked for better advisors over the past 4 years.

And while not members of the dissertation committee, I would like to thank both Prof. Liu and Prof. Sarter for their indispensable support and assistance throughout the doctoral process. Thanks also to Eyvind Claxton, Charles Woolley, Rajiv George, Shwetarupalika Das, Olof Minto, Tina Picano Blay, Rod Capps, Wanda Dobberstein, Elizabeth Fisher, Matt Irelan, Christopher Konrad and Amy Warhaft for their invaluable technical and administrative support and in a few special cases the friendships offered and accepted.

Thanks also to my friends in the THInC lab for providing a much needed conversational retreat. And to my most steadfast friends - Huiyang Li and Rebecca Britten - for the strength, courage, laughs, comfort, practical advice shared.

And finally to my family, thank you so much for your continued love and support. Without you, this would have been impossible.

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ABSTRACT

Asymmetry in upper limb performances may have multiple origins. The aim of this research is to determine the contribution of sensory and motor processes to asymmetries in movement sense and sense of effort when considering gender and handedness. The distinction between gender and handedness effects, while often ignored, may shed new light on human performances. The first study investigated asymmetry in movement sense using contralateral reproductions of vibration induced illusions of movements in right (RH) and left (LH) handed young adults of both genders. Females were found more sensitive to vibratory stimulations and less asymmetric than males in movement reproduction. The asymmetry observed in males was related to handedness. Both asymmetry and sensitivity were primarily sensory in origin. The second study investigated asymmetries in the sense of effort and targeted the motor component. Both RH and LH adults were divided into three groups based on hand strength differences. A 20% MVC reference grip force was matched with the same or opposite hand (of the reference). The matching error increased with hand strength differences for RH only, suggesting that the sense of effort is a consequence of both muscle strength differences and an intrinsic asymmetry of the motor component that may vary with handedness. The last study investigated the relative contributions of efferent copy and sensory feedback to the sense of effort. Vibration was used to distort the sensory information from muscles providing the reference in the grip matching task. Visual feedback of the reference hand was also manipulated. The hand/hemisphere systems were found to differ significantly in their dependence on proprioceptive information during force reproduction, with the left hand being more feedback dependent. These findings lead us to suggest that hand preference and gender contribute to differences in movement representation, force production and sense of effort that may result from the combination of cortical structural differences and information processing specific to each hemisphere, gender and handedness group.

CHAPTER 1

INTRODUCTION

The importance of our hands cannot be overstated; philosopher Immanuel Kant probably said it best when he said that the hands are our "outer brain"[1]. And like the two halves of our brain, while the right and left arm biomechanical systems share similar characteristics, there are definite right-left differences. Specifically, the sensorimotor performance or ability of our right and left biomechanical systems differs. The study of this asymmetry in upper limb motor control has focused on three 'senses': position sense, movement sense and sense of effort. Position sense refers to the awareness of body's/limbs' location in space, movement sense to the ability to discern motion of body/limbs, and sense of the effort to the subjective perception of the force exerted by muscles (Roland & Ladegaard - Pedersen,1977). Asymmetry in position sense, as demonstrated by differences in upper limb motor performance in matching tasks, had been initially attributed in this context to directional differences in inter-hemispheric transfer of information (Yamauchi et al. 2004); however, more recently, Adamo and Martin (2009) proposed an asymmetry of the sensorimotor systems with an emphasis on the sensory components. Asymmetry in the sense of effort was primarily attributed to difference in strength between the homonymous muscles (Carson et al., 2002; Jones, 2003; Park et al., 2008). However, early interpretations failed to consider the whole sensorimotor system. In addition, the effect of gender and handedness on asymmetries in upper limb control remains unexplored. The overall goals of this research are therefore to determine the contribution of sensory and motor processes to asymmetries in upper limb control (i.e. movement sense and sense of effort) and to evaluate the effects of both gender and handedness on these asymmetries.

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[1] The Hand: How its use shapes the brain, language and human culture (Frank R. Wilson, 1999)

This research, by focusing on the asymmetries in two aspects of upper limb motor control (movement sense and sense of effort) can positively impact the lives of millions of individuals. Specifically, this information can assist in the analysis of neurological disorders (e.g. from stroke) affecting upper limbs and the design of rehabilitation processes following onset of these disorders and by doing so possibly improve the lives of e.g. the 10 million stroke survivors worldwide each year[2], and reducing the 18.8 billion dollars in direct stroke related medical cost in the United States[3] alone. Another possible application may be in the design of preventive strategies aimed at reducing the effects of aging on motor abilities. Indeed, deviations from natural asymmetries may be used to distinguish the sensory and/or motor contributions to disorders as well as to evaluate the efficiency of movement practice and training regimen used in rehabilitation procedures. Furthermore, understanding how our hands work together to produce force and movement can also aid in the design of work tasks of over two million industry assemblers and fabricators[4]. And finally, the results of the proposed research may also be used in the development of control algorithms for movement simulation in the design of human machine interfaces (Kim & Martin, 2008).

Also, while upper limb asymmetries have been investigated in the past, this research study will incorporate gender and handedness (i.e. varying degrees of left and right hand dominance) as main factors while considering all the components of the sensorimotor systems investigated.

The aims of this chapter, are therefore, to (1) review the scientific literature concerning behavioral, functional and anatomical asymmetries related to upper limb motor control, and the methodologies used to study them; and (2) detail the theoretical framework, overarching themes (assumptions) and experimental methodologies employed during the course of this research.

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[2] World Health Report 2002 – Reducing Risks, Promoting Healthy Life (World Health Organization)

[3] Heart Disease and Stroke Statistics – 2012 update (American Heart Association)

[4] Occupational Employment and Wages, May 2010: 51-2099 Assemblers and Fabricators (Bureau of Labor Statistics)

REVIEW OF LITERATURE

It is widely accepted that dexterity and skill are not distributed equally between the left and right hands and that males and females have different cognitive and sensorimotor strengths. In dextrals for example, the preferred (right) hand is usually faster and more accurate in finger tapping and sequencing, and targeted movement (see Elliot & Chua (Manual Asymmetries in Motor Performance, Chap. 7); 1996). But the non-preferred hand (left) generally initiates aimed movements faster than the right hand (Helsen et al., 1998; Velay & Benoit-Dubrocard, 1999), and outperforms the right hand in tactile matching (Witelson, 1974).

In terms of sex differences – statistically behavioral studies have shown that mental rotation visuospatial tasks are better performed by men than women; while verbal fluency (Hyde & Linn, 1988; Crucian & Bernbaum, 1998) and emotional processing (Rahman et al., 2004; Davis, 1999; Canli et al., 2002) tasks are better performed by women than men.

These observed differences in performance have been associated with handedness, hand laterality or hand dominance (e.g. Goble & Brown, 2008; Serrien et al., 2006; van den Berg et al., 2011; Adamo et al, 2012) and gender (e.g. Grabowska et al, 1994; Kimura, 1999; Cheng et al., 2007; Luders et al, 2005, 2007; Wisniewski, 1998) related morphological and functional asymmetries between cortical areas (e.g. Nathan et al, 1990; Amunts et al, 1996; White et al., 1997; Bradshaw et al, 1998; Haaland & Harrington, 1996).

In the following sections, these upper limb behavioral, functional and neuroanatomical asymmetries will be discussed and their impact on the present research detailed. An overview of the matching paradigm used and the applicability of vibration to modulate the sensory information provided will also be provided.

UPPER LIMB BEHAVIORAL DIFFERENCES

In this section behavioral asymmetries such as hand preference and grip strength will be discussed.

Hand Preference

Strong preferences have been observed for several body parts and systems e.g. footedness, eyedness, and earedness (Bradshaw & Nettleton, 1983). But perhaps the most obvious manifestation of lateral asymmetry is human dextrality or handedness (Corbalis & Morgan, 1978; Morgan & Corbalis, 1978; Porac & Coren, 1979). While visual and lower limb systems are not the focus of this research, briefly, Peters and Petrie (1979) generalized that 80% of the population would prefer to use the right foot over the left, and disclosed that this preference was observable in infants as young as seventeen days. Porac and Coren (1976) found that approximately 65% of the population preferred to use the right eye (in cases where a deliberate choice had to be made) and 32% preferred to use the left eye, with males and right handed individuals being the most consistent. Peters and Durding (1979), using hand and foot tapping rate performance, also found that handedness and footedness were positively correlated: the right limbs of dextrals (right handers) performed better than the left and vice versa for sinistrals (though performance deficits between dextrals' right and left limbs were greater than those observed in sinistrals).

Both the definition and types of handedness have been long debated. Approximately 90 percent of the North American population consider themselves to be right handed as they prefer to use their right hand for writing (Oldfield, 1971; Annett, 1985; Gilbert & Wisocki, 1992), while in other countries/cultures (e.g. Korea) this increases to 99% (Kang & Harris, 1993). Gilbert and Wisocki (1992) based on their survey of 509,552 U. S. males and 665,223 U.S. females, estimated that 13% of (U. S.) males and 10.5% of (U.S.) females were self- reported left handers.

Within the scientific community, however, handedness refers to either the individual's preferred hand, strongest hand and/or hand which performs motor tasks more efficiently (Barnsley & Rabinovitch, 1970). In the former case, hand preference questionnaires are used to systematically categorize participants based on consistency of hand use. And, performance tasks (manual dexterity (precision and speed), hand steadiness tasks) evaluate the relative ability/superiority of one hand over the other. Johnstone and colleagues (1979) found that, of the two loosely related methods, the hand preference questionnaire was considered to be the better general predictor of handedness. This assertion was based on the fact that speed, strength and dexterity were each better correlated with the results of the questionnaire than with each other. Nonetheless, the use of questionnaires is not without pitfalls - how many and which questions to include and most importantly how to categorize individuals based on their responses are issues still debated (Barnsley & Rabinovitch, 1970). Individuals can be classified on either discrete (2, 3 or 5 level scales e.g. left/right, left/right/mixed, strongly left/left/mixed right/strongly right) or continuous scales (e.g. laterality index -1 to +1). The use of a continuous scale seems better suited to the continuous nature of handedness (Bradshaw & Nettleton, 1983; Peters, 1992), but Peters (1992) still noted that handedness classification was very sensitive to questionnaire procedures (e.g. forced or graded responses) and cut-off criteria. In the current study the Edinburgh Handedness Inventory (Oldfield 1971) was used to assess the handedness of participants on a scale of -1 to 1.

Grip Strength Differences

Even with the caveat that the definition of right/left handedness may vary somewhat between studies – there appears to be definite gender and handedness differences in grip strength. In terms of male-female grip strength differences between dominant and non-dominant hands - a common misconception, dating back to Bechtol (1954), is that the dominant hand is typically 10% stronger than the non-dominant hand (Petersen et al, 1989). Schmidt and Toews (1970), using a series of questions to establish hand dominance, found that for the 1208 participants tested (1128 right and left handed males, aged 18 – 62 years), the dominant hand was generally stronger than the non-dominant hand. But for males this difference in strength was 3.2% on average, and for females the strength difference was 9.2%. They also noted that the non-dominant hand was stronger than the dominant hand for 22.6% of males, while the same was true for 20% of females tested. They did not however report the strength difference for left or right handed participants only.

Mathiowetz and colleagues (1985) later conducted a grip strength study with 250 participants (n=228 right handers). They found that for right handed males and females, the dominant hand was respectively 12.9% and 16.5% stronger than the non-dominant hand. While the non-dominant hand was 3.3 % and 11.8% stronger than the dominant hand for left handed males and females respectively. Deeming these differences functionally equivalent across the male-female/left-right subgroups, the authors concluded that the right hand was generally stronger than the left hand regardless of hand preference or gender.

Petersen and colleagues came to a different conclusion in their 1989 grip strength study, which individually analyzed 310 self-identified left and right handed participants. As found in Schmidt and Toew's earlier work, the non-dominant hand was stronger than the dominant hand for about 20% of the 310 participants tested. But they noted that the non-dominant hand was stronger than the dominant for 48% of the 48 left-handed participants and for only 6.9% of the 262 right handed participants. This was reflected in the average grip strength differences, the dominant hand of right handed males (n=108) was 9.2% stronger than the non-dominant hand, while the dominant hand of right handed females (n=154) was 15.8% stronger than its counterpart. In contrast, the dominant hand of the left handed male (n=17) was 1.9% stronger than the non-dominant hand on average, while the dominant hand of the left handed female (n = 31) was weaker than the dominant hand by 1.2%. Peters (1992) investigated the seeming lack of asymmetry displayed by left-handed participants. He found that left-handers who both throw and write with their left hands had significantly stronger left hands, while left handers who throw with the right but write with the left had significantly stronger right hands.

While these three studies have employed a discrete left/right classification of handedness, together they suggest that: (1) the dominant hand of right handed individuals is more likely to be the stronger of the two hands; (2) grip strength differences for left handed individuals are more difficult to predict, as it appears equally likely that the dominant/non-dominant hand may be the stronger of the pair; and (3) regardless of handedness, the *non-dominant* hand is stronger than the dominant hand in a notable proportion of the population.

UPPER LIMB FUNCTIONAL DIFFERENCES

In this section functional differences such as asymmetries in the cortical representation of the upper limbs, processing specialization of the two limb systems, peripheral information and interhemispheric information processing will be discussed.

Asymmetries in Hemispheric Processing Specialization and Control

Given the results of the neural imaging studies (see pages 14 - 18) three main theories attempt to explain either hemispheres' involvement in motor control: (1) motor dominance theory, (2) open/closed-loop hypotheses, and (3) dynamic dominance theory. Proponents of the motor dominance theory, first introduced by Liepmann (1908), posit that the motor control capabilities of the hemisphere contralateral to the preferred hand (generally left hemisphere) exceeds that of the hemisphere ipsilateral to the preferred hand, and is therefore integral to the control of both hands during voluntary movement. Support for this theory comes from brain imaging studies (see pages 14 - 18), which have consistently shown that for right handers: the left hemisphere is more active during contralateral (Dassonville et al., 1997; Volkmann et al., 1998; Kim et al., 2003; Kawashima et al., 1997), ipsilateral (Kawashima et al., 1993, 1998; Kim et al., 1993; Babiloni et al., 2003; Verstynen et al., 2005; Callaert et al., 2011; van den Berg et al., 2011) and bimanual movements of the upper limbs (Viviani et al., 1998) . Clinical studies of patients with unilateral brain damage have also revealed that, for right handers, left hemisphere dysfunction/lesions resulted in movement deficits in both arms, while right hemisphere dysfunction appeared to affect the deftness/dexterity of the left arm only (Liepmann, 1908, 1920; Haaland et al. 1977; Haaland & Delaney 1981; Haaland & Harrington 1989b, 1994, 1996; Heilmann et al., 2000).

In contrast to the motor dominance theory, the open loop/closed loop hypotheses were based on the assumptions that the dominant arm/hemisphere specialized in open-loop movements, while the non-dominant arm/hemisphere specialized in closed loop (feedback dependent) control. Motivated by the findings of Woodworth (1899) and Fitts (Fitts & Radford, 1966; Fitts, 1992) regarding the two component model of aiming, these assumptions were also supported by observations made during clinical studies. For example, Winstein and Pohl (1995) who found, through their study of the movement kinematics of individuals with left and right cerebral lesions (n = 20 stroke patients), that while the left hemisphere was necessary for the efficient timing and triggering of the various movements (so more dependent on planning), the right hemisphere was integral to the processing of visual information during aiming movements (so more dependent on feedback). But while several studies have supported one of these assumptions (e.g. Haaland & Harrington, 1989a, 1989b; Hermsdorfer et al., 1999a, b), simultaneous support for both was lacking. This lack of definitive support prompted Haaland et al. (2004) to conduct a kinematic study of 69 right-handed individuals (n = 23 with left hemisphere damage, 15 with right hemisphere damage, and 31 without hemisphere damage). They found that the advanced planning performance of stroke patients with left hemisphere damage was unaffected, while patients with right hemisphere damage were more dependent on visual feedback. Both results contradicted the underlying assumptions of the open/closed-loop hypotheses, and were thought to be more in keeping with the expectations of the dynamic dominance hypothesis.

While acknowledging that the dominant hemisphere is essential to the movement of both arms, Sainburg (2002) argued that the non-dominant hemisphere/arm was equally important. This assertion was also supported by the previously discussed observations of Winstein and Pohl (1995) i.e. left hemisphere specialized dependent on planning while right hemisphere more dependent on feedback. Sainburg (2002) further proposed that the preferred hand/dominant hemisphere specialized in the control of limb dynamics, having found that during rapid reaching movements the elbow muscle torques of 6 right-handed individuals (n = 3 males, LI = 100) were used more effectively by the dominant arm (Sainburg, 2002; Sainburg & Kalakanis, 2000). He and Bagesteiro later proposed that the non-dominant arm specialized in the control of static posture (Bagesteiro & Sainburg, 2003) as it was better able to adjust to changes in load during controlled elbow flexion movements. They further suggested that this observation somewhat bridged the gap between the dynamic dominance theory and the open-loop/closed-loop hypotheses of hemispheric specialization since the performance of the non-dominant arm was consistent with the idea that the non-dominant arm specialized in closed-loop control utilizing somatosensory feedback. They also refined their initial hypothesis concerning the specialization of the dominant arm by stating that the “open-loop specialization of the dominant limb/hemisphere system is limited to feedforward specification of task dynamics” (Bagesteiro & Sainburg, 2003, pg. 1512).

Asymmetries in Sensory Information Utilization

Both the open loop/closed loop hypotheses and the dynamic dominance theory suggest that there may be handedness related differences in the use of visual and proprioceptive feedback. Honda (1982, 1984) examined the use of visual feedback in rapid uni-manual and bimanual aiming tasks in search of plausible explanations for the superior aiming performance of the preferred hand (Flowers, 1975). Based on his observation of 10 right handed (assessed using Edinburgh Inventory) male students (20 – 24 years old), Honda (1982) concluded that the performance of the right (dominant) hand was dependent on visual feedback as performance time decreased when the movement of the right hand was monitored. In contrast, the performance time of the left (non-dominant) hand was unaffected by visual monitoring. These results contradict those of Winstein and Pohl (1995) and Haaland and Harrington (1989), who found a non-dominant arm/hemisphere dependence on visual information/feedback processing. This visual guidance dependence was also observed in symmetric bimanual movements, where gaze was systematically directed to the non-dominant (left) hand when accuracy was required, while the right dominant hand could continue to move in the direction of the target without visual feedback (Srinivasan & Martin, 2010).

In terms of proprioceptive information – several studies have investigated the position matching performance of the upper limbs (Roy & MacKenzie 1978*;* Riolo-Quinn 1991; Carson et al. 1990a, b*;* Yamauchi et al., 2004; Goble et al., 2006; Goble & Brown, 2007*;* Adamo & Martin, 2009; Adamo et al., 2007). With regard to handedness, the matching performance was dependent on which arm/hemisphere system provided the reference (Goble et al., 2006; Goble & Brown, 2007*;* Adamo et al., 2009). Yamauchi et al. (2004), in their study of the contralateral matching ability of 30 males (n = 15 strong right handers, 15 strong left handers), found that the right arm match resulted in position matching overshoots, while the left arm matching error was close to zero. For left handers, they found the opposite to be true. Based on these results, they suggested that observed overshoots were related to the direction of transfer of spatial information and were the result of a poorer representation of the reference limb position. A similar interpretation was suggested by Goble et al. (2006). Surprisingly these studies neglected to consider all the components of sensory-motor systems involved in the task. More recently, Adamo and Martin (2009) recruited 12 right hand dominant (n = 6 males, 22.1 ± 2 years old) adults to perform a wrist position-matching task. In the contralateral matching conditions, they observed a large overshoot when matching with the right hand and a similar undershoot when matching with the left hand. These matching errors were greater than those observed when matching with the ipsilateral hand. Martin and Adamo (2009) explained these asymmetries in position matching using a “proprioceptive sensory-motor gain hypothesis”, showing that the matching asymmetries resulted from the fact that the gains of the upper limb sensorimotor systems were also asymmetric.

Asymmetries in Interhemispheric Transfer of Information

Interhemispheric communication is mediated by the corpus callosum (e.g. Bernard et al., 2011; van den Berg et al., 2011). And while the corpus callosum can have either a net excitatory or inhibitory effect (see Bloom & Hynd, 2005 for review), it has been assumed that the corpus callosum facilitates an inhibitory influence between left and right primary motor cortices during uni-manual movement (De Gennaro et al., 2004, Netz et al., 1995). Using paired pulse TMS, De Gennaro et al. (2004) and Netz et al. (1995) found that magnetic conditioning stimuli on one hemisphere respectively reduced the motor evoked potential (MEP) amplitude of the abductor digiti minimi *(*ADM) and first dorsal interosseous (IDI) muscle contralateral to the other hemisphere. This reduction in amplitude was thought to reflect the magnitude of inhibition between the hemispheres.

Marzi and colleagues (1991) conducted a meta-analysis, of 16 studies (320 subjects) that used simple uni-manual reaction time, to investigate the interhemispheric transfer time in right handers. The assumption being that the response time would increase if required to initiate movement in the motor cortex contralateral to the one receiving the visual stimuli (Poffenberger, 1912). In the case of right handers, they found that the mean reaction times (1) were less when the visual stimuli were presented to the left visual field as compared to the right visual field in 11 of the 16 studies reviewed, (2) of the right hand were less than that of the left hand in 81% of the studies, (3) in the uncrossed conditions (left visual field/left hand and right visual field/right hand) were equivalent, and (4) were less when visual stimuli were presented to the left visual field and participants asked to respond with their right hand as compared to when the visual information was presented to the right visual field and participants responded with their left hand and vice versa. Marzi and colleagues (1991) argued that this asymmetry was due to “asymmetries in the direction of transfer”.

In keeping with the above, Bernard et al. (2011) in their TMS and interhemispheric transfer time study (n=48, 13 male, 18 left handed), found that the time of transfer from dominant hemisphere to non-dominant hemisphere and from non-dominant to dominant were related to the laterality of dexterity – where the less lateralized had the shortest interhemispheric transfer times. While Cherbuin & Brinkman (2006), in their expanded study of right handed (n = 80, 40 males) and left handed (n= 20, 10 males) participants, did find that handedness and efficiency of interhemispheric transfer or bilateral distribution advantage (calculated by subtracting reaction times observed when letter match was found in visual field ipsilateral to responding hand from reaction times for letter matches found in visual field contralateral to responding hand)) were positively correlated. Extreme left handers' interhemispheric interactions being the most efficient as the average difference in reaction times was the largest of the four handedness groups (i.e. extreme left hander, left hander, right handers, extreme right handers). Neither study found gender to be a significant factor.

Hemispheric Lateralization

Clinical observations combined with neuroimaging studies have led to greater insight into the functioning of the human brain. Serrien et al. (2006) identified two complementary theories/assumptions of cortical function - functional specialization or functional integration. Functional specialization refers to the underlying assumption that certain regions of the brain perform "specialized computations". And functional integration refers to the theory that certain tasks require the collaborative efforts of "specialized neural regions". In keeping with the former theory Liepmann (1908) was among the first to posit, based on his observation of right-handed stroke patients, that the hemisphere contralateral to the preferred hand (left) was integral to upper limb motor control. Numerous studies have, to some extent, supported this conclusion, though the exact nature of the relationship between the 'dominant' hemisphere and both the contralateral and ipsilateral arm systems is not completely understood.

Early imaging studies focused on the role of the primary motor and sensorimotor cortices in contralateral and ipsilateral hand movements. Triggs et al. (1999), using transcranial magnetic stimulation (TMS) on 3 females (2 right handed) and 6 males (4 right handed) young adults, found that the motor evoked potential (MEP) maps of *right* abductor pollicis brevis (APB) and flexor carpi radialis (FCR) muscles were larger than respective *left* MEP maps in right handers. But the reverse was true of the maps of their left-handed counterparts – the MEP maps of left APB and FCR were larger than respective right NEO maps. They interpreted this, and the fact that the number of scalp stimulation sites causing MEP's with mean areas greater than 10% of the maximum recorded for APB was greater for the preferred hand, to mean that the cortical motor representations of the APB and FCR muscles were greater for the preferred hand. This asymmetry in cortical representation was also observed by Wassermann et al. (1992) for the APB muscles in 8 (6 right-handed) participants and Krings et al. (1997) for the first dorsal interosseous muscle of 3 right-handed participants. These results are further supported by the observation that, physically, the dominant hand is generally larger than the non-dominant hand in both right and left handers although the difference is hand size is smaller for the left-handed population (Purves et al., 1994).

These results are also consistent with Macdonell et al.'s (1991) and Triggs et al.'s (1994) earlier findings, that the threshold for eliciting MEPs was less for the preferred hand than the non-preferred hand in right and right/left handed individuals respectively. It should be noted that Cicinelli et al. (1997) and Wilson et al. (1993), in their TMS studies, failed to observe differences in motor cortical representations of the abductor digiti minimi (ADM) and APB-ADM muscles respectively. However, Triggs et al. (1999) attributed this to differences in methodology and precision of imaging equipment used.

TMS, positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) studies have also been used to study the activation patterns of the primary motor (M1), sensorimotor (S1) and premotor cortices, and the supplementary motor area (SMA) during unimanual/bimanual and simple/complex finger movements. It has been consistently shown that motor areas in the contralateral hemisphere are activated during movements performed with either the left or the right hand (e.g. Kim et al., 1993; Kawashima et al., 1994; Dassonville et al., 1997; Volkmann et al., 1998; Baraldi et al., 1999; Seibner et al., 2002; Kloppel et al., 2007a, 2007b; Jung et al., 2008; Bernard et al., 2011). In addition, the use of the dominant/preferred hand is associated with a greater volume of activation in the contralateral M1 – S1 in uni-manual tasks (Dassonville et al., 1997; Volkmann et al., 1998 (MEG); Kim et al., 2003). However, left handers show more bilateral activation in the motor areas (Kim et al., 1993; Seibner et al., 2002).

While the above is consistent with the contralateral ‘organization of the motor system’ (Callaert et al., 2011), the role of these motor areas in ipsilateral hand movements is a little more difficult to explain. It is known that afferent inputs from both hands ascend to ipsilateral cortices (Blatow et al., 2007), with as much as 10-15% of corticospinal projections innervating ipsilateral muscles (Carson, 2005). However, others have observed that left, but not right, parieto-premotor damage affects both hands’ ability to produce skilled movement (Heilman et al., 2000; Kertesz & Hooper, 1982; Liepmann, 1920), hence it may not be surprising that the ipsilateral motor cortices were activated during hand movements. Nevertheless, ipsilateral activation of the left M1 – S1 was found to be greater than ipsilateral activation of the right motor areas in right handers (Kawashima et al., 1993, 1998; Kim et al., 1993; Babiloni et al., 2003; Verstynen et al., 2005; Callaert et al., 2011; van den Berg et al., 2011). The results vary for left handers: a) mirrored asymmetry i.e. greater ipsilateral activation of the dominant hemisphere during right hand movements (Kawashima et al., 1997); b) similar asymmetry i.e. more left than right hemisphere activation during ipsilateral hand movements (Verstynen et al., 2005; Kim et al., 1993) or c) two groups of left handers i.e. one group whose ipsilateral activity was the same as their right handed counterparts and a second group whose ipsilateral activity mirrored that of right handers (van den Berg et al., 2011).

Irrespective of handedness, ipsilateral activity has also been associated with degree of laterality (assessed through tapping circles performance) - Bernard et al. (2011) showed that ipsilateral activity was greatest for less lateralized (assessed based on dexterity) individuals. Other researchers have found ipsilateral activity (especially in the parietal and premotor areas) to increase with movement complexity (Bablioni et al., 2003; Haaland et al., 2004; Hlustik et al., 2002; Kim et al., 1993; Koeneke et al., 2004a, b; Verstynen et al., 2005; Vines et al., 2008).

Even though both females and males participated in the above studies, gender was rarely considered as an independent factor. Instead, gender differences in brain activity have been investigated and discovered using resting state fMRI (rs-fMRI). Rs-fMRI measures spontaneous brain activity while individuals are relaxed, and is thought to provide insight into the functional communication network between brain regions (Biswal et al., 1995). Biswal and colleagues (2010) aggregated rs-fMRI data on 1,100 volunteers (522 males) collected independently at 35 international centers. They found that activity in the posterior cingulate cortex, medial prefrontal cortex, medial prefrontal cortex and inferior parietal lobe were greater for females than males. The reverse was true (males greater than females) for activity in the dorsal anterior cingulate cortex, insula, superior temporal gyrus, superior marginal gyrus and occipital regions. After dismissing male-female differences in hemoglobin concentrations and hematocrit as possible explanations for the observed 'regionally-specific' asymmetries, Biswal et al (2010) suggested that hormonal differences (e.g. estrogen) during brain development may be a contributing factor to gender differences in cortical activation. But they urged caution in interpreting the results as this was the first rs-fMRI study to discover gender-related differences and inter-center variability was high. Corroborating evidence of this gender-asymmetry results was soon provided by a similar rs-fMRI study (Zuo et al. 2010) of 214 right handed participants (n = 96 males).

More recently, Allen et al. (2011) and Filippi et al. (2013) tested 603 (n = 298 males, 46 ambidextrous or left handed, 12 – 71 years) and 104 right handed adults (n = 48, 20 – 29 years) respectively. Both groups found gender related differences in resting-state functional connectivity, as observed by Biswal et al.'s (2010) study. Primarily, Filippi and colleagues noted stronger functional connectivity in regions of the visual network in males (when compared to females), including areas involved in processing information about the shape and location of objects. They suggested that this result, combined with the fact that their analysis revealed a stronger connectivity between sensory and cognitive networks for men instead of women, give credence to the idea that males may solve cognitive problems through the use of mental imagery and visuo-spatial representations (Christakou et al., 2009; Thomsen et al., 2000) and may also explain males' greater ability to perform visuo-spatial tasks.

They also found that the functional connectivity in frontal and cerebellar regions was higher for women (as compared to men). This paralleled results obtained for females performing attentional switching tasks during an event related MRI brain imaging study (Christakou et al.

2009). The latter group had suggested that this reflected the enhanced role of the fronto-cerebellar pathway in inhibitory control in women.

Gender differences were also found in the organization of the functional neural networks. Tian et al. (2011) used rs-fMRI to investigate these differences in 86 right-handed adults (n = 38 males, 17 – 25 years old). They found that the normalized clustering coefficient (measure of regional proximity) in the right hemisphere network was higher for males than females. While, the normalized clustering coefficient in the left hemisphere was higher for females than males. Finally, both males and females tended to be more ‘globally efficient’ (measure of path length between nodes) in the right hemisphere (hemisphere contralateral to the preferred hand).

NEUROANATOMICAL DIFFERENCES

Though the question of whether hemispheric asymmetry is an inborn brain characteristic (Witelson, 1987; Hellige, 1993) or develops over time (Lenneberg, 1967; Rasmussen & Miler, 1977) is still very much debated, the idea that behavioral and functional lateralization may be correlated with or a function of anatomical lateralization has gained widespread support. Many researchers (e.g. Galaburda et al., 1978; Geschwind and Levitsky, 1968; Witelson, 1977, 1985, 1989), employing post mortem examination or in vivo brain imaging techniques, have identified left-right quantitative differences in proportion of the brain tissue allocated to architectonic areas or gross anatomic landmarks. When interpreting the functional relevance of these asymmetries, three assumptions are common; firstly the directionality of this asymmetry in size (whether left structure is greater than its right counterpart, or vice versa) is directly related to the directionality of functional dominance. The hemisphere in which the larger structure is located is assumed to be functionally dominant, in keeping with the notion that the larger the brain area dedicated to a structure, the greater the number of neurons and connections assigned to that role. Secondly, the magnitude of the hemispheric asymmetry is also relevant as it is typically considered a reflection of the degree of functional asymmetry. And finally, these allometric relationships (i.e. correlation between size and function) are not necessarily consistent across individuals and with time (Galaburda et al., 1978; Fling et al., 2011, 2012).

Early models of brain asymmetry focused on language. The planum temporale (PT) was one of the original brain regions studied in search of structural correlates to cerebral asymmetry. Since located in Wernicke's (1874) posterior receptive area, it was said to be associated with both spoken and written language recognition. Geschwind and Levitsky (1968), among the first to identify left-right asymmetries in this region, conducted a post-mortem study of 100 adult human brains. They found that the left PT was larger in 65% of the samples and that the right PT was larger in 11 % of the samples. While handedness data were not available, they assumed that their 100 samples were predominantly right handers given that "93% of adult population are right handed, and 96% are left brained for speech".

Steinmetz (1991) and colleagues (1996) later used in vivo MRI to study the morphometry of the PT in 154 intact human brains. While they noted the same asymmetry in the size of the PT in 121 right handed participants, they observed that the leftward PT asymmetry was weaker in left-handers. Steinmetz (1991) did not observe significant gender differences or gender x handedness interaction effects on the size of the PT.

Given that the planum temporale includes much of Wernicke's area and is an integral part of the association cortex associated with language, this leftward asymmetry in its size is/was thought to be an anatomical correlate to observed (left) brain language lateralization. This potential link between anatomical asymmetry and behavioral asymmetry supports the possibility that differences in areas of the brain associated with voluntary movement and force production and control may be associated with observed behavioral differences. In the later sections, differences in the gross anatomical structures associated with voluntary motor control will be described with the aim of understanding the asymmetries in upper limb motor control previously discussed and investigated during the course of this research.

Hemispheric Differences

Like many of their peers, Kertesz et al (1990) used MRI to determine in vivo linear and area measurements and their relationship to handedness and gender in a study involving 108 right and left handed males and females. They found that, for the cross-sectional (linear) measurements, right side anterior frontal widths and left side parietal and occipital widths were significantly larger for right handers than left handers. However, the study did reveal some inconsistencies.

Contrary to the expectation that the frontal lobe contralateral to the preferred or dominant hand would be the larger of the two lobes, the study found that the left frontal lobe was larger than the right in left handers and the frontal lobes of right handers were equal or the right frontal lobe was slightly larger than the left frontal lobe. The same inconsistency was seen when computerized tomography (CT scan) was used to observe the petalia (imprints on the surface of the skull formed by hemispheric protrusions). Specifically, the right frontal petalia was larger for right than left handers, while the reverse was true for left frontal petalia i.e. the left frontal petalia was larger for left than right handers (Bear et al, 1986; Pieniadz & Naeser, 1984; Lemay, 1977). Nopoulos et al. (2000) conducted a MRI study of 42 male and 42 female right handers, where age and IQ were rigorously controlled. They similarly found that the right cerebral hemisphere was slightly larger than the left hemisphere. But they also found that both intracranial and tissue volumes were approximately 8% larger for males than females (as did Dekaban & Sadowski, 1978; Zatz et al., 1982; Swaab & Hofman, 1984; Delisi et al., 1991; Filipek et al., 1994; Pfefferbaum et al., 1994). This is in keeping with Sowell et al. (2007) who collected brain imaging from 176 right-handed subjects (n = 90 males, 7 – 87 years old). They found that the total (unadjusted) brain, gray matter and white matter volumes were large in males than females.

Other MRI brain imaging studies have compared the intracranial tissue composition (white matter, gray matter and cerebrospinal fluid volumes) of males and females, and the results have been ambiguous at best. White matter (myelinated connective brain tissue) is thought to facilitate information transfer and gray matter (somatodendritic tissue) to facilitate computation and decision-making (Gur, 1999; Fields, 2008). Schlaepfer and colleagues (1995), who studied the brain tissue of 17 women and 43 men (handedness not specified), found that the gray matter volume (once corrected for brain volume) was significantly greater for women than men in the dorsolateral prefrontal cortex (by 23.2%) and superior temporal gyrus (by 12.8%). There were no significant differences in gray matter volume in the inferior parietal lobe, overall gray matter, white matter, and cerebrospinal fluid between males and females. In contrast, Filipek et al (1994), for their 10 males (n = 7 right handed) and 10 females (n= 8) right handed subject pool, found that the white matter volume was 8% less for females than males. While Passe et al. (1997), for the 43 participants (n = 33 males; n= 37 right handed) considered, noted that the volume of white matter was significantly larger in males than females, but the gray matter volume was not significantly different between them. Gur et al. (1999), in their study of 80 right handed young adults (n = 40 males), found that the volume of gray matter was greater for females than males, and that males had greater volumes of white matter and cerebrospinal fluid volumes (when brain size adjustments were made). Interestingly, they also found that the volume of gray matter in left and right hemispheres were equivalent in females, but higher left hemispheric volume of gray matter and right hemispheric volume of cerebrospinal fluids were found in males. And finally, Nopoulos et al. (2000) - based on their age, IQ and gender controlled participant distribution – did not observe gender related differences in gray or white matter.

Gender related asymmetries in cortical thickness have also been observed. Luders et al. (2006) used MRI to observe 60 self-reported right handed (n = 30 males, women: 24.32 ± 4.35 years; men: 25.45 ± 4.72 years) adults. Similar to Im et al. (2006) and Sowell et al. (2007), they found that cortical thickness in all four lobes was greater for females than males both before and after measurements were scaled based on individual differences in brain size. And that these differences were larger in the right hemisphere (Sowell et al., 2007). Only in the left lateral temporal lobes were (unscaled) thicker/more depth noted for the males. It should be noted that while the cortical layers were thicker in females, the number of neurons (Stark et al., 2007), neuronal density (Rabinowicz et al. 1999), and synaptic density were found to be higher in males than females in all cortical layers (Alonso-Nanclares et al., 2008).

Differences in Primary Motor and Sensorimotor Cortices

As the structure responsible for generating neural signals controlling voluntary movement, the primary motor cortex (M1), located in the frontal lobe, has been the focus of many studies. White et al. (1995) conducted a post mortem examination of the central sulcus (Rolandic fissure), which separates the frontal and parietal lobe of the cerebral cortex, of twenty-two brain specimens (males and females 17 – 78 years old) to determine the extent of the cortical surface within. They found that the sulcal surface was greater in the left hemisphere than in the right and postulated that this meant that more cortical and sub-cortical “circuitry” was dedicated to the right upper extremity than to the left. However, they (White et al, 1995) later reported in an expanded study that these measurements did not conclusively prove/show structural asymmetry in the depth of the central sulcus.

The discrepancy in White's findings prompted further investigations by Amunts and colleagues. Amunts et al (1996) conducted an in vivo MRI study to investigate interhemispheric asymmetry in the depth of the central sulcus as an indication of the size of the cortical motor hand representation area. Consisting of 35 male subjects (31 right handers, 14 left handers as categorized by a hand dominance test (Steinmetz et al., 1991; Jancke, 1996; Steingruber, 1971), this study found that the central sulcus was deeper on the side contralateral to the dominant hand, and that this difference in size was greater for right handed participants. Amunts et al (1996) also noted the corresponding difference in neutrophil volume. Foundas' and colleagues' (1998) results paralleled Amunts' for the 15 right handed participants (n=9 males) they tested. But they found that the left and right sulcal areas were not significantly different in the 15 left handers (n = 9 males) tested. This inconsistency between Amunts' and Foundas' results may be attributed to differences in the distribution of subjects (since Amunts and colleagues focused on males only while 6 out of 9 left handers in Foundas' and colleagues' cohort were female) or in the methods used to assess handedness. Foundas and colleagues, whose handedness determination was based on preferred writing hand and participant's score on Briggs and Nebes (1975) handedness inventory, readily acknowledged that their left handed participants were not as strongly left handed as their right handers were right handed. Amunts later expanded her study (Amunts et al, 2000) to include 103 male and female left and right handed participants. The previous asymmetry in males was confirmed, however similar interhemispheric asymmetry was not observed in females.

Differences in Corpus Callosum

Given the functional differences between the cerebral hemispheres, efficient processing would require both the exchange of information and coordination of activity between the cerebral hemispheres (Baynes et al., 1998; Gazzaniga, 2000). The corpus callosum or colossal commissure is the (primary) neural fiber network connecting homologous areas of the cerebral hemispheres. Estimated to contain over 200-300 million fibers (Tomasch, 1954; Aboitiz et al., 1992a, 1992b; Hofer & Frahm, 2006), the corpus callosum is thought to play a major part in the transfer of information between the two hemispheres (Chiarello, 1980; Sperry, 1982; Zaidel, 1983, Schmahmann & Pandya 2006). Specifically Fling et al. (2013), in their transcallosal mapping study, found interhemispheric tracts between homologous primary motor cortices, supplementary motor areas (SMA) and pre-SMA, and dorsal pre-motor and somatosensory cortices.

It has been hypothesized that differences in the structure of the corpus callosum and differences in the degree of lateralization across gender and handedness groups are related (Witelson & Goldsmith, 1991; Hines et al., 1992; Moffat et al, 1998; Amunts et al., 1996; Preuss et al., 2002; Welcome et al., 2009, 2010). Witelson (1985) measured the midsagittal area of the corpus callosum in 42 individuals (27 consistent male and female right handers, 15 male and female mixed handers based on Annett's questionnaire (Annett, 1972) and concluded that the overall callosal area was 11% greater in mixed and left handers, than in right handers. Gender related differences in absolute or relative callosal area were not observed in this study.

In an expanded postmortem study of the corpus callosum of 50 subjects (32 consistent right handers (9 males), 18 non-consistent right handers/mixed handers (6 males)), Witelson (1989) reported that the cerebrum was larger in males than females. Using a multivariate analysis of variance of callosal area with gender and handedness (and their interaction) as factors, the previous result (Witelson, 1985) was duplicated. Further analysis revealed that these differences in overall callosal area could be attributed to differences in the area of the posterior (isthmus and adjacent posterior midbody combined) of the callosum. Interhemispheric tracts through this region are thought to connect homologous sensorimotor and primary motor cortices (Fling et al., 2013; Wahl et al., 2007). Both the isthmus and posterior midbody of the corpus callosum were larger in non-consistent handed males than in right consistent handed males. However, Witelson did not observe differences in the areas of the posterior of the corpus callosum of consistent right handed and non-consistent handed female subjects.

Habib et al (1991) also explored the relationship between callosal morphology and brain lateralization but used MRI to investigate (in vivo) the callosal area of 53 participants (35 males). Study participants were categorized by both the direction (consistent right handers (n=26 participants, 19 males) and non-consistent right handers) and degree (exclusive right/left hand user (n=31 participants, 21 males) versus non-exclusive right/left hand users) of handedness. As in Witelson's studies (1985, 1989), callosal areas were larger in non-consistent right handers than in consistent right handers. However Habib et al (1991) found that the anterior callosal area was significantly larger for non-consistent right handers, while the posterior callosal areas of consistent right handers and non-consistent right handers were not significantly different (although the trend observed was in keeping with Witelson's results (1985, 1989)). In terms of the degree of handedness, the magnitude of the laterality quotient (calculated using the Edinburgh inventory (Oldfield, 1971)) and the callosal areas were weakly and positively correlated. Finally, when participants were further categorized by gender, the above-mentioned differences in callosal areas were only observed in males (there were no significant differences in callosal areas of females).

Similar handedness effects were observed in some later studies (Elster et al., 1990; Denenberg et al., 1991; Kertesz et al, 1993; Clarke and Zaidel, 1994; Moffat et al., 1998), and more recently, Westerhausen et al. (2004), using diffusion tensor MRI, found that fiber density may be greater in left handers than in right handers. While other researchers (Nasrallah et al., 1986; Kertesz et al., 1987; O'Kusky et al., 1988; Reinarz et al., 1988; Steinmetz et al., 1992, 1995; Jäncke et al, 1997) failed to observe handedness related differences in callosal area. Though the results are ambiguous, it is worth noting that participants' handedness was assessed based on hand preference (i.e. questionnaires) in the studies for which handedness and corpus callosum size were correlated. But handedness related differences were never observed when handedness was assessed using performance measures (e.g. tapping test).

It should also be noted that *absolute* callosal areas were generally larger for males than females in post mortem and MRI studies (see reviews by Dreisen (1995) and Bishop (1997)) and that gender accounted for a minute amount (1-2%) of variation in callosal size (Westerhausen et al., 2004). This gender effect is most often overlooked as it disappears (Bishop, 1997; Fling et al., 2011a, 2011b) or is reversed (Dreisen, 1995; Clarke et al., 1993; Clarke & Zaidel, 1994) once callosal area measurements are adjusted/normalized based on male-female differences in overall brain area (i.e. callosal area measured as a percent of total brain/intracranial area).

Why are the observed differences in callosal area across males/females and right/left handers important? Witelson (1989) was among the first to propose that a larger corpus callosum area was equivalent to greater interhemispheric connectivity which in turn corresponds to increased ambilaterality (i.e. excitatory model of corpus callosum). While this view is widely quoted, the assumption that callosal area is a good indicator of the strength of interhemispheric communication is unproven.

Clarke and colleagues (Clarke et al., 1993; Clarke & Zaidel, 1994) have put forward an alternate hypothesis. They compared the dichotic listening performance and callosal area (using MRI) of 60 healthy right and left handed males and females (all groups being equally represented) and 4 patients with forebrain commissurotomy. The latter participants' dichotic listening performances confirmed that callosal pathways were used when recounting left ear auditory input. But, neither laterality nor *left* ear listening performance (requiring cross-callosal communication) was related to callosal size. In contrast, the participants' reporting accuracy of the *right* ear auditory input decreased with increasing callosum area and consistent right handers performed significantly better than mix handers, with consistent left handers' performances somewhere between the two.

With regard to the size of the corpus callosum - the callosum body width and isthmus areas were not significantly different between consistent right handers and left handers (latter includes mixed and consistent left handers). However, these areas were significantly larger in females as compared to males. Further, the isthmus area (expressed as a percent of the callosal area) of consistent right handed females was larger than that of consistent right handed males (replicating Witelson's (1985) results). Also, while there were no differences between the callosal areas of consistent right handed and mix handed females, the callosal areas of consistent right handed males were smaller than that of their mixed handed counterparts.

Since *left* ear performance depended on cross-callosal sensory transfer, Clarke and colleagues (1993, 1994) posited that corpus callosum size may not be a good indicator of interhemispheric transfer of sensory information. Instead they suggested that corpus callosum morphology may be related to the "higher-order associative functions of the corpus callosum" i.e. gives an indication of interhemispheric inhibitory-facilitatory control. They also pointed out that if there is an allometric relationship between callosal morphology and behavioral patterns, this relationship may vary across gender and handedness subgroups.

Jäncke and Steinmetz (2003) failed to replicate Clarke and colleagues' results and dismissed their functional interpretation of the callosal size – excitatory/inhibitory association. They instead hypothesized that normalized corpus callosum size was larger in participants with smaller brains irrespective of gender, so what was previously interpreted as a gender effect was a reflection of the fact that females typically have smaller (volume) brains. This parallels Ringo and colleagues' (1991, 1994) theory that larger brains would be more lateralized than smaller brains. Despite this, like Clarke and colleagues, Jäncke and Steinmetz suggested that the callosal morphology – behavioral relationship may differ even if the difference was across brain size differentiated individuals as opposed to gender differentiated individuals. The fact that the midsagittal area of the corpus callosum is neither correlated with callosal fiber density (Aboitz et al., 1992) nor with number of axons (Lamantia & Rakic, 1990) further confuses the issue.

Differences in Cerebellum

Most scientists agree that the cerebellum is more than the brain's coordination center (Marr, 1969; Black et al., 1990; Seitz et al., 1994; Kim et al., 1994; Raichle et al., 1994; Fiez et al., 1996; Gao et al., 1996; Kleim et al., 1997; Holcomb et al., 1998; Mauk et al., 1998; Schmahmann & Sherman, 1998; Thach, 1998; Timmann et al., 2002, Bernard et al., 2012). It is now thought to be involved in motor learning and cognitive functions such as planning and error detection. But the cerebellum's involvement in the control of finger movements and sensory acquisition and discrimination (Gao et al., 1996) are what makes its morphology very relevant to this research. Raz et al (1998) conducted an in vivo MRI study of 1155 right handed participants (685 women) between 27 – 87 years of age to measure cerebellar volume. They found that the intracranial area adjusted cerebellar volume was greater for men than women. In keeping with those results, Filippi et al. (2013) found that gray matter volume in the left vermis of the cerebellum (area of cerebellum thought to be associated with maintaining posture) was greater for males than females. Raz and colleagues (1998) also found that right cerebellar volume was greater than left cerebellar volume.

The observed gender asymmetry was replicated in studies by Escalona and colleagues (1991) and Raz and colleagues (2001) on adult participants; and in studies of children between 4-18 years old (Gied et al., 1996; Reiss et al., 1996; Lawson et al., 2000). However, left-right cerebellar volume differences were not reported in these studies. Szabó et al. (2003), studied a much smaller cohort of 20 right handers (n = 11 females, consistently used right hand for 8 – 10 out of 10 possible tasks, mode = 10) and 14 left handers (n = 8 females, consistently used left hand for 0 - 4.9 out of 10 possible tasks, mode = 1). While they did not indicate any gender differences in cerebellar volume, they did find that on average the cerebellar volume (normalized to total intracranial volume) was significantly greater in the left hemisphere than in the right. This leftward asymmetry was observed for 65% of the right handed participants, and 36% of the left handed participants.

OVERVIEW OF METHODOLOGY: MATCHING PARADIGMS, USE OF VIBRATION

In this research study, the asymmetries in upper limb movement and force production were investigated. Three matching paradigms have been used: ipsilateral remembered (IR), contralateral remembered (CR), and contralateral concurrent (CC). In the ipsilateral remembered condition, the reference movement, position or force is produced by either the left or right hand, and then matched with the same (ipsilateral) hand. In the contralateral remembered condition, the reference is produced by either the left or right hand, and then matched with the opposite (contralateral) hand. And finally, in the contralateral concurrent condition, the reference and the matching force, position, or movement are produced simultaneously. Both the ipsilateral remembered and contralateral remembered conditions require the use of working memory to reproduce the reference; however the contralateral condition also requires the transfer of information between hemispheres. The contralateral concurrent condition also requires the interhemispheric transfer of information, but differs from the contralateral remembered condition as it is considered a bimanual task since both arms are working simultaneously.

In addition to the matching conditions, vibration was used to (1) induce an illusion of movement in the reference hand during the investigation of upper limb asymmetries in movement sense (chapter 2), and (2) distort the sensory information from the associated muscles during the second sense of effort study (chapter 4). The use of vibration is particularly suited to these applications as, briefly, vibration-induced activity of muscle spindles change the gain of peripheral reflex loops (Martin et al., 1984; Martin et al., 1986; Martin & Park, 1997; Park & Martin, 1993), alters movement control (Gauthier et al., 1983; Martin et al., 1991) and perception (Goodwin et al., 1972; Lackner, 1984), and gives rise to movement and/or postural illusions (Calvin-Figuiere et al., 2000; Goodwin et al., 1972; Lackner & Levine, 1979; Redon et al., 1994; Roll & Vedel, 1982; Roll et al., 2009). Further, the speed of the illusionary movement produced is positively correlated with the frequency (with a maximum perceived velocity achieved at around 100 Hz (Roll and Vedel, 1982) and amplitude of the vibratory motion (Clark et. al, 1979). This combined with the fact that vibration can supplant the "natural" messages generated by movements (Ribot-Ciscar et al., 1996; Roll et al., 1989), has made its use in this context highly relevant as indicated by the use of vibration. Previous studies have used vibration to investigate the relative contributions of neural regions to kinesthesia and sensorimotor control (e.g. Naito et al., 1999; Romaiguere et al. 2003; Izumizaki et al., 2010).

SUMMARY

One of the goals of this chapter was to review the relevant handedness and gender related morphological and neurophysiological differences that may be associated with the behavioral and motor output asymmetries of our two hands. While, many of these differences have been discussed, the variability in the outcome of the studies referenced is readily apparent. These inconsistencies may be partially attributed to methodological differences such as the: classification of handedness, brain imaging technique or stimulation parameters used, cohort size, and lack of attention to individual factors.

In brain imaging studies, Fling et al. (2013) noted the possible effects of differing parsing techniques and stimulation settings while Triggs et al (1999) discussed the impact of the number of stimulation sites, and the precision/limitations of the equipment used. Also, few studies have rigorously controlled variables that may confound brain morphology and function such as age (Murphy et al., 1996, Fling et al 2011, 2012; Bernard & Seidler, 2012; Adamo et al., 2007; Mahmood et al., 2009, Luders & Toga, 2010), IQ (Andreasen et al., 1993), gender (Biswal et al., 2010) and sample size (Biswal et al., 2010; Amunts et al, 2000; Schlesselman, 1974). And finally handedness - given the relative scarcity of left handers, most studies have either focused exclusively on right handers or lumped all inconsistent right handers together, or failed to completely assess handedness (whether right or left handed) which, when investigating asymmetry/lateralization, limit both the interpretation and application of their results (Peters, 1992; Foundas et al., 1998; Adamo & Taufiq, 2011; Beaton, 2003).

Despite all this, there are two lingering perceptions concerning laterality - (1) females, and (2) left handers are less lateralized. But are these assumptions well supported?

(1) Females are less lateralized than males

Quite a few studies promote the idea that the male brain is more asymmetrical/lateralized. For example, cortical areas (Sowell et al., 2007), cerebellar hemispheres (Witelson, 1985; 1989; Raz et al., 1998, 2001; Filippi et al., 2013) and intracranial tissue volume (Nopoulos et. al, 2000; Filipek et al., 1994) are larger; and neuronal density (Rabinowicz et al. 1999), number of neurons (Stark et al., 2007) and synaptic density are higher in males than females. Further, while the gray matter volume is greater in the left than right hemisphere for males, the left and right gray matter volumes are equivalent in females (Gur et al., 1999). The depth of the central sulcus was larger on the side contralateral to the dominant hand in males, while this difference was not observed in females (Amunts et al., 2000). And finally, the relative area of the corpus callosum (or parts of the corpus callosum e.g. isthmus comprising intracallosal fibers from M1 associated with the control of the upper limbs), thought to facilitate interhemispheric communication and coordination, is larger in females (Witelson et al., 1985, 1989; Clarke et al., 1993; Clarke & Zaidel, 1994; Steinmetz et al., 1992); while the white matter (thought to facilitate information transfer) is greater in males. Combined, they suggest that females have a greater capacity for communication and coordination between hemispheres despite having less neural circuitry (volume), and less interhemispheric differences to accommodate. While males appear to have a greater capacity for intrahemispheric communication (Filipek et al., 1994; Gur et al., 1999; Passe et al., 1997). Further the fact that these neurophysiological male advantages do not necessarily result in corresponding cognitive and physical advantages, would suggest that females may make more efficient use of both hemispheres (Ringo et al., 1991, 1994). And as such, are less lateralized.

Alternatively, females and males may be equally but differently lateralized i.e. differences in some neural structures may be compensated for in other brain and physical areas (Chiarello et al., 2009). While neural structures were larger in males, cortical thickness was greater in all four lobes for females (Luders et al., 2006; Im et al., 2006; Sowell et al., 2007). And while overall tissue volume was greater in males, the distribution of gray and white matter is also interesting – corrected volume of gray matter (facilitates computation) was larger in females (Schlaepfer et al., 1995; Gur et. al, 1999) while volume of white matter (communication) was found to be larger in males (Filipek et al., 1994; Gur et al., 1999; Passe et al., 1997). Functional connectivity in frontal and cerebellar regions was also larger for females (Allen et al., 2011; Filippi et al., 2013) despite the size advantage reported for males. Further, the normalized clustering coefficient (measure of degree to which nodes in the resting state networks tend to cluster together) was greater in the left hemisphere for females, and in the right hemisphere for males (Tian et al., 2011). And finally, females tend to exhibit larger grip strength differences than males (Petersen et al., 1989), and are less likely to have a stronger non-dominant hand (Mathiowetz et al., 1985; Petersen et al., 1989, Peters, 1992).

And finally, many studies have failed to find significant gender related hemispheric differences (e.g. Foundas et al., 1999; Luders et al., 2006; Fling et al., 2011; Fling et al., 2012). But as Biswal and colleagues (2010) have demonstrated, the effect of gender may be very small compared to other confounding characteristics (specifically age and handedness) and may only be observed in large samples if individual characteristics are not well controlled.

(2) Right handers are more asymmetrical than left and mix handers

While many left-right hemispheric anatomical and functional differences have been detailed above (e.g. Honda, 1982; Sainburg et al., 2000; Sainburg & Bagesteiro, 2003), researchers were predominantly focused on right handers. However, some of the right-handed/left-handed comparison studies that were conducted may suggest that left handed individuals are generally less lateralized than right-handers (McManus, 1995). Support for this comes from the observation of greater bilateral activation in the motor and sensorimotor cortices of non-right handers when performing uni-manual tasks (Seibner et al., 2002; Kim et al., 1993); and more bilateral motor cortical representation (Bernard et al., 2011). Differences in central sulcus depth were less (Amunts et al., 1996) or non-existent (Foundas et al. (1998) in left handers. While Szabó et al. (2003) noted that left handers were less likely to have hemispheric differences in cerebellar volume (36% left handers compared to 65 % in right handers with cerebellar differences). Finally, corpus callosal area was larger (Witelson, 1985, Habib et al., 1991) and fiber density of corpus callosum (Westerhausen et al., 2004) greater in left handers.

However, Beaton (2003) suggested that the premise that left handers are less lateralized than their right handers counterparts may be due to sampling error. Since less than 10% population is left handed, he posited that researchers accepted a more homogeneous/variable spread of left handers. This was found to be the case in Petersen et al.'s (1989) grip strength study where, for left-handed participants, the dominant or non-dominant hand was equally likely to be the stronger of the pair. This parallels van den Berg et al.'s (2011) observation that left handers may be categorized into two groups based on their ipsilateral motor activity. Further, Bernard et al. (2011) found that the less lateralized (based on dexterity) had the shortest interhemispheric transfer time, while this time increased as degree of left/right lateralization increased. And finally, the frontal lobe ipsilateral to the dominant hand was the larger of the two frontal lobes in both left and right handers (Kertesz et al., 1990; Bear et al., 1986), suggesting a mirrored asymmetry between the two handedness groups.

So, while it is clear that there are gender and handedness related differences in brain morphology and function, the effects of these differences are difficult to determine especially since gender is seldom considered in upper limb behavioral studies. This research attempts to address this lack by considering these individual differences while investigating upper limb motor performance (i.e. sense of effort and movement sense).

THEORETICAL FRAMEWORK AND GENERAL HYPOTHESES

Gender differences have been investigated; however few studies considered gender effects in motor performances. A combination of hemisphere dimorphisms present in the sensory and motor cortical areas of both genders and hemisphere distribution of information processing specific to each gender have been noted. Several studies have reported that the normalized volume of cerebra, cortical areas, cerebellar hemispheres, neuronal density and synaptic density are larger/higher in men while the corpus callosum (connective structure between hemispheres) is (whether directly or indirectly as a function of brain size) larger in females.

In terms of handedness related differences, several researchers have found that handedness is associated with differences in the cortical motor representation in left and right handed subjects. Differences in the spinal-motor systems of the preferred and non-preferred arms have also been investigated and multiple hypotheses of motor lateralization proposed: motor dominance, open-loop/closed-loop hypotheses and dynamic dominance. Of the three, the latter two have been reconciled such that the dominant arm/hemisphere is thought to specialize in the feedforward control of limb dynamics and the non-dominant arm/hemisphere specializes in the position/static aspects of action and may preferentially use a feedback mode of control.

However, the dynamic or static aspect of control is primarily associated with a mode of control, which may not fully explain asymmetry in performance since differences in sensory and motor systems do exist. For example, differences between the two hemispheres have been shown for the sensory and motor cortical areas. Specifically, cortical representations were found to be larger for the dominant hand than the non-dominant hand in right handers.

As such, it is hypothesized that these differences in representation may confer a different gain (input-output relationship) to each sensory or motor system (Adamo & Martin, 2009, Adamo et al. 2012)*;* which in turn induces upper limb asymmetries in motor performances. Hence, beside differences in specialization, asymmetries may also be expressed as a function of the motor component gain and the sensory component gain of the upper limb systems. Both gender and handedness may influence these gains and the way in which the information (sensory or motor) is centrally represented. The gain expresses the functional aspects of physiological and morphological differences, as illustrated in Figure 1.

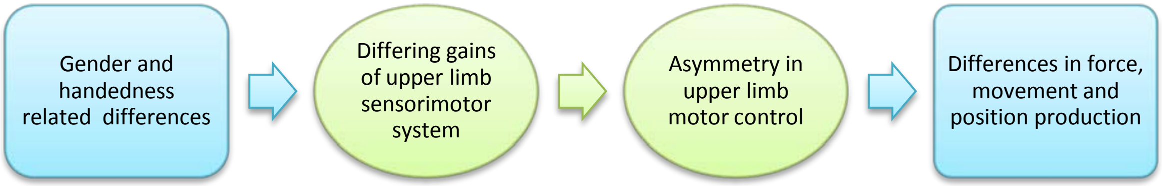

Fig. 1.1: Theoretical Framework

General Hypotheses

Chapter 2 addresses asymmetry in movement sense and more particularly the role of the sensory component in the asymmetry of left and right sensory-motor systems. The aim of this first study was to investigate the effects of handedness and gender on the reproduction of vibration induced movement illusions. In this context, vibration provided a kinesthetic reference based uniquely on proprioceptive information. Given (1) that motor dominance, dynamic dominance (Sainburg, 2002; Bagesteiro & Sainburg, 2003) and open-loop/closed-loop theories suggest that the preferred/non-preferred hand may use proprioceptive/kinesthetic information differently, (2) the asymmetrical representation of hand movement in the motor cortex (e.g. volume of activation of preferred hand greater for the non-preferred hand) in both left and right handers (Kim et al, 2003; Dassonville et al., 2007), and (3) gender and handedness related differences in the somatosensory cortex (Zappasodi et al., 2006); then

H 1.1: Both gender and handedness affect movement representation and thus movement reproduction.

However, this asymmetry may be mediated by gender related interhemispheric exchange differences since contralateral speed reproduction requires interhemispheric transfer. If interhemispheric communication is greater in females than males then

H 1.2: Asymmetry in movement reproduction is more pronounced in males than females.

Chapter 3 addresses the asymmetry in the sense of effort and more specifically the contribution of the motor component to the asymmetry of left and right sensory-motor systems. The aim of this study was to investigate asymmetries in the perception and reproduction of grasp force. Considering that 1) the strongest hand is not necessarily the dominant hand (Incel et al., 2002; Petersen et al., 1989), 2) the dominant motor hemisphere is associated with the preferred hand in right handers but not in left handers (e.g. van den Berg et al., 2011), 3) the use of the preferred/non-preferred hand to establish the reference may affect the direction (overestimation/underestimation) of the matching error in the contralateral condition due to the difference in the sensorimotor gain of each hand/hemisphere system (Adamo & Martin 2009), again resulting from the morphological and functional hemispheric differences detailed above; then

H 2: Asymmetry in force reproduction varies with hand strength differences and is also mediated by the complex interaction of the morphological and functional differences.

Chapter 4 addresses the relative contributions of efferent copy and sensory feedback to the sense of effort and the association of visual or non-visual force information with the perception of effort. The aims of this study were 1) to determine the extent to which muscle proprioceptive feedback contributes to the sense of effort and whether this sensory component contributes to asymmetry in the sense of effort and 2) to determine whether force matching asymmetry in influenced by the way in which force perception is established (visually vs. non-visually). Vibration is known to distort the sensory information mediated by mechanoreceptors (Roll et al., 1989). In addition, past studies using grasp-force matching paradigms have suggested that force perception is based on a sense of effort derived from the efferent copy of the associated motor command (Carson et al, 2002), but peripheral/sensory information is thought to be necessary for force modulation (Johansson and Cole, 1992) and perception of effort as well (Luu et al. 2011). Then

H 3.1: If the sense of effort includes muscle proprioceptive feedback then force matching asymmetry is modulated by vibration-induced alteration of sensory feedback.

H 3.2: Visual feedback of the reference force, which represents the total outcome of the force generating system, may not be associated (by the participants) with the internal representation of effort.

Finally, chapter 5 integrates the results of these three studies in a general discussion.

CHAPTER 2

UPPER LIMB KINESTHETIC ASYMMETRIES: GENDER AND HANDEDNESS EFFECTS

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Neuroscience Letters, May 2012, Volume 516, Issue 2, pp 188-192

ABSTRACT

Proprioceptive and motor information contribute to movement representation; however, the equivalence of homologous contralateral sensorimotor processes as a function of gender and handedness has received little attention. The present work investigated asymmetry in contralateral reproductions of movements elicited by tendon vibration in right and left handed young adults of both genders. With eyes closed, illusions of elbow flexion movement elicited by a 100 Hz vibration applied to the distal tendon of the right or left triceps muscle were matched concurrently with the opposite limb. Overall, movement velocity was larger for females than males, asymmetric and handedness dependent in males. Conversely, consistent symmetry was found between left and right-handed females. These findings lead us to suggest that hand preference and gender contribute to differences in movement representation that may result from the combination of cortical structural differences and information processing specific to each hemisphere and gender.

INTRODUCTION

[5]Sensory messages from muscle spindles contribute to movement sense / kinesthesia (Proske, 2006; Roll et al., 1989), as demonstrated by vibration-induced alteration of position sense (Goodwin et al., 1972), movement control (Martin et al., 1991), and movement illusions

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[5] *Abbreviations*: RH, right handed; LH, left handed; RVLM, right vibration left match; LVRM, left vibration right match

(Goodwin et al, 1972; Roll et al., 1989). Furthermore, movement speed perception, derived from these receptors, is frequency dependent, as shown by microneurography (Roll & Vedel, 1982) and vibration-induced illusory movements (Jones, 1988; Roll & Vedel, 1982). However, the equivalence of illusory (or real) movement speed and thus movement representations between the right and left upper limb systems or between genders has not been questioned. A number of factors lead to the supposition that movement sense may be asymmetric and different for men and women.

Limb/hemisphere differences in movement sense may be due to intrinsic (anatomical and neurophysiological properties) and extrinsic (perturbations such as fatigue or vibration) factors. Position control asymmetry resulting from intrinsic factors has been observed in unperturbed matching conditions (Adamo & Martin, 2009; Goble & Brown, 2009; Worringham & Stelmach, 1985). Likewise, extrinsic position control asymmetry may be induced by muscle fatigue (Allen et al., 2007), vibration Goodwin et al., 1972, White & Proske, 2009), or conditioning (Allen et al, 2007, White & Proske, 2009).

A model-based demonstration showed that intrinsic position sense asymmetry resulted from a difference in the *gain* (magnitude) of the input-output relationship of each sensorimotor system (Adamo & Martin, 2009). The overall *gain* of a system is the product of all elements, which includes sensory and motor components. The *difference in gain* concept provides a unified interpretation of position sense asymmetries of intrinsic or induced origins and is applicable to movement sense (Martin & Adamo, 2011) and sense of effort (Adamo et al., 2012) asymmetries. Furthermore, extrinsic factors such as vibration, muscle fatigue or muscle conditioning manipulations show that the relative contribution of motor and sensory processes to induced gain inequalities may be context dependent (Allen et al, 2007, Goodwin et al., 1972). These latter results also confirm that equivalence in movement perception reveals an asymmetry and adaptability of sensorimotor gains. They are also congruent with sensory gain adaptations associated with functional adjustments in perceptual acuity (Jones & Burgess, 1998) and sensory re-weighting (Jeka et al., 2008). Hence, the concept of gain appears to formalize the analysis of the components of a system and help define more specifically the possible origin(s) of kinesthetic asymmetries.

Further, it is assumed that functional differences associated with behavioral asymmetries likely reflect differences between homologous cortico-spinal structures (e.g. (Triggs et al, 1999)). Functional asymmetry of hand movement representation in the motor cortex has been illustrated by a volume of activation in the primary motor cortex larger for the preferred than the non-preferred hand/hemisphere system in both left- (LH) and right-handed (RH) males (Kawashima et al., 1997, Volkmann et al., 1998). Somatosensory evoked potentials in response to median nerve stimulation show asymmetries associated with hand dominance and gender (Zappasodi et al., 2006). Further, hand preference has been associated with hemispheric specialization for processing movement related information (e.g. (Sainburg, 2005)), as well as structural (Amunts et al., 2000, (Kawashima et al., 1997, Kim et al., 1993) and functional (Kawashima et al., 1997, Kim et al., 1993) cortical asymmetries. In addition, vibration-induced activity of proprioceptive afferents evokes activation in limb specific cortical areas (Romaigiuere et al., 2003) and the ipsilateral cerebellum (Johnson & Ebner, 2000, Naito et al., 1999). These findings, obtained in RH individuals, indicate that movement kinematics are processed in multiple regions, which may be assumed to contribute to the integration of perception and thus to differences in perception.

Taken together, these findings suggest that hand preference and gender are associated with regional differences in sensory and motor cortical activation, as well as structural and functional cortical differences. Yet, the effect of these factors on sensorimotor relationships governing movements is largely unknown. It is hypothesized that perception associated with vibration-induced movement illusions will differ as a function of gender and handedness. Differences in sensorimotor relationships are presumed to reflect differences in movement representations, which should be translated in the reproduction of movement illusions. To test the influence of these factors on upper limb/hemisphere systems, contralateral matching of concurrent vibration-induced elbow flexion illusions, where both the right and left forearms provided the sensory reference to be matched with the opposite arm, were compared in LH and RH males and females. This methodology presents the advantage of providing a kinesthetic reference based uniquely on proprioceptive information.

METHODS

Participants

Two groups of young adults participated in the study: eighteen RH (9 Females + 9 Males; age: 24.6 ± 4.5 years) and eighteen LH (9 Females + 9 Males; age: 24.8± 3.7 years). Inclusion was based on their perception of movement illusion, as detailed below. Hand Laterality Indices (LI) for RH ($LI_{female} = .83$, $LI_{male} = .81$) and LH ($LI_{female} = -.79$, $LI_{male} = -.59$) were not significantly different between males and females of each group ($p > 0.1$). All participants were free from any disorders and signed an informed consent form approved by the Ethic Committees at both universities.

Experimental Set-up

Participants were seated with the forearms and hands supported by horizontal levers free to pivot around a vertical axis (see Fig. 2.1) (Adamo & Martin, 2009). The lever positions were adjusted to obtain a standardized symmetric posture corresponding to 60° shoulder abduction, 30° shoulder flexion and 120° elbow flexion. The elbow joint center of rotation coincided with the rotation axis of each lever. The forearms were pronated and less than 2%MVC was necessary to produce arm movements. A vibration frequency of 100 Hz with a 40-100 μm amplitude was delivered through a polycarbonate probe (2 x 15 mm rounded edge) mounted on a vibrator (LDS® V203) driven by a power amplifier connected to a waveform generator. Vibration was perpendicular to the triceps muscle distal tendon. The location of probe contact with the skin was marked to ensure accurate repositioning. Pre-amplified surface electrodes placed on the belly of biceps and triceps muscles in each arm monitored their activity to verify the absence of TVR/AVR that could interfere with movement illusion. RMS EMG signals, displayed on an oscilloscope, were monitored to ensure relaxation before vibration and to detect tonic reflex contractions during vibration. When a tonic contraction developed during a trial, rest was provided and the trial was replaced. Minor muscle contractions were neglected.

Experimental Procedure

Participants were encouraged to remain relaxed in order to enhance illusory movement perception. Prior to the experiment, two practice trials were performed to determine participant's sensitivity to vibration in eliciting movement illusion. With eyes closed, the perceived speed of the vibration-induced illusory movement elicited in the reference arm was reproduced with the opposite arm. “Matching the velocity of the illusory movement” was explicitly requested. If vibration did not induce an illusion during practice trials, the participant was excluded from further testing (e.g. (33)). Four individuals, not included in the 36 participants, were excluded from the study. Vibration was applied for 10 s.

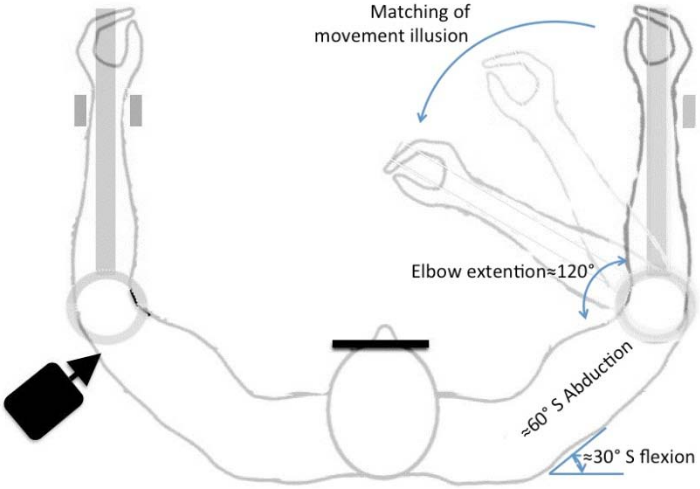

Fig. 2.1: Experimental set-up. Participants seated with forearms and hands supported by horizontal levers free to pivot around vertical axis. Elbow joint center of rotation coincided with rotation axis of each lever. Forearms pronated and less than 2% MVC necessary to produce arm movements. Vibration, at a frequency of 100 Hz delivered through a polycarbonate probe (2 x 15 mm rounded edge) mounted on a vibrator (LDS® V203) driven by a power amplifier connected to a waveform generator, applied perpendicular to the triceps muscle distal tendon.

The reference arm lever was clamped to prevent displacement during movement illusion. The matching arm was free to rotate in the direction of flexion. During 15 s rest breaks provided between trials, participants were encouraged to open their eyes and “shake out” their hands or produce isometric contractions in order to dissipate any residual post vibration effects (6), reset muscle proprioception and minimize muscle thixotropy (28, 35). Two practice trials were followed by five test trials. The experimental conditions were randomized.

Precision potentiometers coupled to the shaft of each lever encoded elbow rotations. The matching side signal was digitized at 1000Hz and low pass filtered at 6Hz with a fourth order Butterworth filter. A custom-designed LabVIEW™ software was used for data processing. Position and velocity profiles were presented on a chart display. Two vertical cursors were shifted along the time axis to capture the sections of the recording corresponding to the illusory movement reproduction. The slope of each section ($\Delta_{position}/\Delta t$) was determined by a least square linear fit to the selected data and the corresponding fitted line segment was displayed in real time to facilitate cursor adjustments and thus the superposition of the computed slope line with the movement trajectory (Fig. 2.2). Hence, eventual periods corresponding to zero velocity (no movement most likely due to a temporary fading of illusion) were eliminated from the velocity computation. The average of the velocity over all "movement" segments of each trial (1-2 in large majority of trials) was used as the trial perceived velocity.

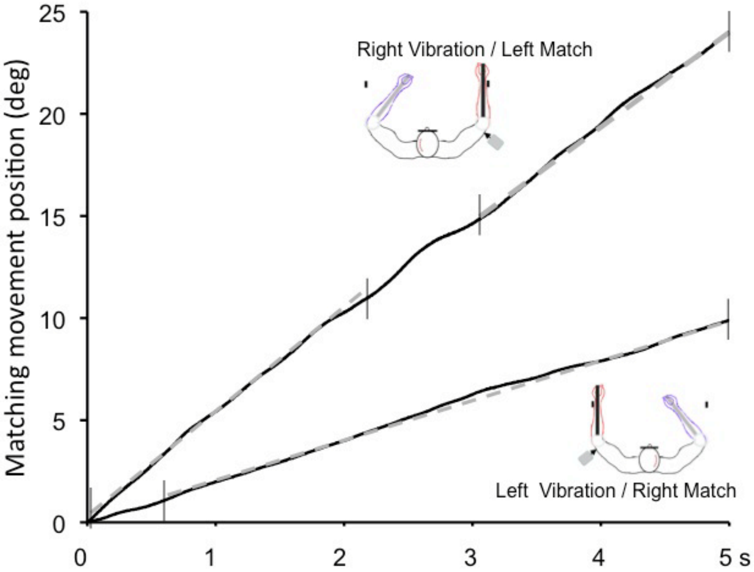

Fig. 2.2: Typical examples of matching movements for LH and RH males. Two vertical cursors were shifted along the time axis to capture the sections corresponding to the reproduction of the movement perception elicited by vibration. The movement velocity was determined by the average of the slopes ($\Delta_{position}/\Delta t$) for each section. Inset drawings represent the experimental conditions and subject standardized symmetric posture. The support of the vibrated arm is immobilized while the contralateral support is free to move.

The analysis was stratified to clearly interpret the results. First a three-way repeated measure ANOVA was used to test high order interactions and compare handedness influences using Tukey HSD post-hoc tests. Since the three-way interaction was significant, then 2 two-way ANOVAs, each based on a linear mixed model, were conducted respectively to test for each group (RH, LH) the main fixed effects of gender, matching arm, and interaction effects for the velocity of matching movements. To determine which factors influenced interaction effects, Tukey HSD post-hoc tests were conducted.

RESULTS

The three-way ANOVA indicated significant interactions for gender x dominant hand ($F_{(1, 46)}$= 5.5, $p = 0.02$), matching hand x dominant hand ($F_{(1, 323)} = 18.4$, $p < .0001$) and dominant hand x gender x matching hand ($F_{(1, 323)} = 9.39$, $p = .002$). Post hoc multiple comparisons showed that the difference in velocity reproduced with the respective dominant hand when movement illusion was elicited in the non-dominant limb was not significant between right- and left-handed males ($p > 0.05$). Similarly, the difference in velocity reproduced with the respective non-dominant hand when movement illusion was elicited in the dominant limb was not significant between RH and LH males ($p > 0.05$).

In RH participants, the two-way ANOVA indicated a “gender x matching arm” interaction effect ($F_{(1, 161)} = 14.6$, $p = 0.0002$) showing a significant asymmetry in velocity matching for male participants only ($p < 0.05$). For males, left arm velocity matching was on average 38 % greater than right arm velocity matching while in females right and left arm matching velocities were similar showing a 7% non-significant difference (Fig. 2.3). In addition, for the left match right vibration condition, matching movement velocity was significantly higher for females than males ($p < 0.05$).

In LH participants, the two-way ANOVA indicated a “gender x matching arm” interaction effect ($F_{(1, 162)} = 5.5$, $p = 0.02$) showing a significant asymmetry in velocity matching for male participants only ($p < 0.05$). For males, right arm velocity matching was on average 58 % greater than left arm velocity matching while in females right and left arm matching velocities were similar showing a 1% non-significant difference (Fig. 2.4). In addition, matching movement velocities were significantly higher for females than males in both conditions ($p < 0.05$).

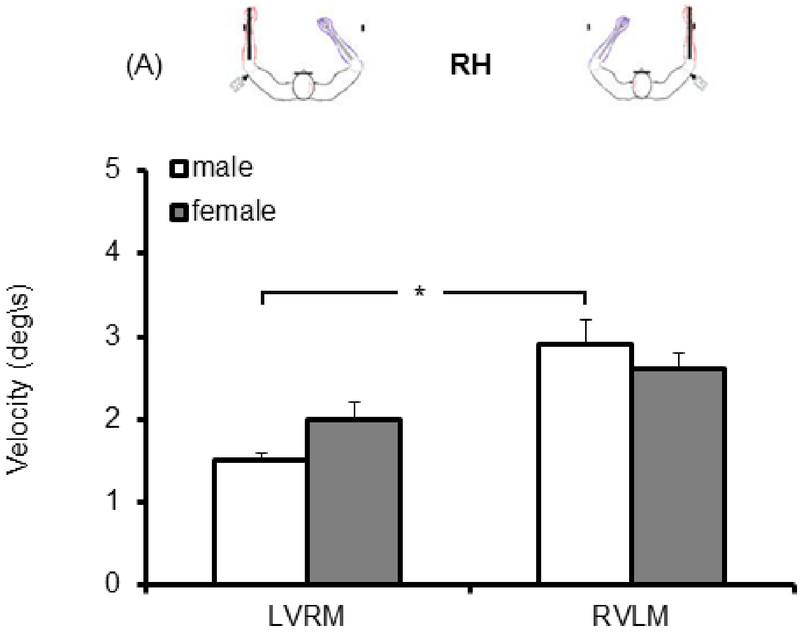

Fig. 2.3: Matching velocity for right handed. Mean (+ SE) matching velocity for males (□) and females (■) in the left vibration right match (LVRM) and right vibration left match (RVLM) conditions. Asymmetry is significant for males only. * P < .05. I Inset drawings correspond to experimental conditions, as in fig. 2.2.

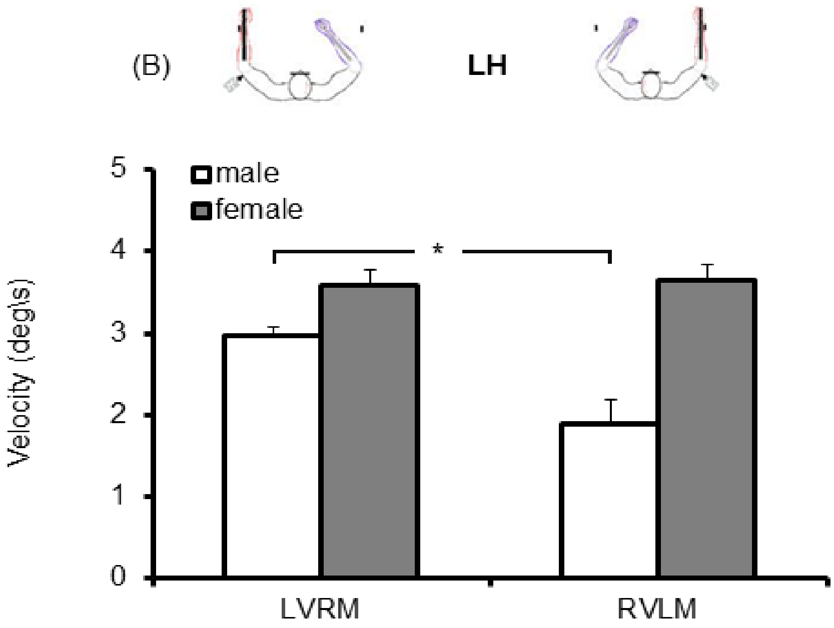

Fig. 2.4: Matching velocity for left handed. Mean (+ SE) matching velocity for males (□) and females (■) in the left vibration right match (LVRM) and right vibration left match (RVLM) conditions. Asymmetry is significant for males only. * *P* < .05. Inset drawings correspond to experimental conditions, as in fig. 2.2.

DISCUSSION

Movements made in response to vibration-induced illusions in RH and LH individuals were consistently asymmetric in males but not in females. For RH males, the reproduced velocity was greater for left than right hand matching of the contralateral reference and this asymmetry was reversed in direction but of similar magnitude for LH males. In addition, the velocity of matching movements was significantly higher for females than males except in the right match left vibration condition for RH individuals.

Gender differences related to sensorimotor gain and sensitivity

Asymmetry in matching movement velocity was significant in both male groups, and reversed between right- and left-handed males. Conversely, a consistent symmetry/ absence of asymmetry was observed for both female groups. The combination of cortical structural and physiological differences associated with gender specificities may contribute to differences in the representation of movement speed that may explain the present results. Several studies support that less hemisphere lateralization exists in females when compared to males. For example, the central sulcus in the region of cortical hand representation is significantly deeper in the left than right hemisphere in right-handed males, while no asymmetry is observed in females (Amunts et al., 2000). In addition, a relatively larger parietal association cortex found in men, (Gell et al., 2010) and stronger inter-hemispheric interactions associated with greater bilateral activation (see for review (Wisniewski, 1998)) mediated by a corpus callosum larger in size and in number of neurons in females (Rabinowicz et al., 2002) supports less lateralization in females. Furthermore, asymmetry and functional lateralization of visual and auditory areas are more pronounced in males than females (see for review (Hiscock et al., 1995)). Hence, for females, smaller and non-significant differences in gain between left and right sensorimotor systems reflected by less kinaesthetic asymmetries in both left and right-handed groups may be associated with less structural and /or less functional lateralization. Note that an equal magnitude of the sensory-motor relationships (gain) of the two systems produces equivalent outputs (movement velocities), while differences between the respective gains produce asymmetries (Adamo & martin, 2009, Adamo et al., 2012, Martin & Adamo, 2011).

Although it may difficult to clearly determine the origin of higher sensitivity in females than males, recent findings tend to substantiate this phenomenon. The modulation of the monosynaptic reflex excitability during bipedal locomotion is greater in females that males (Cheng et al., 2007). In addition, the activation of the primary motor cortex during hand action is higher for females than males and the peak amplitude of somatosensory evoked potential in response to median nerve stimulation is higher for females than males in the contralateral secondary somatosensory cortex.

Structural and functional asymmetries and sensorimotor behavior

Descriptions of structural and functional hemispheric differences in the somatosensory and motor cortex areas are somewhat conflicting but generally support that asymmetry is associated with handedness. Conflicting results seem to arise from both the methods used to evaluate asymmetries (fRMI, MEG, EEG, TES, TMS), and/or the delineation of the areas investigated (due to asymmetric somatotopic representations between hemispheres - (Jung et al., 2008)). Nevertheless, asymmetric cortical representations appear to be a predominant result, differ in left and right handed individuals and primarily involve the motor cortex corresponding to right or left hand preference (Sainburg, 2005). Some studies found a strong relationship between handedness and asymmetries in the motor cortex (Triggs et al., 1997, Volkmann et al., 1998) while others found that asymmetry was less pronounced in left than right-handers (Jung e al., 2003, Soros et al., 1999). Similar issues were observed when testing the somatosensory cortex. Tecchio et al. (1997) found that the size of hand sensory representation from thumb to little finger was similar in the two hemispheres, while Legon et al. (2010) found mirror asymmetric activation between the dominant and non-dominant hand in both LH and RH individuals.

Further, a proprioceptive interaction between the two arms may reduce the perceived speed of the illusory movement (Izumizaki et al., 2010). This “sensory-to-sensory” interference caused by concurrent matching, may be viewed as a modulation of the sensory gain but does not conflict with our interpretation. This rather supports the suggestion that non-equivalent sensory information between the right and left arm would produce a differential interference likely to reinforce the kinesthetic asymmetry observed when the reference and matching arm are inverted.

Overall, morphological and region specific activation differences, as well as interhemipheric interactions are likely to confer different gains to the left and right hand/hemisphere sensory-motor systems, which correspond to functional differences at the behavioral level.

The present results exhibit gender differences. One may assume that the often-suggested weaker lateralization in LH than RH individuals should have lead to a less pronounced asymmetry in the LH group. However, reversed asymmetries were also reported for other tasks (Goble et al., 2009; Triggs et al., 1997, Wang & Sainburg, 2006). Since symmetric performance was observed for females only, and a gender effect was not investigated in many other studies including both RH and LH participants then it may be assumed that more or less asymmetric performance in LH individuals could have reflected the proportion of male/females participants in these studies.

Taken together, asymmetry associated with hand preference in males and gender differences in sensitivity and proprioceptive interaction suggest an important role of sensory processes, and thus sensory gains, in the control of contralateral matching movement velocity. The gender specific kinesthetic asymmetries found in the present study reinforce our earlier suggestion that the source of information is a critical component when performing matching tasks (Adamo & Martin, 2009). Although the gain of the motor component (which should also reflect cortical and muscle strength asymmetries) cannot be ignored (Adamo et al., 2012), the lack of significant asymmetry in females indicates that its influence is relatively small in the present context since a very weak force was sufficient to produce a movement. This substantiates a difference in sensory gains and its relevance in the present context.

To conclude, our results show that movement representation and proprioceptive–based sensorimotor system gains are dependent on handedness and gender. They strongly advocate the consideration of gender in motor control studies, especially when comparing right and left handers.

CHAPTER 3

ASYMMETRY IN GRASP FORCE MATCHING AND SENSE OF EFFORT

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Experimental Brain Research, March 2012, Volume 217, Issue 2, pp 273-285

ABSTRACT

While asymmetries in upper limb force matching have been observed, the mechanisms underlying asymmetry in the sense of effort have not been conceptualized. The aim of this study was to investigate asymmetries in the perception and reproduction of grasp force. Forty-two young adults, 22 right-handed (RH) and 20 left-handed (LH), were, respectively, divided into three groups according to differences between their right and left-hand strength (left stronger than right, right stronger than left and right & left equivalent). A reference force, representing 20% of the maximal voluntary contraction (MVC) produced by the right or left hand, was matched with same hand (Ipsilateral Remembered—IR) or opposite (Contralateral Remembered—CR) hand. The matching relative error was 92% (for RH) and 46% (for LH) greater in the CR than IR condition. Asymmetries in matching were significant for RH participants only in the CR condition and were dependent on right/left differences in hand strength as shown by the constant error (CE). For this RH population, right-hand overshoot of the left-hand reference and left-hand undershoot of the right-hand reference were significant when the right hand was stronger than the left. Asymmetry remained significant when CE was normalized (%MVC). Asymmetry was reduced when the strength of each hand was equivalent or when the left hand was stronger than the right. These findings suggest that effort perception is asymmetric in RH but not in LH individuals. The hand x strength interaction indicates that asymmetry in force matching is a consequence of both a difference in the respective cortical representations and motor components, which confer a different "gain" (input–output

relationship) to each system. The similarity with position sense asymmetry suggests that the gain concept may be generalized to describe some functional/performance differences between the two hand/hemisphere systems. The more symmetrical performance of the LH than RH group underlines that context specific influence of handedness, hemisphere dominance and hemispheric interactions modulate performance symmetries/asymmetries.

INTRODUCTION

Force-matching tasks have been widely employed in an attempt to elucidate the relative contributions of central and peripheral components to force perception. Most studies agree that the ability to perceive force is centrally mediated and based on an efferent copy of the descending motor command that presumably reflects the effort required to generate force (McCloskey 1974; Gandevia & McCloskey 1977; Jones & Hunter 1982; Jones 1986; Carson et al. 2002; Lafargue & Sirigu 2006).

Support for a sense of effort has evolved from studies comparing the force generated when matching a fatigued limb with a non-fatigued limb (see Gandevia et al. 1995 for review). Under these circumstances, subjects generated non-equivalent forces despite their perception that equal forces were produced with both limbs. When matching with a fatigued limb, the perceived intensity of the required force needed to perform the match was greater such that the force generated in the fatigued limb was scaled relative to the force-generating capacity of the non-fatigued muscle. These findings, as demonstrated by Jones and Hunter (1982,1983) and others (McCloskey 1974; Cafarelli & Bigland-Ritchie 1979; Gandevia 1982), lend support to the hypothesis that alterations in force perception are based on a sense of effort derived from the efferent copy. In addition, as a result of a fatigue-induced overestimation of a reference force, Carson et al. (2002) hypothesized that the gain of the relationship between the motor command and the perception of effort is regulated by activity upstream of the motor cortex.

Although there is strong evidence to support a centrally derived sense of effort in force production tasks, the contribution of peripheral components mediating the perception of force must also be considered. At the periphery, Golgi tendon organs encode information about muscle tension (Crago et al. 1982; Jami 1992) that, in turn, is used to update the central commands

(McCloskey 1974). Muscle tension information used in conjunction with force-derived peripheral feedback from tactile receptors monitor small changes in force production needed to sustain steady-state force exertions (Johansson & Westling 1984; Johansson & Cole 1992). However, peripheral information, which may modulate the perception of effort when considering the influence of dynamic actions and fatigue (Gandevia & McCloskey 1977, Taylor & Gandevia 2008), does not appear necessary to generate a signal of effort since individuals deprived of afferent feedback can reproduce force accurately (Lafargue et al. 2003; Lafargue & Sirigu 2006). Additionally, effort perception is absent during upper limb hemiplegia (Gandevia 1982), and cutaneous feedback modifies perception in static/isometric conditions (Gandevia & McCloskey 1977). Each point supports, respectively, that the motor command is necessary, but cutaneous information is not necessary when performing isometric tasks. Taken together, these findings suggest that afferent information may be more strongly associated with calibrating and modulating the required force magnitude rather than contributing to the initial generation of force (Kilbreath et al. 1995; Toffin et al. 2003; Lafargue & Sirigu 2006) or sense of effort.

Force-matching paradigms have also been used to determine if force is matched on an absolute (Li 2006; Park et al. 2007, 2008) or relative (Carson et al. 2002; Jones 2003; Jones & Piateski 2006) scale. In terms of an absolute scale (Newton), contralateral force matching in non-homologous muscles showed that forces are overestimated when larger muscles match forces from smaller muscles. Conversely, forces are underestimated when smaller muscles match forces from larger muscles (Jones 2003). However, when differences in strength were scaled relative to each muscle's maximum force-generating capacity, the matching forces were similar. Further, absolute forces were matched accurately during homologous contralateral matching tasks (Jones 2003). In contrast to findings from Jones (2003), Park et al. (2008) showed that absolute matching forces were similar across fingers that varied in terms of individual maximum strength-generating capacity. According to these authors, centrally derived perceptions associated with individual finger forces within the same hand were necessary to assist with precise control needed to perform many functional tasks. Overall, the contribution of discerning differences in relative and absolute force-matching performances depends upon muscle groups tested, and whether force matching occurs in ipsilateral or contralateral conditions.

Although several force-matching studies have been conducted, only one (Park et al. 2008) compared the force-matching abilities when the reference force is generated from the dominant and non-dominant limb and matched with the same or opposite limb. Thus, knowledge about how force information from one hand/arm/hemisphere system is used as a function of the matching limb and differences between force/effort representations corresponding to the two hand systems are limited. Given that, the purpose of this study was to investigate differences in grasp force-matching performance in young, right-handed and left-handed healthy adults (RHs and LHs, respectively) under two conditions requiring reproduction of a grasp force established with the same (ipsilateral) or opposite (contralateral) hand.

It was hypothesized that matching errors would be greater and differ in direction (overestimation/underestimation) in the contralateral condition as a function of reference hand (right/left). Directional differences in matching errors found to result from a difference in the sensorimotor gain of each hand/hemisphere system (Adamo & Martin 2009) for a wrist-position-matching task support this proposition. In addition, a reversed asymmetry between RHs and LHs would support the hand dominance hypothesis, in which the dominant motor cortex is primarily involved in the control of both hand exertions.

However, the contribution of the left primary motor cortex (M1) to movement control regardless of hand dominance is well-established (Kim et al. 1993; Chen et al. 1997; van den Berg et al. 2011). Motor cortex activations and organization are more asymmetric in RHs than LHs (Kim et al. 1993; Singh et al. 1998; Verstynen et al. 2005). Further, TMS-induced movement alterations by stimulation of the left M1 are more variable in LHs than RHs as disruptions were more pronounced by stimulation of the left M1 for some LHs, while other LHs exhibited more disruptions when the right M1 was stimulated. In addition, disruption of the M1 area ipsilateral to a unimanual movement shows an interaction between hand dominance and hemisphere dominance in LHs (van den Berg et al. 2011). Hence, we hypothesized that asymmetry would be less pronounced in LHs than RHs due to an interaction between hemisphere dominance and hand dominance in the context of the proposed matching task.

Thus, the extent to which limb differences may exist in force-matching tasks were investigated to determine whether asymmetries were present, and to more clearly delineate the contribution of the motor component to matching performance. In addition, since the dominant hand is not necessarily the stronger hand (Incel et al. 2002; Petersen et al. 1989), the interaction between hand strength difference and hand preference was also investigated. Overall, the intent of this work was to the further understanding of the components associated with potential motor asymmetries including the perceptual basis of information/representation (force in the present case), transfer between the hemispheres (contralateral matching), the motor command and muscle strength.

METHODS

Participants

Twenty-two (17 females and 5 males, mean age: 26.2 ± 4.8 years) RH individuals with a mean laterality index of .83 ± .14 (range: .6–1) and twenty (11 females and 9 males, mean age: 23.4 ± 3.5 years) LH individuals with a mean laterality index of −0.65 ± 0.20 participated in the experiment. The laterality index of each participant was assessed using the Edinburgh Handedness Inventory (Oldfield 1971).

All participants were free from any upper limb neurological and musculo-skeletal conditions that might impair task performance. Exclusion criteria included a long-standing history of highly skilled motor activity such as dancing or playing a musical instrument. All participants were recruited from the local community and signed an informed consent form approved by the Human Investigations Committee at Wayne State University.

Experimental setup

Participants were comfortably seated at a table with shoulders slightly flexed and abducted, elbows flexed at 90 deg, forearms fully pronated and wrists positioned at 25–30 deg of extension. Seat height was adjusted to keep the forearms in the horizontal plane. The custom-designed grasp devices, composed of a split aluminum force transducer embedded with strain gauges and equipped on each side with semicircular wooden handles 4.0 cm in radius, 13 cm in length, were held horizontally by a coupling support fixed to the table, as illustrated in Fig. 1.

The device was positioned directly in front of the participant and allowed for adequate finger clearance. A power grip pattern was used to position the hand around the device, whereby the thumb was positioned under and digits (II–V) were positioned on top of the grasping device. The size of the grasp device (gap between semi-circular parts) was adjusted for each individual's hand size to ensure the distance between the fingers and thumb was constant across hands and participants.

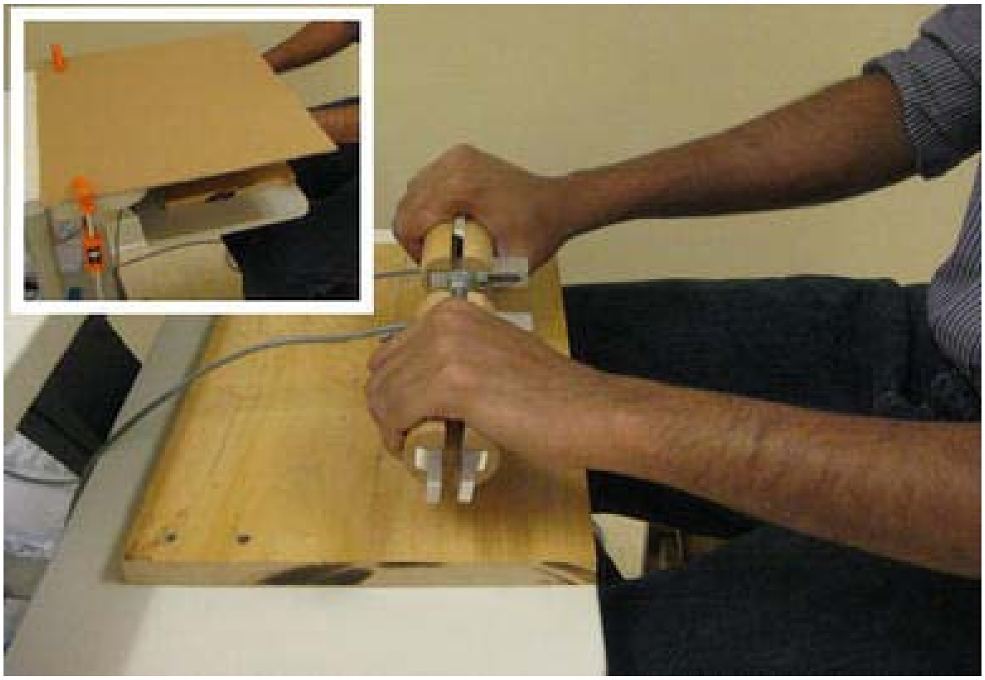


Fig. 3.1: Custom-designed grasp devices. They were composed of a split aluminum force transducer embedded with strain gauges and equipped on each side with semi-circular wooden handles (4.0 cm in radius, 13 cm in length). The grasp devices were held horizontally by a coupling support fixed to the table. *Insert* shows that the hands were masked during the experiment

Signals corresponding to participants' hand grasp forces were simultaneously displayed on vertical scales presented on a monitor to provide visual feedback to the experimenter only about the participant's performance. For each individual, each scale was calibrated to the respective 100% MVC, and a cursor indicated the 20% MVC reference force from which the experimenter was able to provide qualitative verbal feedback during the practice session, instructing them to increase or decrease their grip force exertion to reach the desired force output. Visual feedback was only available to the experimenter during the practice and test trials. For the duration of the experiment, an opaque screen masked the hands of the participant to encourage them to focus on the perception of effort associated with the grip exertion and to avoid any potential contribution visual information, such as monitoring the position of the hands on the devices, to matching performance (see insert Fig. 3.1). This procedure ensured that force perception was based on a “memory” of the reference force independent of visual information.

Experimental Procedure

Determination of maximal voluntary contraction

Prior to the experiment, maximum voluntary contractions (MVC) for each hand were measured with the hands placed on the devices in the testing posture. Instruction was given to increase force gradually over a 2-s period and then continue to exert the maximum grasp force for an additional 3 s. The MVC value was computed as the maximum of a 500-ms moving average window displaced in 1 data point increments along the most stable region of the force record. The MVC was defined as the greater of the two grip exertions produced by each hand and used to calculate the corresponding right and left 20% MVC reference forces used in the experimental trials. To avoid fatigue, maximal exertions were alternated between hands and followed by 3-min rest periods. Then a 10-min rest period followed the maximum force measurements.

Learning of reference force

A brief practice session was provided to learn how to establish the 20% MVC reference grasp force without visual feedback. Participants were instructed to grasp the handle and establish the required grasp exertion within 2 s and then sustain the force for an additional 3 s. Verbal indications were given during the exertion. If variation from the intended grasp force during the holding phase was greater than 5%, an additional trial was requested. Within two to three practice trials for each hand, all participants learned to consistently exert the required force level based on effort perception. No matching occurred during this learning of the reference force.

Experimental conditions

The force-matching task was performed in two conditions: Ipsilateral Remembered (IR) and Contralateral Remembered (CR). Variations of this well-established paradigm have been commonly used (Jones 1989) McCloskey 1974; Cafarelli and Bigland-Ritchie 1979; Cafarelli and Kostka 1981; Jones and Hunter 1983; Carson et al. 2002). Briefly, in the IR condition, the reference force was established and maintained with either the right or left hand for 3 s and then released. After an additional 2 s, the reference was matched with the same hand (Fig. 2a). This required reliance on a memory-based internal representation of the reference force to generate the matching force. In the CR condition, memory-based information from the reference force exerted by one hand/hemisphere system was used to produce a force match with the opposite hand, 2 s after relaxation of the reference (Fig. 3.2b).

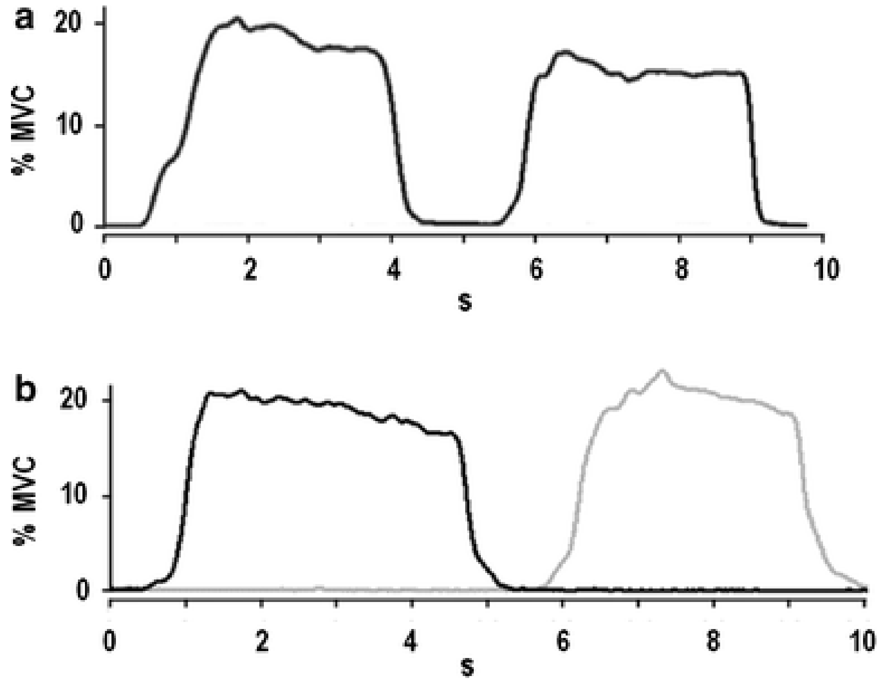


Fig. 3.2**:** Force profiles representative of force-matching paradigm in both experimental conditions: **a** ipsilateral remembered matching performed with the same hand (*black line*) and **b** contralateral matching with the opposite hand (*gray line*). The reference hand forces are represented by black lines in both conditions

The time at which the matching occurred remained constant across conditions. A software-generated visual timer indicated when to provide the verbal command “match with the right” or “match with the left”. All matching was performed without any visual feedback related to force production. Reference hand (R, L) and condition (IR, CR) were counterbalanced across participants using a randomized block experimental design (trials pertaining to the same condition were performed consecutively and not randomized). Two to three practice trials preceded the three test trials for each condition. Practice trials were not included for analysis. All participants performed a total of 12 test trials.

Data Acquisition and Processing

The analog signals from both force transducers were digitized at 100 Hz and low-pass filtered (4th order Butterworth, zero phase lag, 6 Hz cut-off frequency) using customized software (LabVIEW, National Instruments). Reference forces were computed by averaging the force signal over the most stable region (<5% variation over a 2 s period). The reference and matching forces were obtained by averaging the force signal over a 2-s period and was based on the most stable region of the force profile (<5% variation). The average % target difference $|F_{\text{ref}} - F_{\text{match}}|/F_{\text{ref}} \times 100$) between the reference and matching force constituted the relative error. Constant errors were calculated by averaging the difference between the matching and reference forces expressed in Newton or % MVC. A positive value indicated an overestimation, and a negative value indicated an underestimation. Thus, the dependent variables were relative and constant force-matching error.

Data Analysis

The analysis was stratified to avoid high-order interactions and to simplify graphical representations and result descriptions. First, a two-way analysis of variance (ANOVA) with repeated measures was conducted to test for main and interaction effects for condition (IR, CR) and matching hand (right, left) for each dependent variable. If a condition showed significant effects, then, main effects of matching hand, hand strength difference, laterality index and interactions were tested for that condition. To determine which factors influenced main and interaction effects, post hoc multiple comparisons based on Tukey honestly significant difference (HSD) were conducted.

To test the influence of hand strength differences (strength asymmetry) on matching performance, participants were divided into three groups, negative (N), equal (E) and positive (P) that corresponded to three ranges of hand strength differences between the dominant and non-dominant hand. For right-hand-dominant individuals, the N group referred to those individuals who showed at least a 5% stronger left than right hand, the E group referred to those individuals who showed a less than 5% difference between the right- and left-hand-grip strengths and the P group referred to those individuals who showed at least a 5% stronger right than left hand. For left-hand-dominant individuals, the N group referred to those individuals who showed at least a 5% stronger right than left hand, the E group referred to those individuals who showed a less than 5% difference between the right- and left–hand-grip strength and the P group referred to those individuals who showed at least a 5% stronger left than right hand.

To compare matching errors between LH and RH populations, the equality of variance was determined using a Levene's test, and means were compared using the Welch's test. Grip strength measurements are reported as the mean ± SD. Matching errors are reported as the mean ± SE. Significance was set at $P \leq .05$.

RESULTS

Right-Handed Participants

Grip strength

For all RHs, the mean MVC was 296.6 ± 86 N and 291.7 ± 86.3 N for the right and left hand, respectively. The average .015% difference between the right and left hand MVCs was not statistically significant (*t* test,$P > .1$). However, grip strength differences existed between individuals. To address the contribution of grip strength differences to force matching, participants were grouped accordingly (N, E, P). Thus, for right-handed individuals, 8 were included in the N group, 6 in the E group and 8 in the P group.

Force-matching absolute error

When the reference and corresponding matching forces were normalized to each hand's %MVC, the two-way ANOVA (hand, condition) showed a significant difference in absolute error for condition only ($F_{(1,239)} = 44.4$;$P < .0001$). Matching errors were 92% greater in the CR than IR condition, as illustrated in Fig. 3. , and corresponded to a statistically significant ($P < .001$) error difference of 7.5 ± 1.3 N when errors were quantified in N.

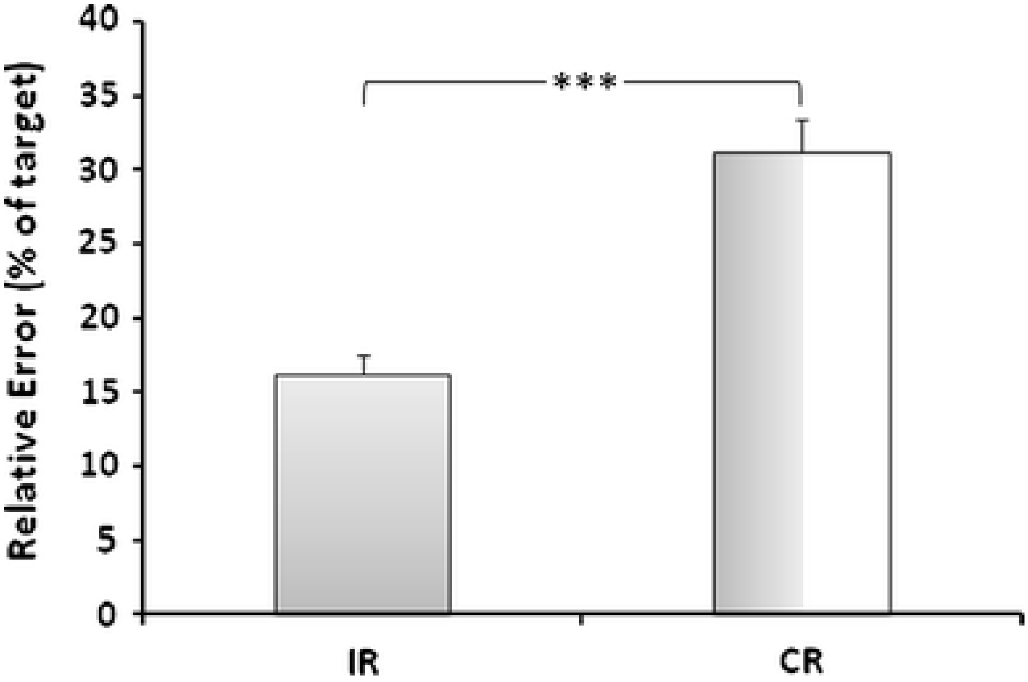


Fig. 3.3: (Right Handers) Mean (+1 SE) percent target error in each condition (IR-ipsilateral remembered and CR-contralateral remembered). The CR matching error was 7.5 ± 1.3 N or 92% greater than the IR matching error ($P < .001$)

Force-matching constant error

Stratified ANOVAs were used to determine the factors influencing the direction and magnitude of the error, that is the overshoot or undershoot of the reference force expressed in Newton (absolute force scale) or in %MVC (normalized force scale).

Constant error (N)

The two-way ANOVA (hand, condition) showed a significant main effect for hand ($F_{(1,239)} = 4.42$; $P = .036$) and a hand x condition interaction effect ($F_{(1,239)} = 7.78$; $P = .005$). Post hoc multiple comparisons (Tukey HSD) showed a significant difference between right-hand overshoots (mean ± SE, 6 ± 2.4 N) and left-hand undershoots (mean ± SE, −3 ± 2.4 N) in the CR condition. In the IR condition, the 1.2 ± 1.7 N difference in error between hands was not significant.

Since no significant effects were found in the IR condition, a secondary analysis was used to test for main (hand, strength, LI) and interaction effects in the CR condition only. In this condition, the three-way ANOVA indicated a significant main effect of hand ($F_{(1,107)} = 27.4$; $P = .0001$)

and hand x strength interaction ($F_{(2,107)} = 35.3$; $P = .0001$). Post hoc multiple comparisons (Tukey HSD) showed that the difference between right-hand overshoots (13.2 ± 3.8 N) and left-hand undershoots (−14.0 ± 4.3 N) was significant for the P group only (right-hand strength at least 5% greater than left-hand strength). The mean differences between right- and left-hand errors corresponding to 7.5 ± 4.9 N (E group) and −8.4 ± 4.8 N (N group) were not significant. Figure 3.4 represents the mean matching errors for the right and left hand for each group. Matching errors were not influenced by laterality indices. The absence of an effect may be due to a rather small LI range (.6–1) within our pool of participants, as handedness strength can be associated with differences in performance (Bernard et al.).

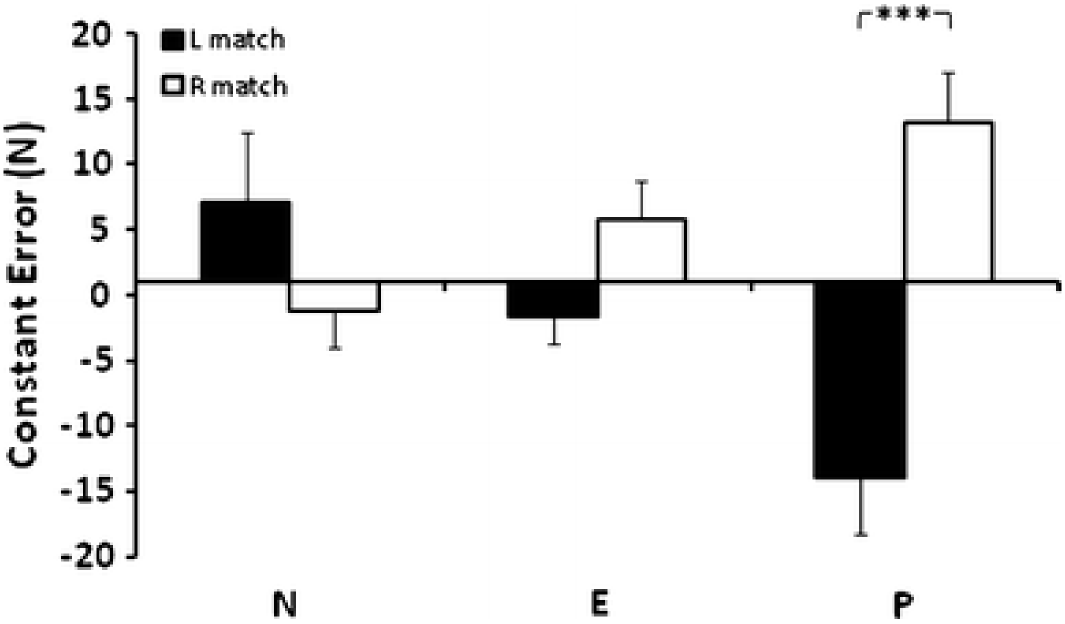


Fig. 3.4: (Right Handers) Mean (±1 SE) constant error (in Newton) in the contralateral matching condition for the left (*solid bar*) and right (*open bar*) hands for N group (left hand stronger than right), E group (equal strength) and P group (right hand stronger than left). The mean right-hand overshoot (13.2 ± 3.8 N) and left-hand undershoot (−14 ± 4.3 N) difference was significant ($P = 0.0001$) for the P group only

The difference in matching error between the right and left hand was correlated with the difference in hand strength for the P group in the CR condition (correlation coefficient $r = .75$, $P = .001$), as illustrated in Fig. 3.5.

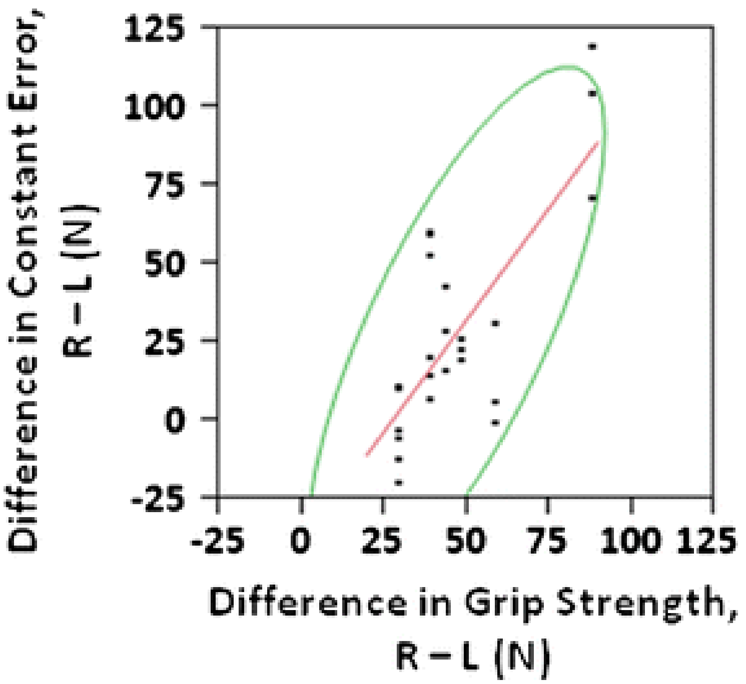


Fig. 3.5: (Right Handers) Correlation between the difference in right- and left-hand matching errors (in Newton) and the difference in hand strength (in Newton) in the CR-contralateral remembered condition for the P group (right hand stronger) only. The correlation coefficient was $r = .75$ ($P = 0.001$)

Constant error (%MVC)

When the errors were normalized to %MVC, the two- way ANOVA showed a significant main effect for hand ($F_{(1,239)} = 7.03$; $P = .008$) and hand x condition interaction ($F_{(2,239)} = 10.9$; $P = .001$). Post hoc multiple comparisons (Tukey HSD) showed a significant difference between right-hand overshoots (mean ± SE, 2.3 ± .7% MVC) and left-hand undershoots (mean ± SE, −.75 ± .6% MVC) in the CR condition. In the IR condition, the .3 ± .7% MVC difference between hand errors was not significant.

Since no significant effect was found for the IR condition, the secondary analysis was applied to the CR condition only. In this condition, the three-way ANOVA indicated a significant main effect of hand ($F_{(1,107)} = 29.6$; $P = .0001$) and hand x strength interaction ($F_{(2,107)} = 28.2$; $P = .0001$). Post hoc multiple comparisons (Tukey HSD) showed that the difference between right-hand overshoots (2.35 ± 1.1% MVC) and left-hand undershoots −(1.6 ± .9% MVC) was significant for the P group (at least a 5% stronger right than left hand). The mean differences of 3.1 ± 1.7% MVC and 2 ± 1.7% MVC for the N group (at least a 5% stronger left than right hand) and E group (equal strength), respectively, were not significant. Figure 3. represents the mean matching errors (%MVC) of each hand for each strength group. Matching errors were not influenced by laterality indices.

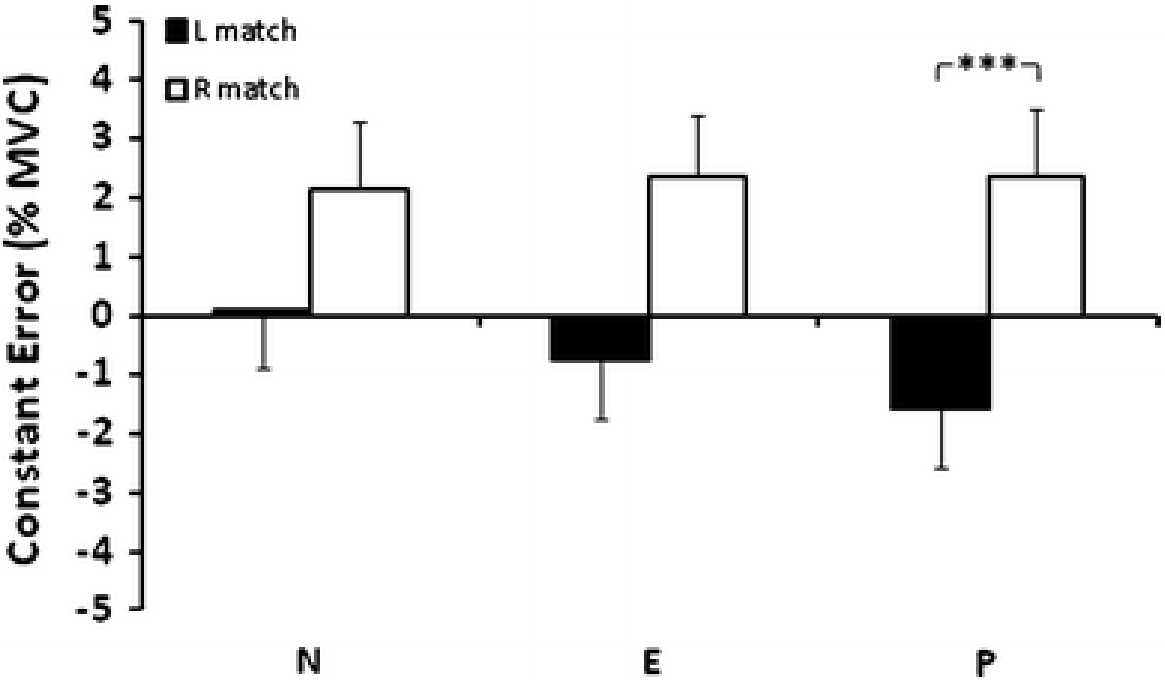


Fig. 3.6: (Right Handers) Mean (±1 SE) constant error (in %MVC) in the contralateral matching condition for the left (*solid bar*) and right (*open bar*) hands for N group (left hand stronger than right), E group (equal strength) and P group (right hand stronger than left). The mean right-hand overshoot (2.35 ± 1.1%MVC) and left-hand undershoot (−1.6 ± 0.9% MVC) difference was significant ($P = 0.0001$) for the P group only

Left-Handed Participants

Grip strength

For all LHs, the mean MVC was 307.41 ± 102.6 N and 311.07 ± 106.0 N for the right and left hand, respectively. The average .012% difference between the right and left MVCs was not statistically significant (*t*-test, $P > .1$). However, hand strength differed significantly between individuals, and they were grouped (N, E, P) according to these differences. For LH individuals, 7 were included in the N group, 7 in the E group and 6 in the P group.

Force-matching absolute error

When the reference and corresponding matching forces were normalized to each hand's %MVC, the ANOVA showed a significant difference in absolute error between conditions only ($F_{(1,191)} = 4.34$; $P = .039$). The matching errors were 46% greater in the CR than IR condition, as illustrated in Fig. 3.7, and corresponded to an error difference of 3.72 ± 1.9 N, when errors were quantified in N.

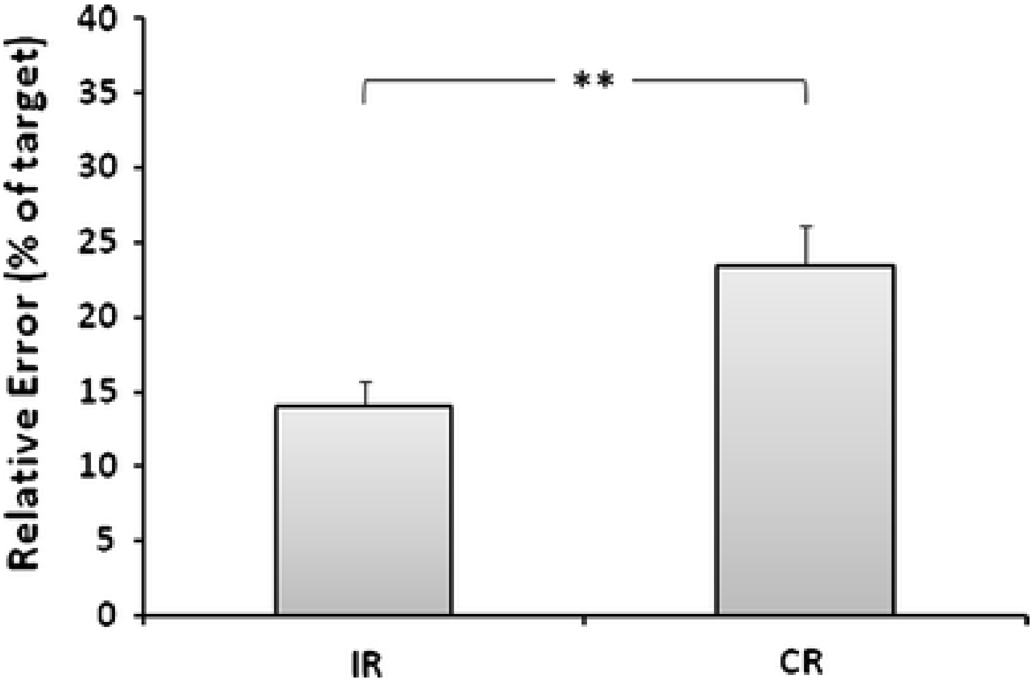


Fig. 3.7: (Left Handers) Mean (+1 SE) percent target error in each condition (IR-ipsilateral remembered and CR-contralateral remembered); *P* = .039

Force-matching constant error

Stratified ANOVAs were used to determine the factors influencing the direction and magnitude of the error, that is the overshoot or undershoot of the reference force expressed in Newton (absolute force scale) or in %MVC (normalized force scale).

Constant error (N)

The two-way ANOVA (hand, condition) did not show significant main or interaction effects in either the IR or CR conditions.

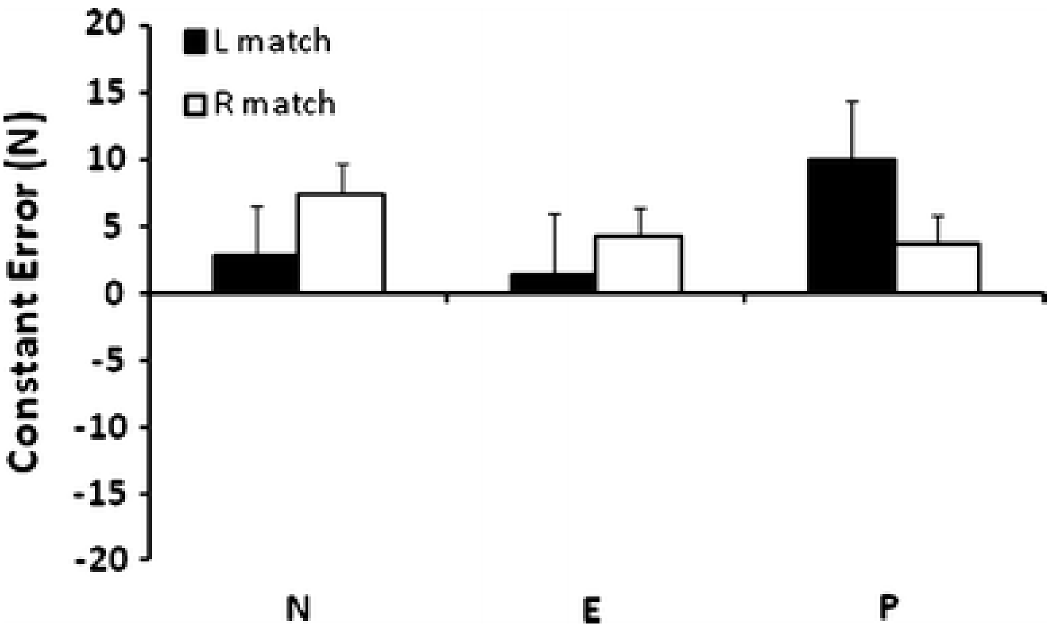


Fig. 3.8: (Left handers) Mean (+1 SE) constant error (in Newton) in the contralateral matching condition for the left (*solid bar*) and right (*open bar*) hands for N group (right hand stronger than left), E group (equal strength) and P group (left hand stronger than right)

As with right handers, a secondary analysis tested main (hand, strength, LI) and interaction effects in the CR condition only. Mean differences between left and right-hand errors, corresponding to −6.2 ± 4.1 N (P group), 2.9 ± 3.9 N (E group) and 4.1 ± 4.1 N (N group), were not significant (*P* > .05, Tukey HSD). Figure 3.8 represents the mean matching errors for each hand in each strength group. As observed for RHs, matching errors were not influenced by laterality indices. However, unlike RHs, the difference in matching errors between the right and left hand was not correlated with the difference in hand strength (correlation coefficient *r* = .17), as illustrated in Fig. 3.9.

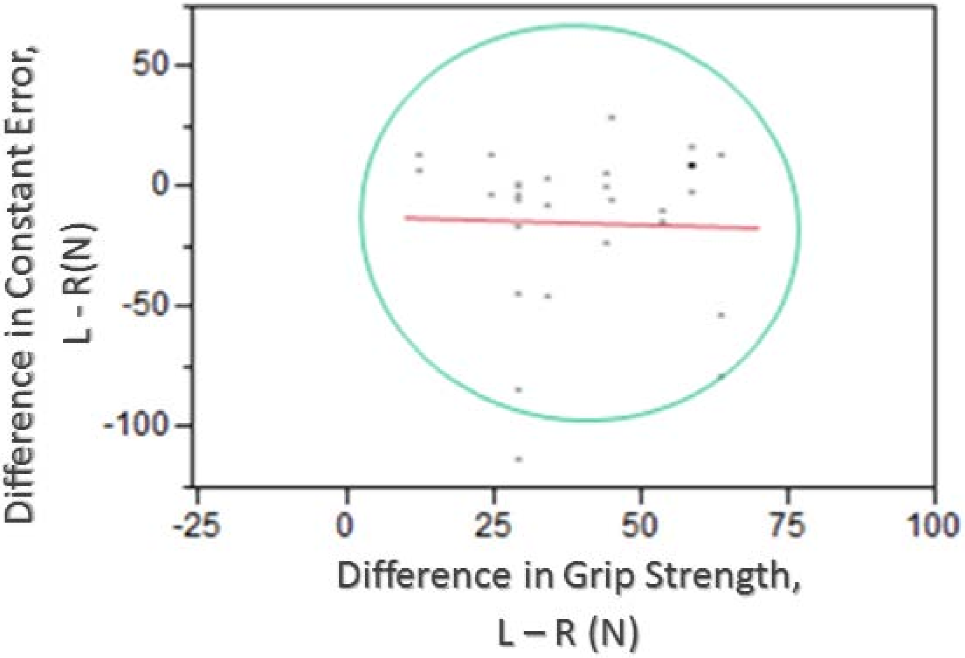


Fig. 3.9: (Left Handers) Correlation between the difference in right- and left-hand matching errors (in Newton) and the difference in hand strength (in Newton) in the CR-contralateral remembered condition for the P group (left hand stronger than right) only. The correlation coefficient was $r = 0.17$

Constant error (%MVC)

When errors were normalized to %MVC, the two-way ANOVA (hand, condition) did not show significant main or interaction effects in either the IR or CR conditions.

A secondary analysis tested for main (hand, strength, LI) and interaction effects in the CR condition only. Mean differences between left- and right-hand errors, corresponding to 0.4 ± 0.8% MVC (P group), −0.7 ± 0.8% MVC (E group) and 0.5 ± 0.8% MVC (N group) were not significant ($P > .05$, Tukey HSD). As observed for the RH participants, matching errors were not influenced by laterality indices. Figure 3.10 represents the mean matching errors (%MVC) of each hand for each strength group.

Matching Error Comparisons

In the IR condition, matching errors and corresponding variances were not significantly different between the LH and RH. In the CR condition, for all strength groups (N, E, P), the absolute errors and variances were significantly less for left than right hand when matching with the dominant or non-dominant hand (Welch's test, $P < 0.014$).

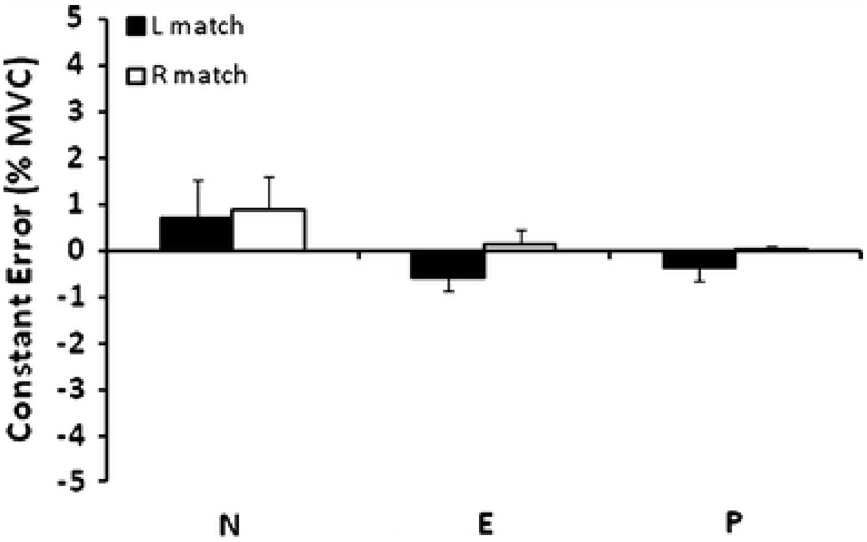


Fig. 3.10: (Left Handers) Mean (±1 SE) constant error (in %MVC) in the contralateral matching condition for the left (*solid bar*) and right (*open bar*) hands for N group (right hand stronger than left), E group (equal strength) and P group (left hand stronger than right)

DISCUSSION

Findings from this study showed that grasp force-matching errors were greater when matching with the opposite than the same hand, and errors were similar when matching with the same hand. As evidenced by the direction of the constant errors, asymmetries in contralateral matching tasks showed right-hand overshoots of left-hand reference forces and left-hand undershoots of right-hand reference forces for RHs. In addition, this asymmetry in RHs appears to be dependent on hand strength differences and corresponds to participants who showed at least a 5% stronger right than left hand (P group). In contrast, for LHs, hand strength differences for any group (N, E, P) did not significantly influence the direction of matching errors, and asymmetries in the contralateral matching condition were not significant. Gender, considered in an initial 3-way ANOVA, was not included as a factor in subsequent analyses since its influences were not significant. Furthermore, when dividing each handedness group as a function of hand strength differences, gender distributions between subgroups were in disparate proportions with few individuals of each gender, which precluded meaningful significant effects that could have been associated with less lateralization in females (Robinson et al. 1990; Wisniewski 1998; Amunts et al. 2000; Cykowski et al. 2008).

Sensory and motor contributions to force reference/perception

Force perception may rely primarily on an internal representation of the force requirement based on the efferent copy of the motor command (Jones 2003; Lafargue et al. 2006; Lafargue & Sirigu 2006) and is modulated by higher order neural systems upstream of the motor cortex (Carson et al. 2002). Nevertheless, it was also shown that an interaction between sensory feedback from cutaneous mechanoreceptors and motor commands alters the perception of force (Gandevia & McCloskey 1977; Jones & Piateski 2006) and is context specific. However, tactile feedback appears to be used when adjusting for unpredictable loads when lifting and manipulating weighted objects (Johansson and Cole 1992) than when grasping an object with constant physical properties (Nowak & Hermsdorfer 2003) or performing an isometric “postural” exertion (Gandevia & McCloskey 1977). In the context of our experiment, a cutaneous interference seems to play a minor role, since there is no movement (Gandevia & McCloskey 1977).

Asymmetry in motor activity

In RHs, nuclear magnetic resonance imaging during contralateral and ipsilateral finger movements showed that the right motor cortex is activated mostly during contralateral finger movements, while the left motor cortex is substantially activated during both contralateral and ipsilateral finger movements (Kim et al. 1993; Babiloni et al. 2003). Building on Kim’s results (1993) and Gordon et al. (1994) assumed that transition of force information corresponding to precision grip tasks may be easier from the right to left hand than vice versa since the left hemisphere may be actively involved in the control of both hands, requiring little or no transfer between hemispheres.

In contrast, right-hand control, driven primarily from the left motor cortex, requires interhemispheric transfer (Gordon et al. 1994) that likely increases neural noise and loss of information. More recently, it was shown that activity of the right supplementary motor area (SMA) was greater during left than right movements, whereas this difference was less evident in the left SMA, which led Babiloni et al. (2003) to conclude that, in right-handed individuals, left SMA plays a major role in the control of voluntary movements. Furthermore, asymmetry of hand cortical motor (Kim et al. 1993; Amunts et al. 1996; Volkmann et al. 1998; Baraldi et al.1999;

Triggs et al. 1999; Brouwer et al. 2001), and somatosensory representations (Soros et al. 1999; Jung et al. 2003, 2008) show that these structures are larger in the dominant hemisphere, suggesting that the preferred hand is associated with greater connectivity than the non-preferred hand (Amunts et al. 1996). In addition, projections of afferent inputs from one hand ascend to both ipsilateral and contralateral somatosensory cortices (Wegner et al. 2000; Nihashi et al. 2005; Blatow et al. 2007). All these results converge to demonstrate significant structural asymmetries and thus assume a relationship between hemispheric asymmetries and functional/behavioral differences (Amunts et al. 1996; Adamo and Martin2009).

In the present study, right-hand matches overshot left-hand references and left-hand matches undershot right-hand references, except for the N group, in which strength was greater for the left than right hand. Similar dominant hand overshoots of non-dominant hand references were previously observed for single finger contralateral force matching (Gordon et al. 1994; Henningsen et al. 1995; Shergill et al. 2003; Park and Leonard 2008; Park et al. 2008). However, in the case of index finger matching, left-match undershoots of right finger references were statistically significant for forces in the range of 35% MVC (Park et al. 2008). Nevertheless, these asymmetries were greater when contralateral matching involved fingers of different strength. The authors suggested that matching asymmetries were possibly related to asymmetries in the somatosensory system and assumed that “the dominant index finger overestimates the force of the non-dominant index finger”. This interpretation can be complemented, as our results clearly suggest interactions between hand strength difference and hand dominance. In the CR condition, asymmetry between matching hands remains whether the error is expressed in Newton or %MVC. In addition, asymmetry is significant when hand strength is equivalent, increases with strength difference when the right hand is stronger than the left hand and is less (i.e., asymmetry not significant) and appears inverted when the left hand is stronger than the right hand. This may be explained from two perspectives.

First, the preferred hand was not necessarily the stronger hand, as observed in other studies (Incel et al., 2002; Petersen et al., 1989). In addition, laterality index was not a significant factor in this RH group. We believe that this may be due to the small dispersion of scores and effect size since only one third of the participants had a LI < .75 but no less than .6. Clearly, assigning individuals to a specific group using only survey-based hand preference scores would appear to be a limitation, yet our results bring to light the need to consider strength asymmetry more explicitly in studies investigating the role of hand preference in upper limb motor control.

Second, hand strength differences appear to be an important factor for RHs. Matching asymmetry is exacerbated when the right hand is stronger than the left and reduced otherwise. These interactions are attenuated when the error is expressed in %MVC. Thus, we propose that grip force-matching asymmetry appears because of both an intrinsic difference between the two hand/hemisphere systems and a peripheral difference associated with muscle strength. Although a significant difference in cortical representation associated with strength difference (i.e., number of muscle fibers) may not be excluded. Further, the reduction of the constant error when expressed in %MVC (about 2% MVC) indicates that force matching was scaled relative to hand strength. Jones (2003) showed similar results. Hence, this scaling primarily implicates the role of the efferent copy in the sense of effort, lessens the role of sensory receptors and takes into account the way in which matching was performed.

In an effort to unify the concepts presented above, it is proposed that intrinsic differences and muscle strength differences confer to each hand system a different gain. Support for this proposition is derived from the application of control theory to motor control (Jagacinski & Flach, 2003), which also served as a basis to model asymmetry of position sense (Adamo & Martin, 2009). For each hand/hemisphere system, the total gain, which quantifies the relationship between the output (force exerted) to the input (force to be generated) in terms of magnitude, is the product of the gain of each component: perceptual (force information/representation), transfer between the two hemispheres (in the case of contralateral matching), motor command and muscle.

In RHs, the dominant hand overshoots and non-dominant hand undershoots parallel the asymmetry found in position sense. In this latter context, the model demonstrated that the gain ought to be lower for the dominant than non-dominant hand system. The same reasoning applies to the sense of effort. The present results also support our earlier proposition that "*cortical representation corresponding to right hand use translates into a higher sensory and motor* *resolution, and as such, the right hand/left hemisphere system may not need a high gain"*. A simple example may illustrate the gain concept. The balance control of an audio amplifier is used to equalize sound perception between the two ears, regardless of the source of this difference. Hence, any adjustment different from neutral is required by the difference in gain between the two channels.

Since the difference between left and right grip strength was a significant factor in the tested population; it is inferred that the gains of the respective muscle components were significantly different, which exacerbates asymmetry even when the error is expressed on the relative scale. Furthermore, the influence of information transfer may contribute to neural noise, but not to a change in direction of the constant error with the observed magnitude. This would persist even if interhemispheric transfer was better (Haude et al. 1987; Yamauchi et al. 2004) in one direction than in the other (which can also be viewed as a small difference in gain) or was not necessary (Gordon et al. 1994).

Therefore, it is assumed that internal force representation may differ between the right and left hand. Asymmetry of the sense of effort may be associated with a difference between the respective efferent copies that stem from the difference in cortico-spinal pathways mediating the motor commands, and/or an asymmetry in the processing of force information associated with cortical connectivity and the size of cortical structures.

Absence of significant asymmetry in left-handed individuals

When compared to the RHs (see Fig. 3.4), results obtained from LHs (see Fig. 3.8) tend to exhibit a smaller error for the left-hand match, an inversion of the sign of the error for the P group and an inversion of the sign of the right match error for the N group. This pattern suggests a possible inversion of the direction of the error between LHs and RHs. However the absence of significant asymmetry, given that the laterality indices of LHs and RHs in the P group were not significantly different ($F_{(1,1)} = 2.1$; $P = .1709$), is likely to stem from a better matching accuracy rather than an influence of laterality strength. Living in a RH world, LH individuals frequently need to control force with their non-dominant right hand; this practice then attenuates differences between the two hand force control systems. Hence, the non-dominant hand benefits from a reduction in neural noise that, in turn, provides better signals for establishing the reference and performing the match when compared to the non-dominant hand of RH individuals. The benefits from more efficient hemispheric interactions in terms of accuracy and speed of transfer shown for visuo-motor tasks in LHs (Marzi et al., 1991; Cherbuin & Brinkman 2006) are in support of this assumption. Although visual information was not transferred in our experiment, it is reasonable to assume that efficiency may also apply to interactions in general. Furthermore, cortical organization is not mirrored between the LH and RH (Klöppel et al. 2007a, b; Bernard et al. 2011), as illustrated by the primary role of the left primary motor cortex (M1) in planning and controlling motor acts regardless of hand dominance (Kim et al. 1993; Verstynen et al. 2005), which may further reduce asymmetry in force control.

Brain imaging studies have also shown that handedness is associated with differences in M1 activation patterns. For example, M1 activation is more bilateral in LHs than RHs (Kim et al. 1993; Siebner et al. 2002). Similarly, during grasp planning, cortical activity increases bilaterally in the anterior intraparietal sulcus and M1 in LHs only, regardless of the hand used (Martin et al. 2011). Furthermore, when comparing unimanual and bimanual tasks, Klöppel and colleagues (2007a) found that bilateral dorsal premotor and right primary motor cortical activations are similar for either tasks in LHs, but increase in RHs for bimanual tasks. Hence, these results support more symmetrical cortical activity in LHs than RHs. Nevertheless, recent results suggest that the degree of laterality is also a factor to consider when estimating the efficiency of information transfer and the symmetry/asymmetry of cortical activity (Bernard et al. 2011). In the present study, the handedness of the participants was rather consistent.

It is worth noting that hand dominance may also be associated with cerebral organization for certain regions, as illustrated by differential activation patterns in anterior intraparietal sulcus and M1 between the LH and the RH (Martin et al. 2011). Although functional hemispheric specialization (left hemisphere dominance hypothesis) for voluntary movements is well supported by a variety of investigations (Kim et al. 1993; Halsband et al. 1993; Rushworth et al. 2003; Haaland 2006; Sainburg 2005, Wang & Sainburg 2006; Verstynen et al. 2005; Schaefer et al. 2007), this hemispheric asymmetry is less pronounced in LHs. In addition, a recent investigation using disruptive TMS also suggests that functional asymmetry of the premotor cortex (PMC) is associated with hand dominance for complex bimanual tasks (van den Berg et al. 2010). However, the latter results also show that the influence of the non-dominant PMC is task-dependent (unimanual vs. bimanual movements). Hence, hand dominance and hemisphere dominance may interfere as a function of interhemispheric interactions required by the task (van den Berg et al. 2010). In the case of the contralateral remembered condition, the task corresponds to consecutive unilateral contractions, which then suggests that interference between two concurrent hemisphere activities may not play a role here.

Finally, a difference in the direction of asymmetry between RHs and LHs is not systematic for all tasks. For example, right-hand versus left-hand reversed direction of asymmetries between LHs and RHs was observed for arm position-matching tasks (Goble et al. 2009) and for adaptation transfer from one arm to the other in a reaching task (Wang & Sainburg 2006). Others performances, such as which hand leads in mirror symmetrical bimanual tasks (Franz et al. 2002; Shen and Franz 2005) or simple manual dexterity tests (Bernard et al. 2011), are less asymmetric in LH than RH. Hence, the lack of significant asymmetry in our LHs results is not surprising, but rather underlines that context specific influence of handedness, hemisphere dominance and hemispheric interactions modulate performance symmetries/asymmetries. Therefore, we assume that more efficient hemispheric interactions, less pronounced asymmetries, more bilateral activities in LHs than RHs and interaction between hand dominance and hemisphere dominance contributes, in the context of the tested motor task, to a reduction in the gain difference between the two hand systems and reduces the influence of hand strength differences in LH.

To conclude, for RH individuals, contralateral force-matching conditions clearly show a strong interaction between an intrinsic asymmetry associated with hand preference and the difference in hand strength. Large differences in grip strength may be accompanied by significant changes in cortical representation that would contribute to asymmetry. The similarity of asymmetries observed in contralateral position (Adamo and Martin2009), and force-matching tasks strongly suggest that the difference in gain between the two upper limb/hemisphere systems is a correlate of cortical asymmetries. Although the contribution of the motor component to asymmetry may be significant in the context of force exertion, the differences in internal representation of the information conveyed by feedback seems to be a key to the differences in perception of that information. The more symmetrical performance of LHs seems to be mitigated by multiple interactions and adaptation imposed by a dominant RH word. Finally, empirical results combined with an analytical model show that each component of a system (internal representation, transfer between hemispheres, motor command and muscle) must be considered carefully to understand the relationship between the perception and the outcome of a motor act.

CHAPTER 4

SENSE OF EFFORT REVISITED: RELATIVE CONTRIBUTIONS OF SENSORY FEEDBACK AND EFFERENT COPY

ABSTRACT

Past studies have suggested that muscular effort perception is derived from the efferent copy of the associated motor command. While peripheral/sensory information is thought to be necessary for force modulation/control, it is not involved in the initial force production. More recently, we showed that, for right handers, the perception of effort was asymmetric in grasp-force tasks and this asymmetry was related to individual differences in right and left hand strength and an intrinsic component. A difference in gain (input/output magnitude relationship) between each limb/hemisphere system was proposed as the mechanism explaining these differences. To further investigate the relative contributions of efferent copy and sensory feedback to the sense of effort, vibration was used to distort the sensory information from the muscles providing the reference force. Visual feedback of the reference hand was also manipulated. The absolute error (AE) was generally larger in the vision than no-vision situation and the influence of reference hand vibration is very minor when matching with the right hand but is significant when matching with the left hand in the CR condition. These two results may not present a paradox but rather reflect an interaction between two phenomena: (1) the visual feedback, which represents the total output of the system (resultant force), may not be congruent with the internal representation of effort associated with the efferent copy and eventually the proprioceptive feedback; and (2) although the efferent copy may play a major role in force matching a larger absolute error for left than right hand matching in the CR condition suggest that proprioceptive feedback is also used by the left hand/hemisphere system. Overall, it may be suggested that in right handers, right hand force matching may be primarily based on the sense of effort associated with the efferent copy

while left hand matching may use a combination of efferent copy and proprioceptive feedback. However, the weight of each type of information may be dependent on the association between motor command and representation of the execution of the motor command (visual vs. internal).

INTRODUCTION

The basis of our ability to judge force and weight has long been debated. The point of contention: is force perception based only on the efferent copy of the descending motor command or is it modulated by peripheral sensory information. The classical, and still predominant view, is that sense of effort is based on the corollary discharge or efferent copy of the descending motor command (Helmholtz, 1925; Sperry, 1950; McCloskey 1974; Gandevia & McCloskey 1977; Jones & Hunter 1982; Jones 1986; Carson et al. 2002; Lafargue & Sirigu 2006). However, some studies acknowledge the possible involvement of cutaneous receptors, muscle spindles (Cafarelli, 1988) and tendon organs (Gandevia & Burke, 1992; Jami, 1992) in sense of force and force modulation (Kilbreath et al., 1997, Luu et al. 2011). Carson and colleagues (2002), acknowledged this fact by suggesting that the sense of force and sense of effort may potentially be “separable sensory elements serving differing sensorimotor functions”.

As mentioned in chapter 3, the results of fatigued/non-fatigued limb force matching studies (e.g. Jones & Hunter, 1982,1983; McCloskey, 1974; Cafarelli & Bigland-Ritchie 1979; Gandevia,1982) have corroborated the notion that force perception is predominantly modulated by a centrally mediated sense of effort. Specifically, these studies have shown that force/weight is perceived to be greater when an increased motor command is required to produce equivalent force (Gandevia & McCloskey, 1977). While the fact the force was correctly reproduced by deafferented individuals (Lafargue et al. 2003; Lafargue & Sirigu 2006) is often used to dismiss/downplay the role of peripheral information in sense of effort mediation.

More recently Luu et al. (2011) have challenged the interpretation of these results. These authors contend that the efferent copy of the motor command could not be the sole mediator of the sense of effort, as the same weight should feel twice as heavy if the muscle had lost half of its strength as a result of fatiguing exertions or partial curarisation. While not completely overlooking the possibility that the efferent copy/sense of effort relationship is non-linear, they posit that “peripheral information is the dominant signal for perceived heaviness”. In their contralateral weight matching study, of healthy individuals and individuals with compromised peripheral sensory systems, they found that with the force of the thumb flexor halved - deafferented persons judged the weight to be twice the initial value, while normal subjects judged the force to be similar or lighter. These results were also obtained when the thumb flexor muscle was partially paralyzed, and were thought to be contrary to what the central mediation of sense of effort would predict.

This new evidence, in support of a peripherally mediated sense of effort, has prompted the re-examination of the contributions of both the motor command and peripheral feedback to the sense of effort. In addition, since Luu and colleagues (2011) emphasized the role of muscle proprioception in the dominant peripheral signal and muscle spindles are extremely sensitive to vibratory stimuli (Burke et al., 1972; Roll & Vedel, 1982, Roll et al., 1989, Fallon et al., 2007), the use of vibration to modify the peripheral signal should affect the perception of effort associated with the reference hand and in so doing the force matching performance. Furthermore, since each hand/hemisphere system is assumed to be specialized in the processing of specific kinematic parameters (Wang & Sainburg, 2004; Bagesteiro & Sainburg, 2003; Mani et al., 2013) and in the mode of control of motor activities then it may be presumed that these differences may be reflected in the utilization of sensory feedback.

Finally, visual feedback in the establishment of the reference force, which represents the output of the system, was assumed to be poorly associated with the internal representation of effort/force exertion in a simple matching task of short duration (Adamo, 2007). It was argued that visual feedback may be more closely associated with sensory information than efferent copy. Then, a lack of congruence between the two sources of information is presumed.

Therefore, the aims of this study were 1) to determine the extent to which muscle proprioceptive feedback contributes to the sense of effort and whether this sensory component contributes to asymmetry in the sense of effort and 2) to determine whether force matching asymmetry is influenced by the way in which the reference force level is acquired (visually vs. non-visually). The following hypotheses were tested in a population of right handed participants:

- The right dominant hand/left hemisphere system may not use proprioceptive feedback and is likely to control the matching force in a feedforward manner. Hence vibration of the right hand reference in the IR condition, or vibration of the left hand reference in the CR condition should not affect significantly the matching error. When the reference hands are respectively reversed than matching errors should be strongly affected by vibration. In other words vibration-induced afferent messages should more strongly affect the perception of effort associated with the left than the right hand.
- Incongruence between visual information and internal representation of effort contribute to greater matching errors with than without visual feedback. Vibration may exacerbate incongruence if sensory feedback contributes to the perception of effort. Hence matching errors should be greater with than without visual feedback and for the left than the right hand.

METHODS

Participants

Twenty-two (17 females; 5 males, mean age 26.2 ± 4.8 yrs) right-handed individuals with a mean laterality index of .83 ± .14 (range: .6 – 1), as determined by the Edinburgh Handedness Inventory (Oldfield 1971), participated in the experiment. All participants were free from any upper limb neurological and musculo-skeletal conditions that might impair task performance. Exclusion criteria included a long-standing history of highly skilled motor activity such as dancing or playing a musical instrument. All participants were recruited from the local community and signed an informed consent form approved by the Human Investigations Committee at Wayne State University and Internal Review Board at the University of Michigan.

Experimental Set-up

As in study 2 (chapter 3) participants were comfortably seated at a table with shoulders slightly flexed and abducted, elbows flexed at 90 deg, forearms fully pronated and wrists positioned at 25-30 deg of extension. Seat height was adjusted to keep the forearms in the horizontal plane. The custom-designed grasp devices, composed of a split aluminum force transducer embedded with strain gauges and equipped on each side with semicircular wooden handles 4.0 cm in radius, 13 cm in length, were held horizontally by a coupling support fixed to the table, as illustrated in Fig 4.1. The device was positioned directly in front of the participant and allowed for adequate finger clearance. A power grip pattern was used to position the hand around the device whereby the thumb was positioned under and digits (II-V) were positioned on top of the grasping device. The size of the grasp device (gap between semicircular parts) was adjusted for each individual's hand size to ensure the distance between the fingers and thumb was constant across hands and participants. Signals corresponding to participants' hand grasp forces were simultaneously displayed on vertical scales presented on a monitor to provide visual feedback to the experimenter about the participant's performance and to the participant to establish the 20% MVC reference force for half of the trials. For each individual, each scale was calibrated to the respective 100 % MVC and a cursor indicated the 20% MVC reference force. For the duration of the experiment, an opaque screen masked the hands of the subject to encourage them to focus on the perception of effort associated with the grip exertion and to avoid any potential contribution visual information, such as monitoring the position of the hands on the devices, to matching performance (see insert Fig.4.1). This procedure insured that force perception was based on an internal representation independent of a visual association between the outcome of the exertion and other sources of feedback that contribute to this internal representation. Vibration, when required, was applied perpendicularly at a frequency of 60 Hz to the distal tendon of finger flexor muscles of the reference hand (right or left) as highlighted in Fig. 4.1.

Experimental Procedure

Determination of maximal voluntary contraction. Prior to the experiment, maximum voluntary contractions (MVC) for each hand were measured with the hands placed on the devices in the testing posture. Instruction was given to increase force gradually over a 2 s period and then continue to exert the maximum grasp force for an additional 2 s. The MVC value was computed as the maximum of a 500 ms moving average window displaced in 1 data point increments along the most stable region of the force record. The MVC was defined as the greatest of the two grip exertions produced by each hand and used to calculate the corresponding right and left 20% MVC reference forces used in the experimental trials. To avoid fatigue, maximal exertions were alternated between hands and followed by 3 min rest periods. Then a 10 min rest period followed the maximum force measurements.

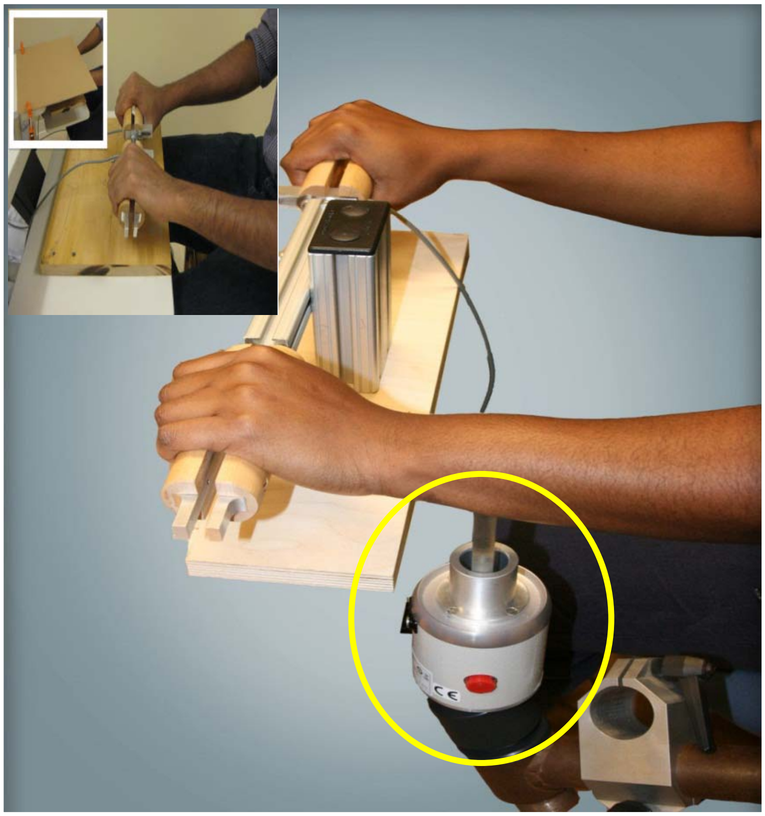


Fig. 4.1: Custom-designed grasp devices. Composed of a split aluminum force transducer embedded with strain gauges and equipped on each side with semi-circular wooden handles (4.0 cm in radius, 13 cm in length). The grasp devices were held horizontally by a coupling support fixed to the table. Insert shows that the hands were masked during the experiment.

Visual feedback modulation. Participants were presented with visual feedback for 50% of the trials. This visual feedback was only available while the reference force was established and stabilized. Visual feedback was never provided during the matching phase of the trial. For the no-vision scenario, a brief practice session was provided to learn how to establish the 20% MVC reference grasp force without visual feedback. Subjects were instructed to grasp the handle and establish the required grasp exertion within 2 s and then sustain the force for an additional 3 s. Verbal indications were given during the exertion. If variation from the intended grasp force during the holding phase was greater than 5%, an additional trial was requested. Within two – three practice trials for each hand, all participants learned to consistently exert the required force level based on effort perception. No matching occurred during this learning of the reference force.

Proprioceptive information modulation (vibration). For the trials with vibration, vibration was applied for 4 s to the limb producing the reference force 200 ms after the peak force was produced. Ten of the 22 participants completed the trials with vibration. Vibration was never applied to the matching hand since the tonic vibration reflex (TVR) would have modified the force output without volitional control. The aim here was to determine the contribution of the possible sources of information only.

Experimental conditions. The force-matching task was performed in two conditions: Ipsilateral Remembered (IR) and Contralateral Remembered (CR) for both visual feedback (with and without visual feedback) and vibration (with and without vibration). Variations of the established IR – CR paradigm have been commonly used (Jones 1989) McCloskey 1974; Cafarelli and Bigland-Ritchie 1979; Cafarelli and Kostka 1981; Jones and Hunter 1983a,b; Carson et al. 2002). Briefly, in the IR condition, the reference force was established and maintained with either the right or left hand for 3s and then released. After an additional 2 s, the reference was matched with the same hand (Fig 2A). This required reliance on a memory based internal representation of the reference force to generate the matching force. In the CR condition, memory-based information from the reference force exerted by one hand / hemisphere system was used to produce a force-match with the opposite hand 2s after relaxation of the reference (Fig 2B).

The time at which the matching occurred remained constant across conditions. A software-generated visual timer indicated when to provide the verbal command “match with the right” or “match with the left”. All matching was performed without any visual feedback related to force production. Reference hand (R, L), condition (IR, CR), vibration (with or without) and visual feedback (with or without) were counterbalanced across participants using a randomized block experimental design (trials pertaining to the same condition were performed consecutively and not randomized). Two - three practice trials preceded the three test trials for each condition. Practice trials were not included for analysis.

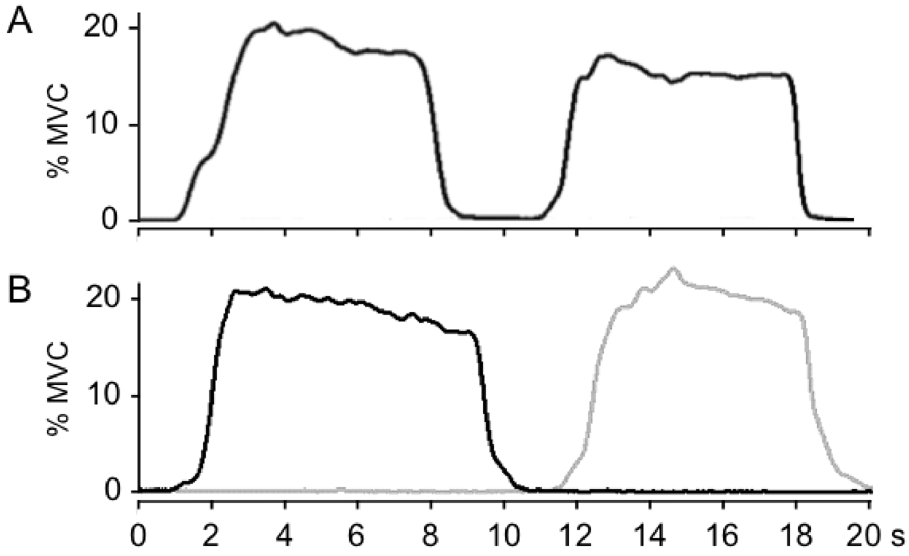


Fig. 4.2: Force profiles representative of force-matching paradigm in both experimental conditions. (A) ipsilateral remembered matching performed with the same hand (black line) and (B) contralateral matching with the opposite hand (gray line). The reference hand forces are represented by black lines in both conditions

Data Acquisition and Processing

The analog signals from both force transducers were digitized at 100 Hz and low pass filtered (4th order Butterworth, zero phase lag, 6Hz cut off frequency) using customized software (LabVIEW, National Instruments). Reference forces were computed by averaging the force signal over the most stable region (< 5% variation over a 2 s period). The reference and matching forces were obtained by averaging the force signal over a 2s period and was based on the most stable region of the force profile (< 5% variation). Absolute errors were calculated as:

$$|F_{ref} - F_{match}|$$

Where F_{match} – was force produced by the matching hand expressed in % MVC

F_{ref} – force produced by the reference hand expressed in % MVC

Because of the limitations associated with the participants'' grip strength differences, the absolute error was used to remove the directionality of the force matching errors detailed in chapter 3.

Data Analysis

The analysis was stratified to avoid high order interactions and to simplify graphical representations and result descriptions. First, a five-way analysis of variance (ANOVA) with repeated measures was conducted for the main effects of condition (IR, CR), hand (R, L), vibration (WV or NV), visual feedback (B or E) and strength group (P, N, E) to confirm that the use of the absolute error (AE) expressed in %MVC as the dependent measure minimized the effects of strength differences discussed in chapter 3. Analysis of the main and interaction effects of the remaining three factors would continue for each condition (IR, CR) if strength difference effect was neutralized. To determine which factors influenced main and interaction effects, post–hoc multiple comparisons based on Tukey Honestly Significant Difference (HSD) were conducted. Grip strength measurements are reported as the mean ± the standard deviation. Matching errors are reported as the mean ± the standard error. Significance was set at $p \leq .05$.

RESULTS

Grip strength

For all participants, the mean MVC was 296.6 ± 86 N and 291.7 ± 86.3 N for the right and left hand, respectively. The average .015% difference between the right and left hand MVCs was not statistically significant (*t* test, $P > .1$). However, grip strength differences existed between individuals. To address the contribution of grip strength differences to force matching, participants were grouped accordingly (N, E, P). Thus, for right-handed individuals, 8 were included in the N group, 6 in the E group and 8 in the P group.

Force matching error: AE (% MVC)

When the reference and corresponding matching forces were normalized to each hand's %MVC, the five-way ANOVA (hand, condition, strength difference, vibration, visual feedback) showed that the effect of grip strength differences was not significant ($F_{(2,18.44)} = 0.33416$; $P = 0.7150$).

A significant difference between conditions (IR and CR) was found ($F_{(1,345.1)} = 42.9096$; $P < 0.0001$). Overall, matching errors were 98% greater in the CR than IR condition as illustrated in Fig. 4.3. Since no significant differences (as a result of matching hand, vibration or vision) were found in the IR condition (Fig. 4.5), only the results of the secondary analysis of the CR condition will be detailed.

In the CR condition, the main effects of vibration, matching hand and their interaction were significant. The AE was 80% greater with than without vibration applied to the reference hand ($F_{(1,161.6)} = 16.0367$; $P < 0.0001$). While matching with the left hand resulted in a 35% increase in the AE overall ($F_{(1,166.9)} = 18.3112$; $P < 0.0001$). Further investigation into the significant matching hand x vibration interaction effect ($F_{(1,166.9)} = 8.0559$; $P = 0.0051$) using post hoc multiple comparisons (Tukey HSD) showed that when matching the right reference with the left hand without visual feedback, the mean difference in AE with and without vibration of 5.98 ±1.22 was significant (Fig. 4.4).

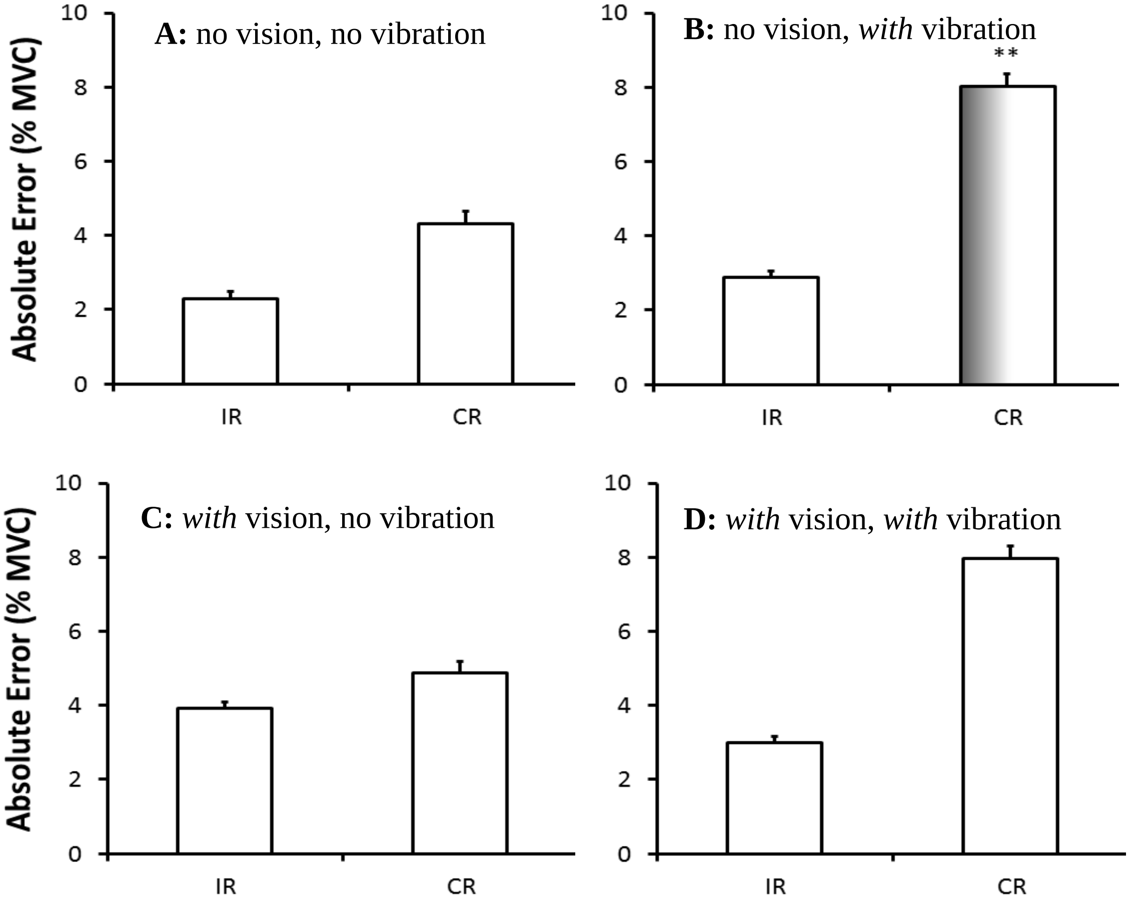
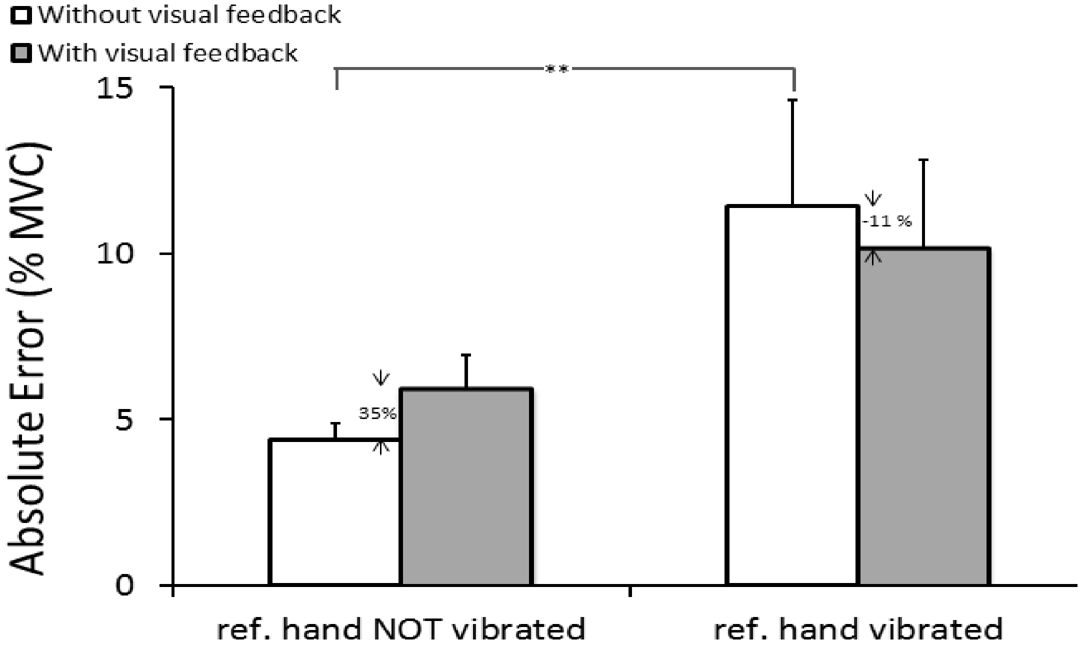


Fig. 4.3: Mean (+1 SE) absolute error in each condition (IR-ipsilateral remembered and CR-contralateral remembered) for – A: no vision, no vibration (CR 88% greater), B: no vision, with vibration (CR 180% greater), C: with vision, no vibration (CR 25% greater), D: with vision, with vibration (CR 167% greater). Overall, the matching error was 98% greater in the CR than the IR condition ($P < 0.0001$).

A: left match, *right* reference



B: *right* match, left reference

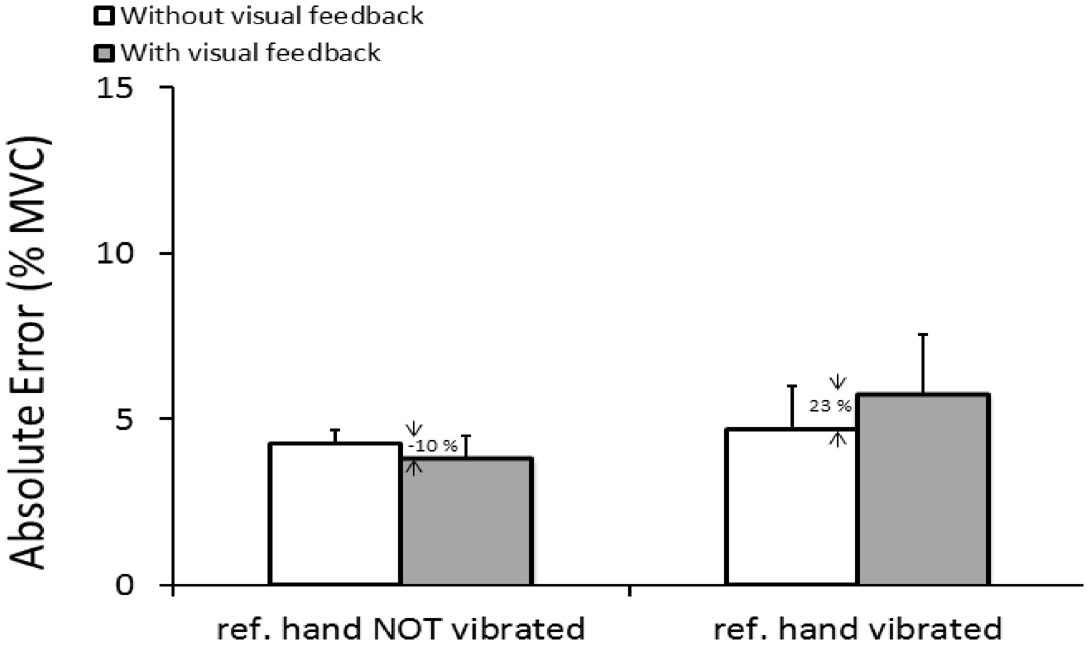
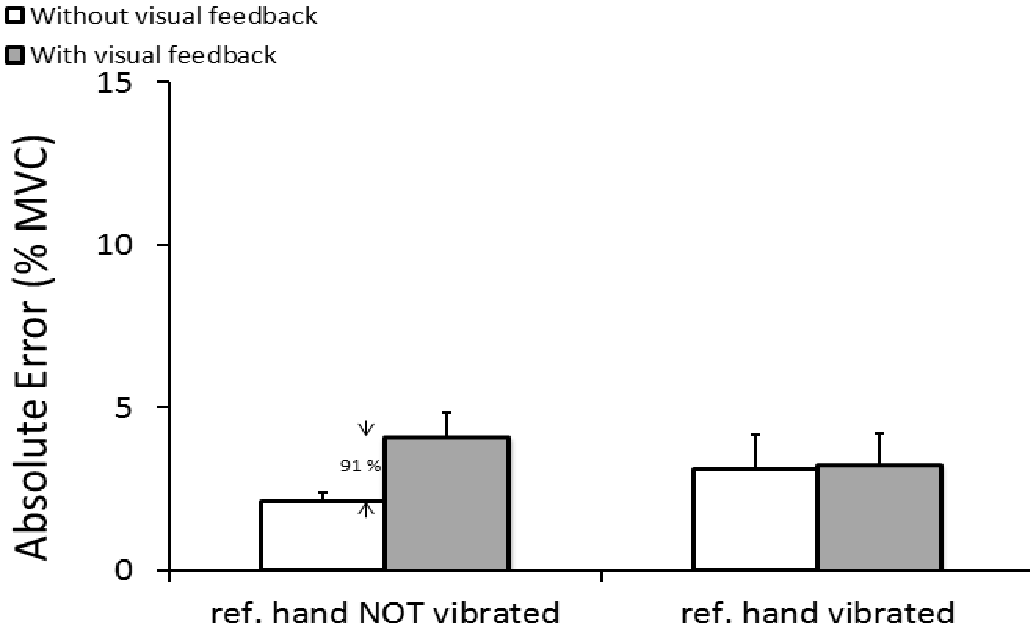


Fig. 4.4: Mean (+1 SE) AE in CR-contralateral remembered condition without visual feedback (open bar) and with visual feedback (solid bar) for A: left match, right reference and B: right match, left reference.

A: left match, left reference



B: right match, right reference

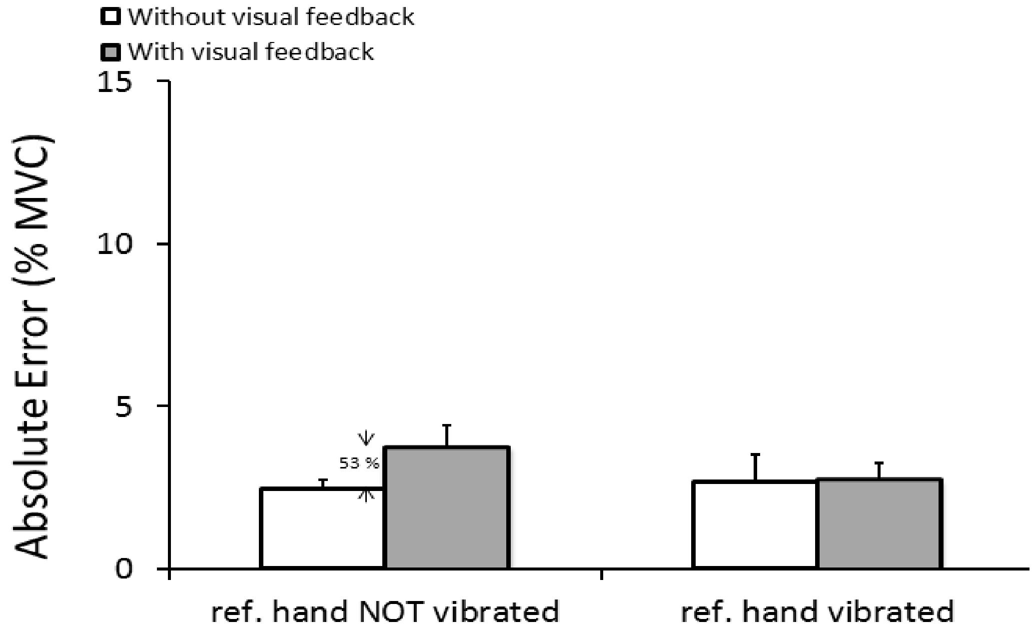


Fig. 4.5: Mean (+1 SE) AE in IR-ipsilateral remembered condition without visual feedback (open bar) and with visual feedback (solid bar) for A: left match, left reference and B: right match, right reference.

DISCUSSION

As observed in the previous study (Chapter 3) grasp force matching errors were greater when matching the reference with the opposite than the same hand, and errors were similar for both hands when matching the reference with the same hand. In this study the absolute error was generally larger when visual feedback was provided and this was more pronounced when matching the right hand reference with the left hand (CR condition). Vibration of the reference hand also contributed to an overall increase in matching error. Since the normalized absolute error was measured, asymmetry in CR matching (error greater for left than right hand matching) was observed only when vibration was applied.

Efferent copy and muscle proprioceptive feedback

Generally, the sense of effort is thought to be derived from corollary discharges (efferent copy) of the descending motor command (McCloskey 1974; Gandevia & McCloskey 1977; Jones & Hunter 1982; Jones 1986; Carson et al. 2002; Lafargue & Sirigu 2006). However, while sensory feedback is not considered necessary for force production/perception (Lafargue et al. 2003; Lafargue & Sirigu 2006), its contribution to force control cannot be overlooked (Johansson & Westling 1984; Johansson & Cole 1992; Jones & Piateski, 2006; Kilbreath et al. 1995; Toffin et al. 2003). The question of the *relative* contributions of the efferent copy and sensory feedback to the sense of effort still remains.

Neuroimaging studies have highlighted morphological and functional interhemispheric/interlimb differences. Given that (1) cortical representation of the dominant arm was found to be larger in the contralateral hemisphere than cortical representation of the non-dominant arm in its contralateral hemisphere (Dassonville et al., 1997; Volkmann et al., 1998; Kim et al., 2003), (2) both contralateral and ipsilateral activations of the cortex have been observed during uni-manual and bimanual movements, with ipsilateral activation of the cortex in response to non-dominant arm movement being greater than ipsilateral activation due to dominant arm movements (Kawashima et al., 1993, 1998; Kim et al., 1993; Babiloni et al., 2003; Verstynen et al., 2005; Callaert et al., 2011; van den Berg et al., 2011), and (3) intermanual transfer during motor learning is affected by ipsilateral involvement of the cortex (Chase & Seidler, 2008) and type of task/information to be transferred (Sainburg, 2002, 2005; Wang & Sainburg, 2004; Teixeira,

2000) – interlimb differences in the use of proprioceptive feedback or in the mode of control of muscle activity are likely.

Muscle spindles are highly sensitive to vibration (Burke et al. 1972; Roll and Vedel, 1982, Roll et al. 1989); however, Golgi tendon organs’ sensitivity to tendon vibration is also notable when a muscle is contracted (Roll et al., 1989). Despite the differences in sensitivity between the mechanoreceptors, it is clear that vibration modifies the peripheral sensory coding of ongoing motor activities (Roll et al, 1989; Martin et al., 1991; Martin & Park, 1997; Park & Martin, 1993, Roll et al., 2009) and muscle tension (Roll et al. 1989). Furthermore, muscle tendon vibration is also known to induce a tonic vibration response in the stimulated muscles (Hagbarth & Eklund, 1965, 1966; Martin & Park, 1997).

Hence, if proprioceptive feedback contributes to the sense of effort, then vibration-induced changes in sensory information should produce changes in matching error. In the present study, regardless of the visual “condition”, right hand matches were rather insensitive to muscle tendon vibration of the left hand reference while vibration of the right hand reference induced an increase in AE for left hand matches (Fig. 4.4). Although a recent study (Luu et al., 2012) suggests that muscle proprioceptive feedback is a component contributing to the sense of effort, the role of the reference/matching hand was not considered as the results and conclusions were based on averages ‘lumping together’ matching performances using either hand as reference and matching hand. Hence the distinction /differentiation of effects exposed by our results suggest that the contribution of proprioceptive feedback to the sense of effort may not be generalized/ applicable to both hand /hemisphere systems. Distinctions may be derived from the propensity of each system to use or not use sensory feedback.

Indeed, previous studies have assessed reaction time, movement time and/or position matching accuracy to explore upper limb differences in mode of control and use of visual and somatosensory feedback. Some researchers have reported a dominant arm advantage in manual aiming tasks (Flowers, 1975; Elliot et al., 1994, 1995; Todor & Cisneros, 1985) thought to result from the dominant arm’s greater ability to use visual information as task accuracy requirements were increased. However, this supposition has been questioned as others have found equivalent arm performances while manipulating visual feedback (Carson, 1992; Carson et al., 1990; Roy & Elliot, 1986), or that visual control dependence is greater for the left than right hand in bimanual tasks (Srinivasan and Martin, 2010). Recently, the dynamic dominance hypothesis (Sainburg, 2002, 2006; Bagesteiro & Sainburg, 2003, 2005) has posited a non-dominant arm advantage for "somatosensory-based error corrections". This assertion was prompted by the assessment of target accuracy when the dominant and non-dominant arms were unexpectedly loaded during rapid targeted elbow extensions. While both arms attempted to compensate for the unexpected load, the response of the non-dominant arm was judged more effective as its target accuracy was less compromised.

The open-loop/closed-loop hypotheses also supports the idea that the non-dominant arm is more dependent on feedback, as it assumes that the dominant arm/hemisphere is specialized in open-loop movements and movement trajectory, while the non-dominant arm/hemisphere is specialized in closed loop (feedback dependent) and movement amplitude control (e.g. Fitts & Radford, 1966; Fitts, 1992; Haaland & Harrington, 1989a, 1989b; Hermsdorfer et al., 1999a, b, Mani et a. 2013).

Hence in light of our results, there are two alternative interpretations of the assumed specialization and mode of control of each hand /hemisphere:

- The right (dominant) hand system may primarily use the efferent copy of the reference motor command to perform the matching task and the execution is performed in a feedforward manner. While the left non-dominant hand system may use a combination of efferent copy and proprioceptive feedback and the matching is based on feedback control.
- The right hand system may use the integration of the efferent copy and the vibration induced increase in grip force (by the TVR). While the left non-dominant hand system uses a combination of efferent copy and proprioceptive feedback and the matching task is based on feedback control.

In the former case, the right hand's force output would be consistent whether muscle proprioception is affected or not by vibration since the sensory information is ignored. This remains true in the CR and IR condition. The difference in error between these two conditions remains consistent with results and interpretations in our previous study (Adamo et al. 2012, Chapter 3). The increase in left hand matching error resulting from vibration is in agreement with an increase in muscle tension indicated by the vibration-induced increase in firing frequency of the Golgi tendon organs (Roll et al. 1989), and the contribution of “vibration-distorted” proprioceptive messages from the muscle spindles (Roll et al. 1989), as suggested by Luu et al. 2012.

In the latter case, the right hand force output attempts to match the sum of forces produced by the motor command (associated with the efferent copy) and the TVR, which would explain why the right hand error matching is not strongly affected by vibration since the reference force is constrained to a constant level. This assumes that in the CR condition, the left hand internal representation of effort is a combination of efferent copy and proprioceptive feedback representing the TVR. However, the proprioceptive feedback, corresponds to the total muscle tension and not to the TVR alone, which means that the CNS would have to compare the motor command and the sensory feedback to extract the TVR force representation. In that case, there is incongruence between the efferent copy and the proprioceptive feedback and there is no demonstration yet showing a close relationship between the TVR and ascending proprioceptive information since the gain of peripheral loops contributing to the TVR is a function of multiple peripheral influences. Therefore, the primary use of efferent copy by the right hand may be a more reasonable interpretation so far.

Nevertheless, since left hand matching in the IR and CR conditions exhibit larger errors with than without vibration, it seems reasonable to assume that the left hand uses a combination of efferent copy and sensory feedback. The larger error with vibration may reflect both the increase in tension simulated by vibration induced increase in afferent flow and the conflict/incongruence between the efferent copy and the proprioceptive feedback.

Since AE is an absolute measure, the direction (over/under estimation of the reference) cannot be ascertained. Given that, and the complexity of the possible interactions between vibration, visual feedback and the incongruity of the visual information and internal representation of force (explained below), gender, and hand strength, our proposition may need to be validated by further investigations.

Perception of effort and visual feedback

In this study, there is a tendency for the AE to increase with visual feedback. Adamo (2007) observed a similar but significant effect in her force matching study. Based on the observation that the rise time of the reference and matching force increased when visual feedback was provided, Adamo posited that this delay resulted from the feedback control mode imposed by the visual tracking of force output. Further, the visual information was thought to represent the force output and was associated with peripheral sensory feedback. Given that the efferent copy contributes to sense of effort (McCloskey 1974; Gandevia & McCloskey 1977; Jones & Hunter 1982; Jones 1986; Carson et al. 2002; Lafargue & Sirigu 2006, Luu et al. 2012), the efferent copy based representation of force formed during the no-vision trials was thought to be a better or more accurate representation of effort than the peripheral information based force representation formed when visual feedback was provided. This difference in representation was thought to be the reason for the increase in error when visual feedback was provided.

This interpretation was supported by the results of Henningsen et al.'s (1995) concerning a bilateral finger force matching task. In this study participants were asked to simultaneously match the force levels produced by each finger. They observed that when continuous visual feedback of the non-dominant finger's force output was provided the matching error was unchanged. However, the matching error was eliminated when the dominant finger's force output was continuously displayed. The asymmetry in force matching was thought to be the result of greater cortical representation and excitability of the dominant hand/finger, so the same motor command would result in higher right than left finger forces. By providing continuous feedback of the dominant hand/finger's force output, the motor command was modified to accommodate the asymmetry in motor drive/cortical representation, and resulted in the equalization of force output between the two hands. In Adamo's and this study, visual feedback was not continuously provided, and therefore it is probable that the association between the visual information and the force perception was not properly made. And as such resulted in the increase in matching error observed when visual information was provided.

Our present results are still in agreement with a likely poor association between the visual feedback and internal representation of the reference force, whether this internal representation is modulated or not by a proprioceptive feedback. In addition, the current results may reinforce the general perspective that force build up (or first phase of the matching task) is primarily based on the efferent copy and that force steady state may or may not use proprioceptive feedback. In the present case the right hand system may disregard the proprioceptive feedback while the left hand system may use it to maintain the force level.

In conclusion, the study exposed significant upper limb differences in sensory information use/dependence during force reproduction. Vibration of the right reference hand resulted in a significant increase in the left match error, while vibration of the left reference did not affect right hand matching performance. While the precise mechanism underlying this asymmetry in performance could not be fully identified, this realization does highlight the need for future studies to further elucidate the relationship between hemispheric specialization, cortical representations, handedness and gender in relation to force and sense of effort.

CHAPTER 5

GENERAL DISCUSSION AND CONCLUSION

How important are our hands? Ethel J. Alpenfels (1955) described the hands as sentient, capable of both serving as a tool and wielding a tool, and as the main characteristic differentiating the human species from all other known life forms.

In the current study, our overall goals were to (1) determine the contribution of sensory and motor processes to asymmetries in upper limb control (i.e. movement sense and sense of effort), and (2) evaluate the effects of both gender and handedness on these asymmetries. The concept of sensory and motor system gains was used to encapsulate the functional and neuroanatomical gender and handedness related differences associated with these systems. Note that the gain represents the input and output relationship of a system in term of magnitude. In the following sections, the major findings with regard to gender, handedness and hand dominance related differences and the sensory and motor components of upper limb motor control will be discussed.

SUMMARY OF MAJOR FINDINGS

- Movement sense is asymmetric in males but not in females regardless of handedness.
- Females tend to be more sensitive to vibration induced activity of proprioceptive receptors, which translates into higher movement velocity reproductions with both hands.
- The sense of effort is clearly asymmetric in right handers (RH) but not in left handers (LH). RH asymmetry appears to be dependent on hand strength differences and an intrinsic motor asymmetry.

- The sense of effort associated with the left hand is modulated by proprioceptive feedback, while the sense of effort associated with the right hand seems to be insensitive to sensory feedback.
- Control of the right hand seems to be primarily based on a feedforward mode, while control of the left hand may be more prone to a feedback mode.
- Visual feedback of the reference force may not be properly associated with the internal representation of effort, at least in the context of our experiment.

Sensory component

Asymmetry in kinesthesia (Chapter 2) was observed in a task requiring the reproduction of a movement velocity based solely on proprioceptive information from the reference hand since the active matching movement required very little force exertion (< 2% MVC). Given this context, the differences in movement reproductions between the left and right upper limbs were assumed to be primarily of sensory origin with negligible interference from the motor component. Indeed, the influence of any asymmetry in the motor system gains would be minimal if force is small since the difference in gain is not expected to be large. For example the asymmetry in position sense (Adam & Martin, 2009) indicates a difference in closed loop gain of about 13% (with a constant error of 4° for a 30° displacement).

An asymmetrical response to sensory modulation was also noted in force matching (Chapter 4), with the left non-dominant hand being the only one affected by the vibration induced alteration of the sensory feedback loop. However, it should be noted that the mediating effects of gender and handedness could not be assessed.

Gender (males vs. females). Two significant differences were identified: (1) the symmetric response of both hands to the kinesthetic reference for left and right handed females, while corresponding handedness related responses where asymmetric for the males, and (2) the higher sensory sensitivity of females as evidenced by their generally higher reproduction of movement speed with either hand, when compared to males.

The strong tendency of higher sensitivity to vibration for females than males is supported by results concerning the sensitivity of muscle spindles (Ribot-Ciscar, personal communication). At our request, Ribot-Ciscar investigated the effect of gender on the dynamic index of Ia afferents (Jansen & Matthews, 1962) from previously recorded activity of these afferents in lower leg muscles. She found that, in response to passive or active movements, the dynamic index of Ia afferents (i.e. difference between peak activity while muscle is being stretched and plateaued activity after stretch complete), which is related to movement velocity (Grill & Hallett, 1995), is higher for females than males. In our experiment, the lack of statistical significance of the difference in "sensitivity" to vibration between males and females may be attributed to the highly variable nature of individual susceptibility to movement illusions (e.g., Roll et al., 1989, Kavounoudias et al., 2008; Adamo et al., 2011).

Neither the lack of asymmetry in females vs. asymmetric performance in males, nor the gender effect on sensitivity was explicitly observed in the sense of effort experiments (Chapters 3 and 4). The sub-optimal distribution of males and females within each of the strength sub-groups may be responsible for a lack of computational power, and was further confounded by the relative dominance/size of the grip strength effect as compared to the possible gender effect in that context. However, given the 3:1 ratio of females to males, it is probable that in right handers the observed degradation of the left hand matching the right hand reference under vibration (Chapter 4) was exacerbated by the higher sensitivity to vibration of the (over represented) females in the sample.

Handedness (right vs. left handers). In the velocity matching experiment, handedness related sensory asymmetry was only observed in males. Asymmetry in right handers was a mirror image of asymmetry in left handers, i.e. the speeds of movements reproduced with the non-dominant hand were higher when illusions where elicited in the dominant hand and vice versa.

Since only right handers were involved in the experiment testing the influence of vibration on effort perception, the assessment of handedness effects on the eventual contribution of the sensory component was not possible.

Hand dominance (dominant hand vs. non-dominant hand). The velocity matching experiment also suggests that the sensory gain may be greater for the dominant than the non-dominant. This is consistent with the fact that the cortical hand representation (in somatosensory cortex) is greater for the dominant than the non-dominant hand (Soros et al., 1999). Hence, the afferent flow may be greater for the dominant than non-dominant hand and therefore the frequency content of the message from the dominant hand may also be higher. Then, since a higher frequency content corresponds to a higher movement velocity (Roll & Vedel, 1989, 1982; Redon et al., 1994; Romaiguiere et al., 2003), this may explain the higher speed of matching movements in response to vibration-induce movement illusions in dominant hand reference.

While, the relative sizes of the sensory gain could not be validated by either of the sense of effort experiments, the last experiment (Chapter 4) further suggests that the left non-dominant hand is more dependent on sensory feedback than the dominant hand (Sainburg, 2002; Bagesteiro & Sainburg, 2003).

Motor component

Asymmetries in the motor component were investigated in the two sense of effort experiments.

Gender (males vs. females). While motor system related asymmetries were observed in both sense of effort experiments, gender's influence on the motor components were not found. This does not preclude possible gender interactions as females are thought to be less lateralized than males (Robinson et al., 1990; Wisniewski, 1998; Amunts et al., 2000; Cykowski et al., 2008). However, the gender distribution across strength groups did not allow for direct statistical comparison.

Handedness (left vs. right). The handedness related asymmetries in the motor systems were identified as (1) asymmetry was significantly less pronounced in left handers than right handers, and (2) asymmetry in right handers was related to grip strength differences. When compared to sensory asymmetry (Chapter 2), the lack of motor asymmetry in left handers may reflect the fact that while they have adapted to living in a right-handed world, not all components of the sensorimotor systems are adapted.

In right handers, the matching errors were neither related to continuous (0 - 1) measure nor dichotomous (High and Low) classification of the laterality index (as assessed by the Edinburgh Inventory). Instead, matching performance was highly correlated to the difference in grip strength between the two hands, and an intrinsic asymmetry remained even when the matching errors were normalized using the maximum grip strength of the hands. Given that the dominant hand is not necessarily the stronger hand (Incel et al., 2002; Petersen et al., 1989), this highlights the fact that laterality is not just a function of consistency of use, but nature of usage as well (Elbert et al., 1995; Adkins et al., 2006). Further, these strength differences may reflect a difference in gain between the two hemisphere systems as strength is correlated to the size of the cortical representation of the upper limbs and larger motor cortical representations are thought to indicate a higher motor resolution and as such a lower gain (Adamo & Martin, 2009).

Finally, this result does make a case for the inclusion of performance based assessments of handedness (Bernard et al., 2011) in behavioral studies.

Hand dominance (dominant hand vs. non-dominant hand). The left non-dominant hand dependence on sensory feedback suggests that the non-dominant hand is feedback controlled. Of course, the effects of strength, gender and task characteristics cannot be ignored.

Overall, these findings lead us to suggest that hand preference and gender contribute to differences in movement representation, force production and sense of effort that may result from the combination of cortical structural differences and information processing specific to each hemisphere, gender and handedness group.

LIMITATIONS AND FUTURE WORK

Do these results reflect gender, handedness and hemispheric lateralization?

Our findings highlight the importance of considering individual factors in both theoretical and practical applications as they support close correlations between neuroanatomical and functional differences and behaviors. However they also show that complex and multilayered interactions are likely to mitigate/modulate sensorimotor activities. Further investigations into the effect of gender and handedness are warranted to refine interpretations and understanding of “movement” representation.

Specifically:

(1) Given the inconsistencies in the neuroimaging results reported, the relationship between structural and functional differences and behavior may not be completely clear.

(2) Effects of gender and handedness could not be fully explored since interactions such as hand strength differences prevented a robust statistical analysis

(3) Some uncertainty about the relative contribution of feedback information and efferent copy to internal representations still remain. In addition, if the feedback mode of control is quasi certain in position control the alternative of different mode of control in velocity matching and force matching may present some uncertainty as well. The open loop mode of control for the dominant hand seems to be well supported, however the mode of control of the non-dominant hand is less evident. This aspect remains a major question in left handers as their sensory and motor behaviors present significant differences. In light of current limitations, complementary experiments investigating the role of the sensory component in the sense of effort have already begun. These experiments explore the role of the TVR in the force generated by the reference hand under vibration and the sensitivity of the TVR between the two hands as a function of gender and handedness, as well as the relationship between the TVR (primarily a peripheral mechanism) and the associated vibration induced sensory information reaching the central level. Furthermore, the phenomena observed in force matching task may also vary with the level of force requires, as indicated by a pilot study.

(4) Overall, interactions revealed by our current results were not easy to predicted based on current knowledge; however, they present an important positive aspect since they also reveal the strong limitation of earlier interpretations that failed to consider the role of all components of the system (e.g. attributing error only to inter-hemispheric transfer of information, the combination of results obtained with either reference hand, neglecting a possible gender effect).

IMPLICATIONS OF CURRENT WORK

Importance of considering both sensory and motor components. Given the fact that both sensory and motor asymmetries were identified, and that individuals differed in their responses to both, the importance of considering both modalities in future studies cannot be overstated.

Laterality and its behavioral correlates. Our findings highlight the need to consider individual factors in both theoretical and practical applications. While, close correlations between neuroanatomical and functional differences and behaviors are supported; the complex and multilayered interactions between these are likely to mitigate/modulate sensorimotor activities. Therefore, future studies in this domain need to take a multidimensional approach – incorporating both neuroimaging and behavioral techniques to fully understand the effect of individual differences on upper limb motor performance.

While it may be tempting to generalize our results by broadly stating that females and left handers appear to be less lateralized than males and right handers respectively, these results, by necessity, were obtained for a controlled series of tasks and may not fully reflect the real world effect of these asymmetries on everyday performance nor differences associated with the requirements of different tasks.

Assessment of handedness. Handedness is a multi-dimensional phenomenon, and therefore simply using a questionnaire to determine consistency of use may be insufficient. Both the frequency and nature of hand use are important. Since questionnaires generally focus on consistency of use, they may need to be complemented by performance assessments.

REFERENCES

Aboitiz F, Scheibel AB, Fisher RS, Zaidel E (1992b) Fiber composition of the human corpus callosum. Brain Res 598:143–153.

Aboitiz F, Scheibel AB, Zaidel E (1992a) Morphometry of the Sylvian fissure and the corpus callosum, with emphasis on sex differences. Brain 115:1521–1541.

Adamo D, Martin BJ, Brown SH (2007) Age-related differences in upper limb proprioceptive acuity. Percept Mot Skills 104: 1297-1309.

Adamo DE, Martin BJ (2009) Position sense asymmetry. Exp Brain Res 192:87–95.

Adamo DE, Scotland S, Martin BJ (2012) Asymmetry in grasp force matching and sense of effort, Exp Brain Res 217: 273-285.

Adamo DE, Alexander NB, Brown SH (2009) The Influence of Age and Physical Activity on Upper Limb Proprioceptive Ability. Journal of Physical Activity and Aging 17(3): 272-293.

Adamo DE, Taufiq A (2011) Hand Preference: why does it matter? Hand 6: 295-303.

Adkins DL, Boychuk J, Remple MS, Kleim JA (2006) Motor training induces experience-specific patterns of plasticity across motor cortex and spinal cord. J Appl Physiol 101: 1776-1782.

Allen EA, Erhardt EB, Damaraju E, Gruner W, Segall JM, Silva RF, Havlicek M, Rachakonda S, Fries J, Kalyanam R, Michael AM,et al (2011) A baseline for the multivariate comparison of resting-state networks. Front Syst Neurosci 5: 1–23.

Allen TJ, Ansems GE, Proske U (2007) Effects of muscle conditioning on position sense at the human forearm during loading or fatigue of elbow flexors and the role of the sense of effort, J Physiol 580: 423-434.

Alonso-Nanclares L, Gonzalez-Soriano J, Rodriguez JR, DeFelipe J (2008) Gender differences in human cortical synaptic density. P Natl Acad Sci. 105: 14615-14619.

Amunts K, Jancke L, Mohlberg H, Steinmetz H, Zilles K (2000) Interhemispheric asymmetry of the human motor cortex related to handedness and gender. Neuropsychologia 38:304–312.

Amunts K, Schlaug G, Schleicher A, Steinmetz H, Dabringhaus A, Roland PE, Zilles K (1996) Asymmetry in the human motor cortex and handedness. Neuroimage 4: 216-222.

Andreasen NC, Flaum M, Swayze VW, O'Leary DS, Alliger R, Cohen G, Ehrhardt J, Yuh WTC (1993) Intelligence and brain structure in normal individuals. Amer J Psychiat 150: 130–134.

Annett M (1972) The distribution of manual asymmetry. Br J Psychol 63: 343-358.

Annett M (1985) Left, right, hand and brain: The right shift theory. Erlbaum, London.

Babiloni C, Carducci F, Del Gratta C, Demartin M, Romani GL, Babiloni F, Rossini PM (2003) Hemispherical asymmetry in human SMA during voluntary simple unilateral movements. An fMRI study. Cortex 39:293–305.

Bagesteiro LB, Sainburg RL (2002) Handedness: dominant arm advantages in control of limb dynamics. J Neurophysiol 88: 2408-2421.

Bagesteiro LB, Sainburg RL (2003) Nondominant arm advantages in load compensation during rapid elbow joint movements. J Neurophysiol 90: 1503-1513.

Bagesteiro LB, Sarlegna FR, Sainburg RL (2006) Differential influence of vision and proprioception on control of movement distance. Exp Brain Res 171: 358-370.

Baraldi P, Porro CA, Serafini M, Pagnoni G, Murari C, Corazza R, Nichelli P (1999) Bilateral representation of sequential finger movements in human cortical areas. Neurosci Lett 269:95–98.

Barnsley RH, Rabinovitch MS (1970) Handedness: Proficiency versus stated preference. Percept Mot Skills 30: 343-362.

Baynes K, Eliassen JC, Lutsep HL, Gazzaniga MS (1998) Modular organization of cognitive systems masked by interhemispheric integration.Sci 280: 902-905.

Bear D, Schiff D, Save, J, Greenberg M, Freeman R (1986) Quantitative analysis of cerebral asymmetries: Fronto-occipital correlation, sexual dimorphism and association with handedness. Arch Neurol 43: 598.

Bear D, Schiff D, Save, J, Greenberg M, Freeman R (1986) Quantitative analysis of cerebral asymmetries: Fronto-occipital correlation, sexual dimorphism and association with handedness. Arch Neurol 43: 598.

Beaton A (2003) The nature and determinants of handedness. Brain Asymmetry 105-108.

Bechtol O (1954) Grip test. The use of a dynamometer with adjustable handle spacings. J Bone Joint Surgery, 36A (4): 820–824

Bernard JA, Taylor SF, Seidler RD (2011) Handedness, dexterity, and motor cortical representations. J Neurophysiol 105:88–99.

Bernard JA, Seidler RD, Hassevoort K M, Benson BL, Welsh RC, Wiggins JL, et al (2012) Resting state cortico-cerebellar functional connectivity networks: A comparison of anatomical and self-organizing map approaches. Frontiers in neuroanatomy 6: 31.

Biswal B, Yetkin FZ, Haughton VM, Hyde JS(1995) Functional connectivity in the motor cortex of resting human brain using echo-planar MRI. Magn Reson Med 34:537–541.

Biswal BB, Mennes M, Zuo XN, et al. (2010) Toward discovery science of human brain function. Proc Natl Acad Sci U S A 107: 4734 – 4739.

Black JE, Isaacs KR, Anderson BJ, Alcantara AA, Greenough WT (1990) Learning causes synaptogenesis, whereas motor activity causes angiogenesis, in cerebellar cortex of adult rats. Proc. Natl Acad. Sci. USA 87: 5568–5572.

Blatow M, Nennig E, Durst A, Sartor K, Stippich C (2007) fMRI reflects functional connectivity of human somatosensory cortex. Neuroimage 37:927–936Brouwer B, Sale MV, Nordstrom MA (2001) Asymmetry of motor cortex excitability during a simple motor task: relationships with handedness and manual performance. Exp Brain Res 138:467–476.

Bloom JS, Hynd GW (2005) The role of the corpus callosum in interhemispheric transfer of information: Excitation or inhibition? Neuropsychol Rev 15: 59-71.

Bradshaw JL, Nettleton NC (1983) Human cerebral asymmetry. Englewood Cliffs, NJ: Prentice-Hall.

Bradshaw JL, Nicholls MER, Rogers MA (1998) An intermanual advantage for tactual matching. Cortex 34 (5): 763-770.

Burke D, Andrews CJ, Lance JW (1972) Tonic vibration reflex in spasticity, Parkinson's disease, and normal subjects. J Neurol Neurosur Ps 35: 477-486.

Cafarelli E (1988) Force sensation in fresh and fatigued human skeletal muscle. Exercise Sport Sci R 16: 139-168.

Cafarelli E, Bigland-Ritchie B (1979) Sensation of static force in muscles of different length. Exp Neurol 65:511–525.

Cafarelli E, Kostka CE (1981) Effect of vibration on static force sensation in man. Exp Neurol 74:331–340Carson RG, Riek S, Shahbazpour N (2002) Central and peripheral mediation of human force sensation following eccentric or concentric contractions. J Physiol 539:913–925.

Callaert DV, Vercauteren K, Peeters R, Tam F, Graham S, Swinnen SP, Sunaert S, Wenderoth N (2011) Hemispheric asymmetries of motor versus nonmotor processes during (visuo)motor control. Hum. Brain Mapp 32: 1311–1329.

Calvin-Figuière S, Romaiguère P, Roll JP (2000) Relations between the directions of vibration-induced kinesthetic illusions and the pattern of activation of antagonist muscles. Brain Res 881: 128-138.

Canli T, Haas B, Amin Z, Constable RT (2003) An fMRI study of personality traits during performance of the emotional Stroop task. Society for Neuroscience Abstracts 33: 725–727.

Carson RG (2005) Neural pathways mediating bilateral interactions between the upper limbs. Brain Res Rev 49: 641-662.

Carson RG, Chua R, Elliott D, Goodman D (1990a) The contribution of vision to asymmetries in manual aiming. Neuropsychologia 28: 1215-1220.

Carson RG, Elliott D, Goodman D, Dickinson J (1990b) Manual asymmetries in the reproduction of a 3-dimensional spatial location. Neuropsychologia 28: 99-103.

Carson RG, Riek S, Shahbazpour N (2002) Central and peripheral mediation of human force sensation following eccentric or concentric contractions. J Physiol 539:1469-7793.

Chase C, Seidler R (2008) Degree of handedness affects intermanual transfer of skill learning. Exp Brain Res 190:317–328.

Chen R, Cohen LG, Hallett M (1997) Role of the ipsilateral motor cortex in voluntary movement. Can J Neurol Sci 24: 284-291.

Chen R, Gerloff C, Hallett M, Cohen LG (1997) Involvement of the ipsilateral motor cortex in finger movements of different complexities. Ann Neurol 41:247–254.

Cheng Y, Decety J, Lin CP, Hsieh JC, Hung D, Tzeng OJ (2007), Sex differences in spinal excitability during observation of bipedal locomotion, Neuroreport 18: 887-890.

Cherbuin N, Brinkman C (2006) Hemispheric interactions are different in left-handed individuals. Neuropsychology 20:700–707.

Chiarello C (1980) A house divided? Cognitive functioning with callosal agenesis. Brain Lang 11: 128–158.

Christakou A, Halari R, Smith AB, Ifkovits E, Brammer M, Rubia K (2009) Sex-dependent age modulation of frontostriatal and temporo-parietal activation during cognitive control. Neuroimage 48:223-236.

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

Clarke JM, Lufkin RB, Zaidel E (1993) Corpus callosum morphometry and dichotic listening performance: individual differences in functional inter-hemispheric inhibition? Neuropsychologia, 31: 547–557.

Clarke JM, Zaidel E (1994) Anatomical-behavioral relationships: corpus callosum morphometry and hemispheric specialization. Behav Brain Res 64:185–202.

Clarke S, Kraftsik R, van der Loos H, Innocenti GM (1989) Forms and measures of adult and developing human corpus callosum: is there sexual dimorphism? J Comp Neurol 280:213–230.

Corballis MC, Morgan MJ (1978) On the biological basis of human laterality: I. Evidence for a maturational left–right gradient. Behav Brain Sci 1: 261-269.

Crago PE, Houk JC, Rymer WZ (1982) Sampling of total muscle force by tendon organs. J Neurophysiol 47:1069–1083.

Crucian GP, Berenbaum SA (1998): Sex Differences in Right Hemisphere Tasks. Brain Cogn 36: 377–389.

Cykowski MD, Coulon O, Kochunov PV, Amunts K, Lancaster JL, Laird AR, Glahn DC, Fox PT (2008) The central sulcus: an observer-independent characterization of sulcal landmarks and depth asymmetry. Cereb Cortex 18:1999–2009.

Dassonville P, Zhu XH, Uurbil K, Kim SG, Ashe J (1997) Functional activation in motor cortex reflects the direction and the degree of handedness. Proc Natl Acad Sci U S A 94: 14015-14018.

Davis PJ (1999) Gender differences in autobiographical memory for childhood emotional experiences. J Pers Soc Psychol 76:498–510.

De Gennaro L, Cristiani R, Bertini M, Curcio G, Ferrara M, Fratello F, et al (2004) Handedness is mainly associated with an asymmetry of corticospinal excitability and not of transcallosal inhibition. Clin Neurophysiol 115: 1305-1312.

Dekaban AS, Sadowsky D (1978) Changes in brain weights during the span of human life: relation of brain weights to body heights and body weights. Ann Neurol 4:345–356.

DeLisi LE, Hoff AL, Schwartz JE, Shields GW, Halthore SN, Gupta SM, et al (1991) Brain morphology in first-episode schizophrenic-like psychotic patients: a quantitative magnetic resonance imaging study. Biol Psych 29:159-175.

Eklund G, Hagbarth KE (1965) Motor effects of vibratory muscle stimuli in man. Electroencephalogr Clin Neurophysiol 19: 619.

Eklund G, Hagbarth KE (1966) Normal variability of tonic vibration reflexes in man. Exp Neurol 16: 80-92.

Elbert T, Pantev C, Wienbruch C, Rockstroh B, Taub E (1995) Increased cortical representation of the fingers of the left hand in string players. Sci 270: 305-307.

Elliott D, Chua R (1996) Manual asymmetries in goal-directed movement. Manual asymmetries in motor performance. CRC, Boca Raton, 143-158.

Elliott D, Chua R, Pollock BJ (1994) The influence of intermittent vision on manual aiming. Acta Psychologica 85: 1-13.

Elliott D, Lyons J, Chua R, Goodman D, Carson RG (1995) The influence of target perturbation on manual aiming asymmetries in right-handers. Cortex 31: 685-697.

Escalona PR, Mcdonald WM, Doraiswamy PM, Boyko OB, Husain MM, Figiel GS, Laskowitz D, Ellinwood EH Jr, Krishnan KRR (1991) In vivo stereological assessment of human cerebellar volume: Effects of gender and age. AJNR 12: 927-929.

Fallon JB, Macefield VG (2007) Vibration sensitivity of human muscle spindles and Golgi tendon organs. Muscle Nerve 36: 21-29.

Fields RD (2008) White matter in learning, cognition and psychiatric disorders. Trends Neurosci 31:361–70.

Fiez JA (1996). Cerebellar contributions to cognition. Neuron, 16, 13-15.

Fiez JA, Raife EA, Balota DA, Schwarz JP, Raichle ME, Petersen SE (1996). A positron emission tomography study of the short-term maintenance of verbal information. J Neurosci 16: 808.

Filipek R, Richelme C, Kennedy D, Caviness V (1994) The young adult human brain: an MRI-based morphometric analysis. Cereb Cortex 4: 344–360.

Filippi M, Valsasina P, Misci P, Falini A, Comi G, Rocca MA (2013) The organization of intrinsic brain activity differs between genders: A resting-state fMRI study in a large cohort of young healthy subjects. Hum. Brain Mapp., 34: 1330–1343.

Fitts PM (1992) The information capacity of the human motor system in controlling the amplitude of movement. J Exp Psych 121: 262-269.

Fitts PM, Radford BK (1966) Information capacity of discrete motor responses under different cognitive sets. J Exp Psychiat 71:475-482.

Fling BW, Benson BL, Seidler RD (2013) Transcallosal sensorimotor fiber tract structure-function relationships. Hum. Brain Mapp 34: 384–395.

Fling BW, Kwak Y, Peltier SJ, Seidler RD (2012) Differential relationships between transcallosal structural and functional connectivity in young and older adults. Neurobiol Aging 33: 2521-2526.

Fling BW, Peltier SJ, Bo J, Welsh RC, Seidler RD (2011) Age differences in interhemispheric interactions: callosal structure, physiological function, and behavior. Frontiers Neurosci 5: 38.

Fling BW, Seidler RD (2012) Task-dependent effects of interhemispheric inhibition on motor control. Behav Brain Res 226: 211-7.

Fling BW, Walsh CM, Bangert AS, Reuter-Lorenz PA, Welsh RC, Seidler RD (2011) Differential callosal contributions to bimanual control in young and older adults. J Cognitive Neurosci 23: 2171-2185.

Flowers K (1975) Handedness and controlled movement. Br J Psychol 66: 39-52.

Foundas AL, Eure KF, Luevano LF, Weinberger DR (1998) MRI asymmetries of Broca's Area: The pars triangularis and pars opercularis. Brain Lang 64: 282–296.

Franz EA, Rowse A, Ballantine B (2002) Does handedness determine which hand leads in a bimanual task? J Mot Behav 34:402–412.

Galaburda AM, LeMay M, Kemper TL, Geschwind N (1978) Right-left asymmetrics in the brain. Science 199: 852-856.

Gandevia SC (1982) The perception of motor commands or effort during muscular paralysis. Brain 105:151–159.

Gandevia SC, Burke D (1992) Does the nervous system depend on kinesthetic information to control natural limb movements? Behav Brain Sci 15: 614-614.

Gandevia SC, Enoka RM, McComas AJ, Stuart DG, Thomas CK (1995) Neurobiology of muscle fatigue. Advances and issues. Adv Exp Med Biol 384:515–525.

Gandevia SC, McCloskey DI (1977) Changes in motor commands, as shown by changes in perceived heaviness, during partial curarization and peripheral anaesthesia in man. J Physiol 272:673–689.

Gandevia SC, McCloskey DI, Burke D (1992) Kinaesthetic signals and muscle contraction. Trends Neurosci 15: 62-65.

Gao JH, Parsons LM, Bower JM, Xiong J, Li J, Fox PT (1996) Cerebellum implicated in sensory acquisition and discrimination rather than motor control. Sci 272: 545-547.

Gauthier GM, Roll JP, Hugon M, Martin B (1983) Motor dyscontrol as a hazard in massive body vibration in man, Adv Neurol 39: 685-697.

Gazzaniga MS (2000) Cerebral specialization and interhemispheric communication Does the corpus callosum enable the human condition? Brain123: 1293-1326.

Gell N, Werner RA, Hartigan A, Wiggermann N, Keyserling WM (2010) Risk factors for lower extremity fatigue among assembly plant workers, Am J Ind Med.

Geschwind N, Levitsky W (1968) Human brain: left-right asymmetries in temporal speech region. Science 161: 186-187.

Giedd J, Snell J, Lange N, Rafapakse J, Kaysen D, Vaituzis C, Vauss R, Hamburger S, Kozuch P, Rapoport J (1996) Quantitative magnetic resonance imaging of human brain development: ages. Cereb Cortex, 6: 551–560

Gilbert AN, Wysocki CJ (1992) Hand preference and age in the United States. Neuropsychologia 30: 601-608.

Goble D, Noble BC, Brown SH (2009) Proprioceptive target matching asymmetries in left-handed individuals. Exp Brain Res 197:403–408.

Goble DJ, Brown SH (2007) Task-dependent asymmetries in the utilization of proprioceptive feedback for goal-directed movement, Exp Brain Res 180: 693-704.

Goble DJ, Lewis CA, Brown SH (2006) Upper limb asymmetries in the utilization of proprioceptive feedback. Exp Brain Res 168: 307-311.

Goodwin GM, McCloskey DI, Matthews PB (1972) A systematic distortion of position sense produced by muscle vibration, J Physiol 221: 8P-9P.

Goodwin GM, McCloskey DI, Matthews PB (1972) Proprioceptive illusions induced by muscle vibration: contribution by muscle spindles to perception?, Sci 175: 1382-1384.

Goodwin GM, McCloskey DI, Matthews PB (1972) The contribution of muscle afferents to kinaesthesia shown by vibration induced illusions of movement and by the effects of paralysing joint afferents, Brain 95: 705-748.

Gordon AM, Forssberg H, Iwasaki N (1994) Formation and lateralization of internal representations underlying motor commands during precision grip. Neuropsychologia 32:555–568.

Grabowska A, Herman A, Nowicka A, Szatkowska I, Szeląg E (1994) Individual differences in the functional asymmetry of the human brain. Acta Neurobiol Exp (Wars) 54: 155–162.

Grill SE, Hallett M (1995) Velocity sensitivity of human muscle spindle afferents and slowly adapting type II cutaneous mechanoreceptors. J Physiol 489 (Pt 2): 593-602.

Gur RC, Turetsky BI, Matsui M, Yan M, Bilker W, Hughett P, Gur RE (1999) Sex differences in brain gray and white matter in healthy young adults: correlations with cognitive performance. J Neurosci 19: 4065–4072.

Haaland KY (2006) Left hemisphere dominance for movement. Clin Neuropsychol 20:609–622.

Haaland KY, Cleeland CS, Carr D (1977) Motor performance after unilateral hemisphere damage in patients with tumor. Arch Neurol 34: 556-559.

Haaland KY, Delaney HD (1981) Motor deficits after left or right hemisphere damage due to stroke or tumor. Neuropsychologia 19: 17-27.

Haaland KY, Harrington D (1989a) The role of the hemispheres in closed loop movements. Brain Cogn 9: 158-180.

Haaland KY, Harrington DL (1989b) Hemispheric control of the initial and corrective components of aiming movements. Neuropsychologia 27: 961-969.

Haaland KY, Harrington DL (1994) Limb-sequencing deficits after left but not right hemisphere damage. Brain Cogn 24: 104-122.

Haaland KY, Harrington DL (1996) Hemispheric asymmetry of movement. Curr Opin Neurobiol 6: 796-800.

Haaland KY, Prestopnik JL, Knight RT, Lee RR (2004) Hemispheric asymmetries for kinematic and positional aspects of reaching. Brain 127: 1145-1158.

Habib M, Gayraud D, Oliva A, Regis J, Salamon G, Khalil R (1991) Effects of handedness and sex on the morphology of the corpus callosum: a study with brain magnetic resonance imaging. Brain Cognit 16:41–61.

Halsband U, Ito N, Tanji J, Freund HJ (1993) The role of premotor cortex and the supplementary motor area in the temporal control of movement in man. Brain J Neurol 116(Pt 1):243–266.

Haude RH, Morrow-Tlucak M, Fox DM, Pickard KB (1987) Differential visual field-interhemispheric transfer: can it explain sex and handedness differences in lateralization? Percept Mot Skills 65:423–429.

Heilman KM (2000) Limb apraxias: higher-order disorders of sensorimotor integration. Brain 123: 860–879.

Hellige JB (1993) Hemispheric asymmetry: What’s right and what’s left. London: Harvard University Press.

Helmholtz HV (1925) Treatise on physiological optics. Vol. 3. Rochester, N. Y.: Optical Society of America.

Helsen WF, Starkes JL, Elliott D, Buekers MJ (1998) Manual asymmetries and saccadic eye movements in right-handers during single and reciprocal aiming movements. Cortex 34:513-530.

Henningsen H, Ende-Henningsen B, Gordon AM (1995) Asymmetric control of bilateral isometric finger forces. Exp Brain Res 105:304–311.

Hermsdörfer J, Laimgruber K, Kerkhoff G, Mai N, Goldenberg G (1999a) Effects of unilateral brain damage on grip selection, coordination, and kinematics of ipsilesional prehension. Exp Brain Res 128: 41-51.

Hermsdörfer J, Ulrich S, Marquardt C, Goldenberg G, Mai N (1999b) Prehension with the ipsilesional hand after unilateral brain damage. Cortex 35: 139-161.

Hines M, Chiu L, McAdams A, Bentler PM, Lipcamon JL (1992) Cognition and the corpus callosum: verbal fluency, visuospatial ability, and language lateralization related to midsagital surface areas of callosal subregions. Behav Neurosci 106: 3–14.

Hiscock M, Israelian M, Inch R, Jacek C, Hiscock-Kalil C (1995) Is there a sex difference in human laterality? II. An exhaustive survey of visual laterality studies from six neuropsychology journals, J Clin Exp Neuropsychol 17: 590-610.

Hlustík P, Solodkin A, Gullapalli RP, Noll DC, Small SL (2002) Functional lateralization of the human premotor cortex during sequential movements. Brain Cogn, 49(1), 54-62.

Hofer S, Frahm J (2006) Topography of the human corpus callosum revisited? Comprehensive fiber tractography using diffusion tensor magnetic resonance imaging. Neuroimage 32: 989-994.

Holcomb HH, Medoff DR, Caudill PJ, Zhao Z, Lahti AC, Dannals RF, Tamminga CA (1998) Cerebral blood flow relationships associated with a difficult tone recognition task in trained normal volunteers. CerebCortex 8: 534-542.

Honda H (1982) Rightward superiority of eye movements in a bimanual aiming task. Q J Exp Psychol A 34: 499-513.

Honda H (1984) Functional between-hand differences and outflow eye position information. Q J Exp Psychol A 36: 75-88.

Hyde JS, Linn MC (1988) Gender differences in verbal ability: A meta-analysis. Psychiat Bull 104: 53– 69.

Im K, Lee JM, Lee J, et al. (2006) Gender difference analysis of cortical thickness in healthy young adults with surface-based methods. Neuroimage 31: 31–8.

Incel N, Ceceli E, Durukan P, Erdem H, Yorgancioglu Z (2002) Grip strength: effect of hand dominance. Singapore Med J 43(5):234–237

Izumizaki M, Tsuge M, Akai L, Proske U, Homma I (2010) The illusion of changed position and movement from vibrating one arm is altered by vision or movement of the other arm, J Physiol 588: 2789-2800.

Jagacinski R, Flach J (2003) Control theory for humans: quantitative approaches to modeling performance. Lawrence Erlbaum Associates, London.

Jami L (1992) Golgi tendon organs in mammalian skeletal muscle: functional properties and central actions. Physiol Rev 72:623–666.

Jäncke L (1996) The hand performance test with a modified time limit instruction enables the examination of hand performance asymmetries in adults. Percept Motor Skill 82: 735-738.

Jäncke L, Steinmetz H (2003) Brain size: a possible source of inter-individual variability in corpus callosum morphology E. Zaidel, M. Iacoboni (Eds.), The Parallel Brain: The Cognitive Neuroscience of the Corpus Callosum, MIT Press, Cambridge.

Jansen JK, Matthews PB (1962) The central control of the dynamic response of muscle spindle receptors. J Physiol 161: 357-378.

Jeka JJ, Oie KS, Kiemel T (2008) Asymmetric adaptation with functional advantage in human sensorimotor control, Exp Brain Res 191: 453-463.

Johansson RS, Cole KJ (1992) Sensory-motor coordination during grasping and manipulative actions. Curr Opin Neurobiol 2:815–823

Johansson RS, Westling G (1984) Roles of glabrous skin receptors and sensorimotor memory in automatic control of precision grip when lifting rougher or more slippery objects. Exp Brain Res 56:550–564

Johnson MT, Ebner TJ (2000) Processing of multiple kinematic signals in the cerebellum and motor cortices, Brain Res Rev 33: 155-168.

Johnstone J, Galin D, Herron J (1979) Choice of handedness measures in studies of hemispheric specialization Int J Neurosci 9: 71-80.

Jones L (1989) Force matching by patients with unilateral focal cerebral lesions. Neuropsychologia 27:1153–1163.

Jones LA (1986) Perception of force and weight: theory and research. Psychol Bull 100:29–42.

Jones LA (1988) Motor illusions: what do they reveal about proprioception?, Psychol Bull 103: 72-86.

Jones LA (2003) Perceptual constancy and the perceived magnitude of muscle forces. Exp Brain Res 151:197–203.

Jones LA, Hunter IW (1982) Force sensation in isometric contractions: a relative force effect. Brain Res 244:186–189.

Jones LA, Hunter IW (1983) Effect of fatigue on force sensation. Exp Neurol 81:640–650.

Jones LA, Piateski E (2006) Contribution of tactile feedback from the hand to the perception of force. Exp Brain Res 168:298–302.

Jones LF, Burgess PR (1998) Neural gain changes subserving perceptual acuity, Somatosens Mot Res 15: 190-199.

Jung P, Baumgartner U, Bauermann T, Magerl W, Gawehn J, Stoeter P, Treede RD (2003) Asymmetry in the human primary somatosensory cortex and handedness. Neuroimage 19:913–923.

Jung P, Baumgartner U, Magerl W, Treede RD (2008) Hemispheric asymmetry of hand representation in human primary somatosensory cortex and handedness. Clin Neurophysiol 119:2579–2586.

Kang Y, Harris L (1993) Social-cultural influences on handedness: A cross-cultural study of Koreans and Americans. Paper presented at the TENNET (Theoretical and Experimental Neuropsychology) meeting, Montreal.

Kavounoudias A, Roll JP, Anton JL, Nazarian B, Roth M, Roll R (2008) Proprio-tactile integration for kinesthetic perception: an fMRI study. Neuropsychologia 46: 567-575.

Kawashima R, Inoue K, Sato K, Fukuda H (1997) Functional asymmetry of cortical motor control in left-handed subjects, Neuroreport 8: 1729-1732.

Kawashima R, Fukuda H (1994) Functional organization of the human primary motor area: an update on current concepts. Rev Neurosci 5: 347-354.

Kawashima R, Satoh K, Goto R, Inoue K, Itoh M, Fukuda H (1998) The role of the left inferior temporal cortex for visual pattern discrimination-; a PET study. Neuroreport 9: 1581-1586.

Kawashima R, Yamada K, Kinomura S, Yamaguchi T, Matsui H, Yoshioka S, Fukuda H (1993) Regional cerebral blood flow changes of cortical motor areas and prefrontal areas in humans related to ipsilateral and contralateral hand movement. Brain Res 623: 33-40.

Kertesz A, Hooper P (1982) Praxis and language: the extent and variety of apraxia in aphasia. Neuropsychologia 20: 275-286.

Kertesz A, Polk M, Black SE, Howell J (1990) Sex, handedness, and the morphometry of cerebral asymmetries on magnetic resonance imaging. Brain Res 530: 40-48.

Kilbreath SL, Gandevia SC, Wirianski A, Hewitt B (1995) Human flexor pollicis longus: role of peripheral inputs in weight-matching. Neurosci Lett 201:203–206.

Kilbreath SL, Refshauge K, Gandevia SC (1997) Differential control of the digits of the human hand: evidence from digital anaesthesia and weight matching. Exp Brain Res 117: 507-511.

Kim H, Martin BJ (2008) Three-dimensional joint kinematics of the upper extremity in reach movements under whole-body vibration exposure. Presented at 52nd HFES (Human Factors and Ergonomics Society) meeting, New York.

Kim SG, Ashe J, Hendrich K, Ellermann JM, Merkle H, Ugurbil K, Georgopoulos AP (1993) Functional magnetic resonance imaging of motor cortex: hemispheric asymmetry and handedness. Science 261:615–617.

Kim SG, Ugurbil K, Strick PL (1994) Activation of a cerebellar output nucleus during cognitive processing. Sci 265: 949-951.

Kimura D (1999) Sex and cognition. Cambridge, MA: MIT Press.

Kleim JA, Vij K, Ballard DH, Greenough WT (1997) Learning-dependent synaptic modifications in the cerebellar cortex of the adult rat persist for at least four weeks. J Neurosc 17: 717-721.

Klöppel S, van Eimeren T, Glauche V, Vongerichten A, Munchau A, Frackowiak RSJ, Buchel C, Weiller C, Siebner HR (2007a) The effect of handedness on cortical motor activation during simple bilateral movements. NeuroImage 34:274–280.

Klöppel S, Vongerichten A, van Eimeren T, Frackowiak RS, Siebner HR (2007b) Can left-handedness be switched? Insights from an early switch of handwriting. J Neurosci Official J Soc Neurosci 27:7847–7853.

Koeneke S, Lutz K, Wüstenberg T, Jäncke L (2004) Bimanual versus unimanual coordination: what makes the difference?. Neuroimage 22: 1336.

Koeneke S, Lutz K, Wüstenberg T, Jäncke L (2004) Long-term training affects cerebellar processing in skilled keyboard players. NeuroReport 15: 1279-1282.

Krings T, Buchbinder BR, Butler WE, Chiappa KH, Jiang HJ, Cosgrove GR, Rosen BR (1997) Functional magnetic resonance imaging and transcranial magnetic stimulation: complementary approaches in the evaluation of cortical motor function. Neurology 48: 1406-1416.

Lackner JR (1984) Some influences of tonic vibration reflexes on the position sense of the contralateral limb. Exp Neurol 85: 107-113.

Lackner JR, Levine MS (1979) Changes in apparent body orientation and sensory localization induced by vibration of postural muscles: vibratory myesthetic illusions. Aviat Space Envir MD.

Lafargue G, Franck N, Sirigu A (2006) Sense of motor effort in patients with schizophrenia. Cortex 42:711–719.

Lafargue G, Paillard J, Lamarre Y, Sirigu A (2003) Production and perception of grip force without proprioception: is there a sense of effort in deafferented subjects? Eur J Neurosci 17:2741–2749.

Lafargue G, Sirigu A (2006) The nature of the sense of effort and its neural substrate. Rev Neurol (Paris) 162:703–712.

LaMantia AS, Rakic P (1990) Cytological and quantitative characteristics of four cerebral commissures in the rhesus monkey. J Comp Neurol 291:520–537.

Lawson JA, Vogrin S, Bleasel AF, Cook MJ, Bye AM (2000) Cerebral and cerebellar volume reduction in children with intractable epilepsy. Epilepsia 41: 1456-1462.

Legon W, Dionne JK, Meehan SK, Staines WR (2010) Non-dominant hand movement facilitates the frontal N30 somatosensory evoked potential, BMC Neurosci 11: 112.

LeMay M (1977). Asymmetries of the skull and handedness: Phrenology revisited. J Neurol Sci 32: 243-253.

Lenneberg EH (1967) Biological foundations of language. NY: Wiley.

Li S (2006) Perception of individual finger forces during multi-finger force production tasks. Neurosci Lett 409:239–243.

Liepmann H (1908) Die linke hemisphere und das handeln. In: Drei Aufsatze aus dem Apraxiefebiet. Karger, Berlin, pp 17-50.

Liepmann H (1920) Die linke hemisphare und das handeln. Munch Med Wochenschr 49: 2322-2326.

Luders E, Narr KL, Bilder RM, Thompson PM, Szeszko PR, Hamilton L, Toga AW (2007) Positive correlations between corpus callosum thickness and intelligence. NeuroImage, 37: 1457-1464.

Luders E, Narr KL, Thompson PM, Woods RP, Rex DE, Jancke L, et al (2005) Mapping cortical gray matter in the young adult brain: Effects of gender. NeuroImage 26: 493-501.

Luders E, Narr KL, Zaidel E, Thompson PM, Jancke L, Toga AW (2006) Parasagittal asymmetries of the corpus callosum. Cereb Cortex 16: 346−354.

Luders E, Toga AW (2010) Sex differences in brain anatomy. Prog. Brain Res., 186: 2–12.

Luu BL, Day BL, Cole JD, Fitzpatrick RC (2011) The fusimotor and reafferent origin of the sense of force and weight. J Physiol 589: 3135-3147.

Macdonell RA, Shapiro BE, Chiappa KH, Helmers SL, Cros D, Day BJ, Shahani BT (1991) Hemispheric threshold differences for motor evoked potentials produced by magnetic coil stimulation. Neurology 41: 1441-1444.

Mahmood O, Adamo D, Briceno E, Moffat SD (2009) Age differences in visual path integration. Behav Brain Res 205: 88-95.

Mani S, Mutha PK, Przybyla A, Haaland KY, Good DC, Sainburg RL (2013) Contralesional motor deficits after unilateral stroke reflect hemisphere-specific control mechanisms. Brain.

Marr D (1969) A theory of cerebellar cortex. J Physiol 202: 437-470.

Martin BJ, Adamo DE (2011) Contribution of sensory and motor components to motor control asymmetries: an analytical model approach., Proceeding of the 33rd IEEE Eng Med Biol Soc Conf 4064-4067.

Martin BJ, Park HS (1997) Analysis of the tonic vibration reflex: influence of vibration variables on motor unit synchronization and fatigue. Eur J Appl Physiol O 75: 504-511.

Martin BJ, Roll JP, Di Renzo N (1991) The interaction of hand vibration with oculomanual coordination in pursuit tracking, Aviat Space Environ Med 62: 145-152.

Martin BJ, Roll JP, Gauthier GM (1984) Spinal reflex alterations as a function of intensity and frequency of vibration applied to the feet of seated subjects. Aviat Space Environ MD 55: 8.

Martin BJ, Roll JP, Gauthier GM (1986) Inhibitory effects of combined agonist and antagonist muscle vibration on H-reflex in man. Aviat Space Environ Med 57:681-687.

Martin K, Jacobs S, Frey SH (2011) Handedness-dependent and -independent cerebral asymmetries in the anterior intraparietal sulcus and ventral premotor cortex during grasp planning. Neuroimage 57:502–512.

Marzi CA, Bisiacchi P, Nicoletti R (1991) Is interhemispheric transfer of visuomotor information asymmetric? Evidence from a meta-analysis. Neuropsychologia 29:1163–1177.

Mathiowetz V, N Kashman N, G Volland G, K Weber K, M Dowe M, S Rogers S (1985) Grip and pinch strength: normative data for adults. Arch Phys Med Rehabil, 66: 69–74.

Mauk MD, Garcia KS, Medina JF, Steele PM (1998). Does Cerebellar LTD Minireview Mediate Motor Learning? Toward a resolution without a Smoking Gun. Neuron 20: 359-362.

McCloskey DI (1974) Muscular and cutaneous mechanisms in the estimation of the weights of grasped objects. Neuropsychologia 12:513–520.

McManus IC (1995) Familial sinistrality: the utility of calculating exact genotype probabilities for individuals. Cortex 31: 3-24.

Moffat SD, Hampson E, Lee DH (1998) Morphology of the planum temporale and corpus callosum in left handers with evidence of left and right hemisphere speech representation. Brain 121: 2369-2379.

Morgan MJ, Corballis MC (1978) On the biological basis of human laterality: II. The mechanisms of inheritance. Behav Brain Sci 1: 270 – 277.

Murphy DGM, DeCarli C, McIntosh AR, Daly E, Mentis MJ, Pietrini P, Szczepanik J, Schapiro MB, Grady CL, Horwitz B, Rapoport SI (1996) Sex differences in human brain morphometry and metabolism: an in vivo quantitative magnetic resonance imaging and positron emission tomography study of the effect of aging. Arch Gen Psychiat 53: 585–594.

Naito E, Ehrsson HH, Geyer S, Zilles K, Roland PE (1999) Illusory arm movements activate cortical motor areas: a positron emission tomography study, J Neurosci 19: 6134-6144.

Nathan PW, Smith MC, Deacon P (1990) The corticospinal tracts in man. Course and location of fibres at different segmental levels. Brain 113 (Pt 2): 303-324.

Netz J, Ziemann U, Homberg V (1995) Hemispheric asymmetry of transcallosal inhibition in man. Exp Brain Res 104: 527-533.

Nihashi T, Naganawa S, Sato C, Kawai H, Nakamura T, Fukatsu H, Ishigaki T, Aoki I (2005) Contralateral and ipsilateral responses in primary somatosensory cortex following electrical median nerve stimulation—an fMRI study. Clin Neurophysiol 116:842–848.

Nopoulos P, Flaum M, O'Leary D, Andreasen NC (2000) Sexual dimorphism in the human brain: evaluation of tissue volume, tissue composition and surface anatomy using magnetic resonance imaging, Psychiat Res-Neuroim 98: 1-13.

Nowak DA, Hermsdorfer J (2003) Selective deficits of grip force control during object manipulation in patients with reduced sensibility of the grasping digits. Neurosci Res 47:65–72.

Oldfield RC (1971) The assessment and analysis of handedness: the Edinburgh inventory. Neuropsychologia 9:97–113.

Oullier O, Kavounoudias A, Duclos C, Albert F, Roll JP, Roll R (2009) Countering postural posteffects following prolonged exposure to whole-body vibration: a sensorimotor treatment, Europ J Appl Physiol 105: 235-245.

Park HS, Martin B (1993) Contribution of the tonic vibration reflex to muscle stress and muscle fatigue. Scand J Work Environ Health 19:35-42

Park WH, Leonard CT (2008) The effect of intervening forces on finger force perception. Neurosci Lett 438:286–289.

Park WH, Leonard CT, Li S (2007) Perception of finger forces within the hand after index finger fatiguing exercise. Exp Brain Res 182:169–177.

Park WH, Leonard CT, Li S (2008) Finger force perception during ipsilateral and contralateral force matching tasks. Exp Brain Res 189:301–310.

Passe TJ, Rajagopalan P, Tupler LA, Byrum CE, Macfall JR, Krishnan KRR (1997) Age and sex effects on brain morphology. Prog Neuro-Psychoph 21: 1231-1237.

Peters M (1976) Prolonged practice of a simple motor task by preferred and non-preffered hands. Percept Mot Skills 42: 447-450.

Peters M (1990) Subclassification of lefthanders poses problems for theories of handedness. Neuropsychologia 28: 279-289.

Peters M (1992) How sensitive are handedness prevalence figures to differences in handedness classification procedures? Brain Cogn 18: 208-215.

Peters M, Durding B (1979) Left-handers and right-handers compared on a motor task. J Mot Behav 11: 103-111.

Peters M, Petrie BF (1979) Functional asymmetries in the stepping reflex of the human newborn. Canadian J Psychol 33: 198-200.

Petersen P, Petrick M, Connor H, Conklin D (1989) Grip strength and hand dominance: challenging the 10% rule. Am J Occup Therapy 43:444–447.

Pfefferbaum A, Mathalon DH, Sullivan EV, Rawles JM, Zipursky RB, Lim KO (1994) A quantitative magnetic resonance imaging study of changes in brain morphology from infancy to late adulthood. Arch Neurol 51: 874-887.

Pieniadz JM, Naeser MA (1984) Computed tomographic scan cerebral asymmetries and morphologic brain asymmetries: Correlation in the same cases post mortem. Arch Neurol 41: 403.

Poffenberger AT (1912) Reaction time to retinal stimulation with special reference to the time lost in conduction through nervous centers. Archs Psychol 23: 73.

Porac C, Coren S (1976) The dominant eye. Psychol Bull 83: 880-897.

Porac C, Coren S (1979) Individual and familial patterns in four dimensions of lateral preference. Neuropsychologia 17: 543-548.

Preuss UW, Meisenzahl EM, Frodl T, Zetzsche T, Holder J, Leinsinger G et al (2002) Handedness and corpus callosum morphology. Psychiat Res 116: 33.

Proske U (2006) Kinesthesia: the role of muscle receptors, Muscle Nerve 34: 545-558.

Purves D, White LE, Andrews TJ (1994) Manual asymmetry and handedness. P Natl Acad Sci 91: 5030-5032.

Rabinowicz T, Petetot JM, Gartside PS, Sheyn D, Sheyn T, de CM (2002) Structure of the cerebral cortex in men and women, J Neuropathol Exp Neurol 61: 46-57.

Rahman Q, Wilson GD, Abrahams S (2004) Sex, sexual orientation, and identification of positive and negative facial affect. Brain Cogn 54: 179-185.

Raichle ME, Fiez JA, Videen TO, MacLeod AMK, Pardo JV, Fox PT, Petersen SE (1994) Practice-related changes in human brain functional anatomy during nonmotor learning. Cereb Cortex 4: 8-26.

Rasmussen T, Milner B (1977) The role of early left-brain injury in determining lateralization of cerebral speech functions. Ann NY Acad Sci 299: 355-369.

Raz N, Dupuis JH, Briggs SD, McGavran C, Acker JD (1998) Differential effects of age and sex on the cerebellar hemispheres and the vermis: a prospective MR study. AJNR Am J Neuroradiol 19:65-71.

Raz N, Gunning-Dixon F, Head D, Williamson A, Acker JD (2001) Age and sex differences in the cerebellum and the ventral pons: A prospective MR study of healthy adults. Am J Neuroradiol 22: 1161-1167.

Redon C, Hay L, Rigal R, Roll JP (1994) Contribution of the propriomuscular channel to movement coding in children: a study involving the use of vibration-induced kinaesthetic illusion. Hum Movement Sci 13: 95-108.

Reiss AL, Abrams MT, Singer HS, Ross JL, Denckla MB (1996) Brain development, gender and IQ in children. A volumetric imaging study. Brain 119: 1763-1774.

Ribot-Ciscar E, Roll JP, Tardy-Gervet MF, Harlay F (1996) Alteration of human cutaneous afferent discharges as the result of long-lasting vibration. J App Physiol 80: 1708-1715.

Ringo JL (1991) Neuronal interconnection as a function of brain size. Brain Behav Evol 38:1–6.

Ringo JL, Doty RW, Demeter S, Simard PY (1994) Time is of the essence: a conjecture that hemispheric specialization arises from interhemispheric conduction delay. Cereb Cortex 4:331–343.

Riolo-Quinn L (1991) Relationship of hand preference to accuracy on a thumb-positioning task. Percept Mot Skills 73: 267-273.

Robinson LM, Fitts SS, Kraft GH (1990) Laterality of performance in fingertapping rate and grip strength by hemisphere of stroke and gender. Arch Phys Med Rehabil 71:695–698.

Roland PE, Ladegaard-Pedersen H (1977) A quantitative analysis of sensations of tension and of kinaesthesia in man. Brain 100: 671-692.

Roll JP, Albert F, Thyrion C, Ribot-Ciscar E, Bergenheim M, & Mattei B (2009) Inducing any virtual two-dimensional movement in humans by applying muscle tendon vibration. J Neurophysiol 101: 816-823.

Roll JP, Vedel JP (1982) Kinaesthetic role of muscle afferents in man, studied by tendon vibration and microneurography, Exp Brain Res 47: 177-190.

Roll JP, Vedel JP, Ribot E (1989) Alteration of proprioceptive messages induced by tendon vibration in man: a microneurographic study, Exp Brain Res 76: 213-222.

Romaiguere P, Anton JL, Roth M, Casini L, Roll JP (2003) Motor and parietal cortical areas both underlie kinaesthesia, Brain Res 16: 74-82.

Roy EA, Elliott D (1986) Manual asymmetries in visually directed aiming. Can J Psychol 40: 109-121.

Roy EA, MacKenzie C (1978) Handedness effects in kinesthetic spatial location judgements. Cortex 14: 250-258.

Rushworth MF, Johansen-Berg H, Gobel SM, Devlin JT (2003) The left parietal and premotor cortices: motor attention and selection. Neuroimage 20 Suppl 1: S89-100

Sainburg RL (2002) Evidence for a dynamic-dominance hypothesis of handedness. Exp Brain Res 142: 241-258.

Sainburg RL (2005) Handedness: differential specializations for control of trajectory and position. Exerc Sport Sci Rev 33:206–213.

Sainburg RL, Duff SV (2006) Does motor lateralization have implications for stroke rehabilitation? J Rehab Res Dev 43: 311–322.

Sainburg RL, Kalakanis D (2000) Differences in control of limb dynamics during dominant and nondominant arm reaching. J Neurophysiol 83: 2661-2675.

Schaefer SY, Haaland KY, Sainburg RL (2007) Ipsilesional motor deficits following stroke reflect hemispheric specializations for movement control. Brain 130:2146–2158.

Schlaepfer TE, Harris GJ, Tien AY, Peng L, Lee S, Pearlson GD (1995) Structural differences in the cerebral cortex of healthy female and male subjects: A magnetic resonance imaging study. Psychiat Res - Neuroim 61: 129-135.

Schlaug G, Schleicher A, Steinmetz H, Dabringhaus A, Roland PE, Zilles K (1996) Asymmetry in the human motor cortex and handedness. Neuroimage 4:216–222.

Schlesselman JJ (1974) Sample size requirements in cohort and case-control studies of disease. Am J Epidemiol 99: 381-384.

Schmahmann JD, Pandya DN (2006) in Fiber pathways of the brain, Corpus callosum, eds Schmahmann JD, Pandya DN (Oxford UP, New York), 485–496.

Schmahmann JD, Sherman JC (1998) The cerebellar cognitive affective syndrome. Brain 121: 561-579.

Schmidt RT, Toews JV (1970) Grip strength as measured by the Jamar dynamometer. Arch Phys Med Rehabil 51: 321-327.

Seitz RJ, Canavan AG, Yagüez L, Herzog H, Teilmann L, Knorr U, et al (1994) Successive roles of the cerebellum and premotor cortices in trajectorial learning. Neuroreport 5: 2541-2544.

Serrien DJ, Ivry RB, Swinnen SP (2006) Dynamics of hemispheric specialization and integration in the context of motor control. Nat Rev Neurosci 7: 160-166.

Shen YC, Franz EA (2005) Hemispheric competition in left-handers on bimanual reaction time tasks. J Mot Behav 37: 3–9.

Shergill SS, Bays PM, Frith CD, Wolpert DM (2003) Two eyes for an eye: the neuroscience of force escalation. Science 301:187.

Siebner HR, Limmer C, Peinemann A, Drzezga A, Bloem BR, Schwaiger M, Conrad E (2002) Long-term consequences of switching handedness: a positron emission tomography study on handwriting in “converted” left-handers. J Neurosci 22:2816–2825.

Singh LN, Higano S, Takahashi S, Kurihara N, Furuta S, Tamura H, Shimanuki Y, Mugikura S, Fujii T, Yamadori A, Sakamoto M, Yamada S (1998) Comparison of ipsilateral activation between right and left handers: a functional MR imaging study. Neuroreport 9:1861–1866

Smith JL, Crawford M, Proske U, Taylor JL, Gandevia SC (2009) Signals of motor command bias joint position sense in the presence of feedback from proprioceptors, J Appl Physiol 106: 950-958.

Soros P, Knecht S, Imai T, Gurtler S, Lutkenhoner B, Ringelstein EB, Henningsen H (1999) Cortical asymmetries of the human somatosensory hand representation in right- and left-handers. Neurosci Lett 271:89–92.

Sowell ER, Peterson BS, Kan E, Woods RP, Yoshii J, Bansal R, et al (2007) Sex differences in cortical thickness mapped in 176 healthy individuals between 7 and 87 years of age. Cereb Cortex 17: 1550-1560.

Sperry R (1982) Some effects of disconnecting the cerebral hemispheres. Bioscience Rep 2: 265-276.

Sperry RW (1950) Neural basis of the spontaneous optokinetic response produced by visual inversion. J Comp Physiol Psychol 43:482–489

Srinivasan D, Martin BJ (2010) Eye-hand coordination of symmetric bimanual reaching tasks: temporal aspects. Exp Brain Res 203: 391-405.

Steingrüber HJ (1971) Zur Messung der Händigkeit. Z Exp Angew Psychol 18:337–357.

Steinmetz H (1996) Structure, functional and cerebral asymmetry: in vivo morphometry of the planum temporale. Neurosci Biobehav Rev 20: 587-591.

Steinmetz H, Volkmann J, Jancke L, Freund HJ (1991) Anatomical left-right asymmetry of language-related temporal cortex is different in left- and right-handers. Ann Neurol 29: 315-319.

Swaab DF, Hofman MA (1984) Sexual differentiation of the human brain: A historical perspective. Prog Brain Res 61: 361-374.

Szabó CÁ, Lancaster JL, Xiong J, Cook C, Fox P (2003) MR imaging volumetry of subcortical structures and cerebellar hemispheres in normal persons. Am J Neuroradiol 24: 644-647.

Taylor JL, Gandevia SC (2008) A comparison of central aspects of fatigue in submaximal and maximal voluntary contractions. J Appl Physiol 104:542–550

Tecchio F, Rossini PM, Pizzella V, Cassetta E, Romani GL (1997) Spatial properties and interhemispheric differences of the sensory hand cortical representation: a neuromagnetic study, Brain Res 767: 100-108.

Teixeira LA (2000) Timing and force components in bilateral transfer of learning. Brain Cogn 44: 455-469.

Thach WT (1998) What is the role of the cerebellum in motor learning and cognition?. Trends Cogn Sci 2: 331-337.

Thomsen T, Hugdahl K, Ersland L, Barndon R, Lundevold A, Smievoll AI, et al (2000) Functional magnetic resonance imaging (fMRI) study of sex differences in a mental rotation task. Med Sci Monitor 6:1186–1196.

Tian L, Wang J, Yan C, He Y (2011) Hemisphere- and gender-related differences in small-world brain networks: a resting-state functional MRI study. NeuroImage 54:191–202.

Timmann D, Drepper J, Maschke M, Kolb FP, Böring D, Thilmann AF, Diener HC (2002) Motor deficits cannot explain impaired cognitive associative learning in cerebellarpatients. Neuropsychologia 40: 788-800.

Todor JI, Cisneros J (1985) Accommodation to increased accuracy demands by the right and left hands. J Mot Behav 17: 355-372.

Toffin D, McIntyre J, Droulez J, Kemeny A, Berthoz A (2003) Perception and reproduction of force direction in the horizontal plane. J Neurophysiol 90:3040–3053.

Tomasch J (1954) Size, distribution, and number of fibres in the human corpus callosum. Anat Record 119: 119-135.

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

Triggs WJ, Calvanio R, Levine M, Heaton RK, Heilman KM (2000) Predicting hand preference with performance on motor tasks, Cortex 36: 679-689.

Triggs WJ, Subramanium B, Rossi F (1999) Hand preference and transcranial magnetic stimulation asymmetry of cortical motor representation. Brain Res 835:324–329 van den Berg FE, Swinnen SP, Wenderoth N (2010) Hemispheric asymmetries of the premotor cortex are task specific as revealed by disruptive TMS during bimanual versus unimanual movements. Cereb Cortex 20:2842–2851

van den Berg FE, Swinnen SP, Wenderoth N (2011) Involvement of the primary motor cortex in controlling movements executed with the ipsilateral hand differs between left- and right-handers. J Cogn Neurosci 23: 3456-3469

Velay JL, Benoit-Dubrocard S (1999) Hemispheric asymmetry and interhemispheric transfer in reaching programming. Neuropsychologia 37: 895-903.

Verstynen T, Diedrichsen J, Albert N, Aparicio P, Ivry RB (2005) Ipsilateral motor cortex activity during unimanual hand movements relates to task complexity. J Neurophysiol 93:1209–1222.

Vines B, Cerruti C, Schlaug G (2008) Dual-hemisphere tDCS facilitates greater improvements for healthy subjects' non-dominant hand compared to uni-hemisphere stimulation. BMC Neurosci 9: 103.

Viviani P, Perani D, Grassi F, Bettinardi V, Fazio F (1998) Hemispheric asymmetries and bimanual asynchrony in left- and right-handers. Exp Brain Res 120: 531-536.

Volkmann J, Schnitzler A, Witte OW, Freund H (1998) Handedness and asymmetry of hand representation in human motor cortex. J Neurophysiol 79:2149–2154.

Wahl M, Lauterbach-Soon B, Hattingen E, Jung P, Singer O, Volz S, et al (2007) Human motor corpus callosum: topography, somatotopy, and link between microstructure and function. J Neurosci 27: 12132-12138.

Wang J, Sainburg RL (2004) Interlimb transfer of novel inertial dynamics is asymmetrical. J Neurophysiol 92: 349-360.

Wang J, Sainburg RL (2006) Interlimb transfer of visuomotor rotations depends on handedness. Exp Brain Res 175:223–230.

Wassermann EM, McShane LM, Hallett M, Cohen LG (1992) Noninvasive mapping of muscle representations in human motor cortex. Electroen Clin Neuro 85: 1-8.

Wegner K, Forss N, Salenius S (2000) Characteristics of the human contra- versus ipsilateral SII cortex. Clin Neurophysiol 111:894–900.

Welcome SE, Chiarello C, Halderman LK, Leonard CM (2009) Lexical processing skill in college-age resilient readers. Reading Writ 22: 353-371.

Welcome SE, Leonard CM, Chiarello C (2010) Alternate reading strategies and variable asymmetry of the planum temporale in adult resilient readers. Brain and Language 113:73-83.

Wernicke C (1874) Der aphasische symptom-complex. Eine psychologische studie auf anatomischer basis. Cohn & Weigert, Breslau.

Westerhausen R, Kreuder F, Dos Santos Sequeira S, et al. (2004) Effects of handedness and gender on macro- and microstructure of the corpus callosum and its subregions: a combined high-resolution and diffusion-tensor MRI study. Brain Res Cogn Brain Res 21:418–26.

White LE, Andrews TJ, Hulette C, Richards A, Groelle M, Paydarfar J, Purves D (1997) Structure of the human sensorimotor system. I: Morphology and cytoarchitecture of the central sulcus. Cereb Cortex 7: 18-30.

White LE, Paydarfar JA, Andrews TJ, Groelle M, Richards A, Purves D (1995) Symmetry of the human sensorymotor system in relation to handedness. Soc Neurosci Abstr 21:438.

White O, Proske U (2009) Illusions of forearm displacement during vibration of elbow muscles in humans, Exp Brain Res 192: 113-120.

Wilson S A, Lockwood RJ, Thickbroom GW, Mastaglia FL (1993) The muscle silent period following transcranial magnetic cortical stimulation. J Neurological Sci 114: 216-222.

Winstein CJ, Pohl PS (1995) Effects of unilateral brain damage on the control of goal-directed hand movements. Exp Brain Res 105: 163-174.

Wisniewski AB (1998) Sexually-dimorphic patterns of cortical asymmetry, and the role for sex steroid hormones in determining cortical patterns of lateralization. Psychoneuroendocrinology 23:519–547.

Witelson SF (1974) Hemispheric specialization for linguistic and nonlinguistic tactual perception using a dichotomous stimulation technique. Cortex 10: 3-17.

Witelson SF (1977) Anatomic asymmetry in the temporal lobes: its documentation, hylogenesis, and relationship to functional asymmetry. Ann NY Acad Sci 299: 328-354.

Witelson SF (1985) The brain connection: The corpus callosum is larger in left-handers. Sci 229: 665–668.

Witelson SF (1987) Neurobiological aspects of language in children. Child Development 58: 653-688.

Witelson SF (1989) Hand and sex differences in the isthmus and genu of the human corpus callosum. A postmortem morphological study. Brain 112:799–835.

Witelson SF, Goldsmith CH (1991) The relationship of hand preference to anatomy of the corpus callosum in men. Brain Res 545:175–182.

Woodworth RS (1899) The accuracy of voluntary movement. Psychological Review 3: 1-119.

Worringham CJ, Stelmach GE (1985) The contribution of gravitational torques to limb position sense, Exp Brain Res 61: 38-42.

Yamauchi M, Imanaka K, Nakayama M, Nishizawa S (2004) Lateral difference and interhemispheric transfer on arm-positioning movement between right and left handers. Percept Mot Skills 98:1199–1209.

Zaidel E (1983) Disconnection syndrome as a model for laterality effects in the normal brain J.B. Hellige (Ed.), Cerebral Hemisphere Asymmetry: Method, Theory, and Application, Praeger, NY.

Zappasodi F, Pasqualetti P, Tombini M, Ercolani M, Pizzella V, Rossini PM, Tecchio F (2006) Hand cortical representation at rest and during activation: gender and age effects in the two hemispheres, Clin Neurophysiol 117: 1518-1528.

Zatz LM, Jernigan TL, Ahumada AJ (1982) Changes on computed cranial tomography with aging: intracranial fluid volume. Am J Neuroradiol 3: 1-11.

Zuo XN, Kelly C, Di Martino A, et al. (2010) Growing together and growing apart: Regional and sex differences in the lifespan developmental trajectories of functional homotopy. J Neurosci 30:15034–43.