Université de Montréal

Ipsi- and Contralateral Corticospinal Influences in Uni- and Bimanual Movements in Humans

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Ipsi- and Contralateral Corticospinal Influences in Uni- and Bimanual Movements in Humans

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Résumé

Il existe des projections corticospinales (CS) vers les motoneurones (MNs) aussi bien contra- (c) qu'ipsilatérales (i). Les influences CSc sur les MNs du poignet sont connues pour être modulées entre autres par la position du poignet et les afférences cutanées. Pour cette raison, notre objectif était de vérifier si ces caractéristiques sont aussi valides pour les influences CSi. En utilisant la stimulation transcrânienne magnétique au niveau du cortex primaire droit, nous avons tout d'abord comparé les influences CSi sur les MNs des fléchisseurs du poignet à des positions maintenues de flexion et d'extension durant une tâche uni-manuelle ainsi que deux tâches bi-manuelles, ceci chez des sujets droitiers (n=23). Nous avons ensuite comparé les influences CSi dans cinq tâches bi-manuelles de tenue d'objet durant lesquelles les sujets avaient à tenir entre leurs mains un bloc à la surface soit lisse, soit rugueuse, dont le poids était supporté ou non, ceci en position de flexion (n=21). Dans une tâche, un poids était ajouté au bloc lisse en condition non supportée pour amplifier les forces de préhension requises. Une modulation position-dépendante était observée au niveau des potentiels évoqués moteurs (iPEM), mais seulement lors de la tâche bi-manuelle quand les deux mains interagissaient via un bloc ($p= 0.01$). Une modulation basée sur la texture était également présente, quel que soit le support de poids, et le bloc lisse était associé avec des iPEMs plus importants en comparaison avec le bloc rugueux ($p= 0.001$). Ainsi, les influences CSi sur les MNs n'étaient modulées que lors des tâches bi-manuelles et dépendaient de la manière dont les mains interagissaient. De plus, les afférences cutanées modulaient les influences CSi facilitatrices et pourraient ainsi participer à la prise en main des objets. Il en est conclu que les hémisphères droit et gauche coopèrent durant les tâches bi-manuelles impliquant la tenue d'objet entre les mains, avec la participation potentielle de projections mono-, et poly-synaptiques, transcallosales inclues. La possibilité de la contribution de reflexes cutanés et d'étirement (spinaux et transcorticaux) est discutée sur la base de la notion que tout mouvement découle du contrôle indirect, de la « référence » (*referent control*). Ces résultats pourraient être essentiels à la compréhension du rôle des interactions inter-hémisphériques chez les sujets sains et cliniques.

Mots-clés: Cortex moteur, contrôle moteur, stimulation magnétique transcrânienne, potentiel évoqué moteur, influences cortico-spinales, bi-manuel, uni-manuel, controlatéral, ipsilatéral, afférences cutanées.

Abstract

There are both contra- (c) and ipsilateral (i) corticospinal (CS) projections to motoneurons (MNs). There is evidence that cCS influences on wrist MNs are modulated by wrist position and cutaneous afferents. Thus, we aimed to test whether these findings are valid for iCS influences as well. Using transcranial magnetic stimulation applied over the right primary motor cortex, we first compared iCS influences on wrist flexor MNs at actively maintained flexion and extension wrist positions in one uni- and two bimanual tasks in right-handed subjects (n=23). We further compared iCS influences in five bimanual holding tasks in which subjects had to hold a smooth or coarse block between their hands, with or without its weight being supported, in flexion position (n=21). In one task, a weight was added to the unsupported smooth block to increase load forces. A position-dependent modulation of the short-latency motor evoked potential (iMEP) was observed, but only in the bimanual task when the two hands interacted through a block ($p=0.01$). A texture-dependent modulation was present regardless of the weight supported, and the smooth block was associated with larger iMEPs in comparison to the coarse block ($p=0.001$). Hence, iCS influences on MNs were modulated only in bimanual tasks and depended on how the two hands interacted. Furthermore, cutaneous afferents modulated facilitatory iCS influences and thus may participate to grip forces scaling and maintaining. It is concluded that the left and right cortices cooperate in bimanual tasks involving holding an object between the hands, with possible participation of mono- and poly-synaptic, including transcallosal projections to MNs. The possible involvement of spinal and trans-cortical stretch and cutaneous reflexes in bimanual tasks when holding an object is discussed based on the notion that indirect, referent control underlies motor actions. Results might be essential for the understanding of the role of intercortical interaction in healthy and neurological subjects.

Keywords: Motor cortex, motor control, transcranial magnetic stimulation, motor evoked potential, corticospinal influences, bimanual, unimanual, contralateral, ipsilateral, cutaneous afferents.

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List of abbreviations

c: contralateral, 16

CC: corpus callosum, 28

CNS: Central Nervous System, 16

CRIR: Center for Interdisciplinary Research in Rehabilitation, 42

CS: corticospinal, 16

CST: corticospinal tract, 18

EMG: electromyography, 23

FA1: Meissner corpuscles, 24

FA2: Pacinian corpuscles, 24

FCR: flexor carpi radialis, 43

FR: frames of reference, 23

i: ipsilateral, 16

IHF: interhemispheric facilitation, 33

IHI: interhemispheric inhibition, 33

IRGLM: Institut de réadaptation Gingras-Lindsay-de-Montréal, 41

ISI: interstimulus intervals, 33

M1: primary motor cortex, 18

MEP: motor evoked potential, 28

MMs: Mirror movements, 35

MN: motor neuron, 18

MVC: maximal voluntary contraction, 43

PMC: premotor areas, 18

PNS: Peripheral Nervous System, 16

Q: actual hand aperture, 63

R: referent aperture, 63

RB: rebound, 28

S1: primary somatosensory cortex, 25

S2: secondary somatosensory cortex, 25

SA1: Merkel cells, 24

SA2: Ruffini endings, 24

SMA: supplementary motor area, 18

SP: silent period, 28

TMS: transcranial magnetic stimulation, 27

vCST: uncrossed CST, 28

À mes parents, Claire et Jean-Christophe, qui m'ont toujours encouragé à relever les défis et tenter ma chance. À ma grand-mère, Mamou Jocelyne (et le fabuleux Pepito) qui me soutient toujours mais aussi aux absents qui nous manquent, Mamie Suzanne, Papi Georges et Papou Jean-Daniel.

To my parents, Claire and Jean-Christophe, who have always encouraged me to undertake challenges. To my grandmother, Mamou Jocelyne (and the all mighty Pepito) who is still supporting me but also the absents who we miss grandly, Mamie Suzanne, Papi Georges, and Papou Jean-Daniel.

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Introduction

The ability to move is a key feature of our life. By activating different muscles, we can execute a broad variety of movements. We use the terms afferent and efferent systems to describe the information that reaches the Central Nervous System (CNS) and the information resulting in action production, respectively. The CNS, consisting of the brain and spinal cord, is responsible for integrating afferent inputs and influencing the Peripheral Nervous System (PNS) which connects the CNS to limbs and internal organs. Studying the motor system is fundamental for getting a better understanding of the brain's functional properties and, in particular, motor control disorders to design effective rehabilitation paradigms.

Before diving into the specific topics of my research – the role of ipsi- (i) and contralateral (c) corticospinal (CS) influences in uni- and bimanual movements in humans, we will briefly describe both motor (section 1) and sensory (section 2) systems. The subjects that will be tackled in this introduction are summarized in the following schematic scope of review (Fig. 1).

1. Motor Systems

Humans interact with the environment, in particular, through movement production. Those can be reflex reactions to environmental stimuli but also volitional and automatic actions.

Multiple brain areas come into play and are responsible for different stages of these essential processes, from the perception of stimuli to motor responses. As a result, several neural circuits are involved in what we call movement control (Fig. 2). To begin, there are descending systems originated from the motor cortex as well as from brainstem centers (1). They participate, among other things, in planning, initiating and controlling of fine movements (2). In addition, there are subcortical nuclei gathered in a structure, called the basal ganglia, which can be considered as a gate for movement initiation. The cerebellum coordinates different movements and learning (for reviews see (3), (4)). Finally, there are the spinal cord and brainstem circuits that receive sensory information and innervate skeletal muscles.

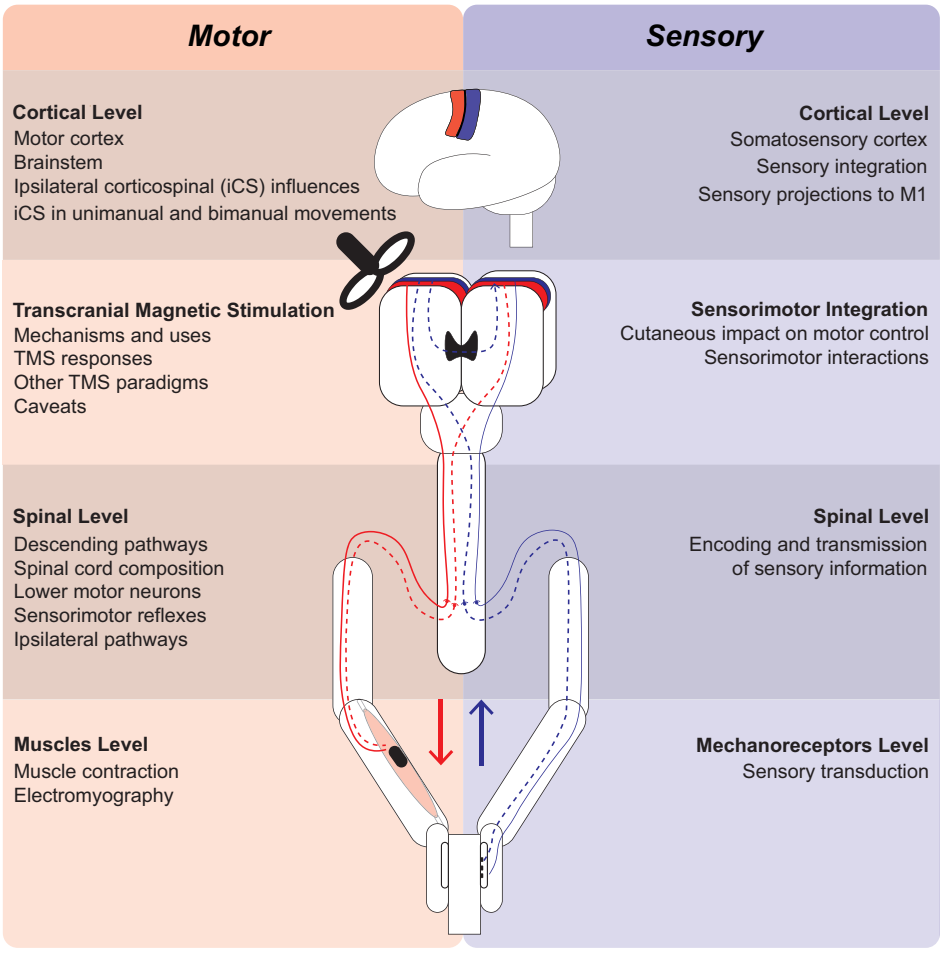

Figure 1. – Scope of Review.

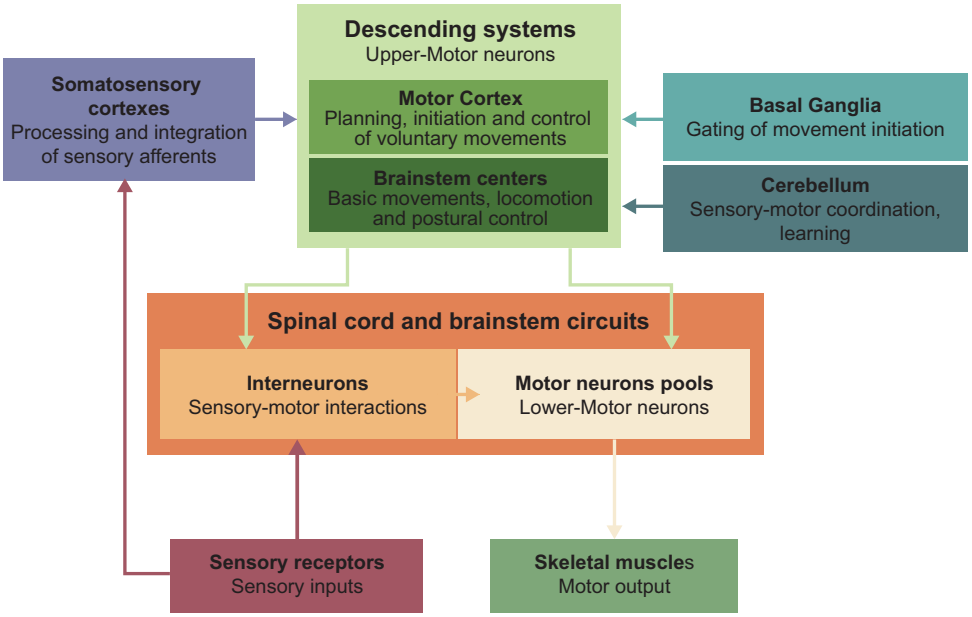

Figure 2. – Overview of the Neural Circuits Involved in Motor Control.

1.1 Cortical level

Neurons that transmit output signals from higher centers in the frontal lobe and the brainstem to descending systems are usually called the upper motor neurons (MN). Their role is to modulate the activity of interneurons and lower MNs to mediate the contraction or relaxation of skeletal muscles.

1.1.1 Motor Cortex

Among the higher centers, the motor cortex is presumably responsible for the planning and execution of volitional movements. It is constituted of the primary motor cortex (M1), the six premotor areas (PMC) and the supplementary motor area (SMA).

The M1, also called Brodmann area 4, is an anatomical region of the brain located in the dorsal part of the frontal lobe, on the anterior bank of the central sulcus (5). Its location and function have been widely investigated by neuroscientists such as Penfield (6). Although his initial goal was to assess which brain regions were vital and should not be removed during surgery in epileptic patients, he found out that stimulations of this area led to highly localized muscle contractions of the contralateral side of the body (6). Furthermore, he discovered that M1 is organized in a somatotopic manner representing motor maps. Even though results of later studies are generally consistent with the idea of motor maps, refined analyses reveal a more distributed, gross and overlapping pattern of subdivisions in M1 (7). A critical aspect of this motor map also called the motor homunculus, is that larger areas are allocated for body parts that are used in more complex tasks, like those involving the hands and face (for review see (8)). Moreover, studies have shown that area size varies through plasticity, meaning that M1 can reorganize itself based on experience (7).

Composed of Betz cells, which are pyramidal cells located in its fifth layer (5), M1 sends axons through the internal capsule to several subcortical structures, creating different pathways in charge of specific motor functions.

There are two major pathways that innervate both the body and face muscles. The corticospinal tract (CST) fibers go from M1 to the spinal cord and synapse onto lower MNs, which innervate skeletal muscles. In this tract, around 90% of pyramidal fibers decussate in the medulla and

descend contralaterally in the spinal cord to form the dorsolateral CST. A remaining 10% descends ipsilaterally and forms the ventral CST (9–11). Meanwhile, the corticobulbar tract fibers go to the medullary pyramids in the brainstem to synapse onto lower MNs via cranial nerves.

In addition, two pathways link the motor cortex to both the basal ganglia and the cerebellum. The corticostriatal fibers descend in the striatum of the basal ganglia, creating a corticostriatal loop while the corticopontical fibers first travel to the pontine nuclei and then project onto the cerebellum.

Finally, two other pathways descend in the spinal cord; (i) the corticorubral fibers, that go to the red nucleus and form the rubrospinal tract and (ii) the corticoreticular fibers that go to the reticular formation of the brainstem to form the reticulospinal tract.

As mentioned, two other brain regions are part of the motor cortex. Situated in the frontal lobe anterior to M1, the PMC is constituted of six spatially separate areas (12) and receives both multisensory inputs from the superior and inferior parietal lobes as well as motivation and intention signals from the prefrontal divisions of the frontal lobe (2,13). It can influence motor control, either indirectly through its reciprocal projections on M1, or directly via axons projecting to the corticobulbar and corticospinal pathways (12). Studies suggest that it uses information from other cortical areas to plan and select context-appropriate movements (for review see (14)). Finally, the SMA is located in the dorsomedial frontal cortex (for review see (15)). Though its overall function remains unclear, there is growing evidence that the SMA may influence the planning of sequential movements, movement initiation as well as interlimb coordination (16–19).

1.1.2 Brainstem

In addition to the motor cortex, multiple subcortical structures in the brainstem also play a role in motor tasks such as locomotion, postural control, balance and orientation of head and eye movements. They are controlled by neurons from the reticular formation, the vestibular complex, and the superior colliculus, respectively.

1.2 Spinal Level

The spinal cord's role is multifaceted, ranging from providing efferent information to the autonomic nervous system to coordinating reflexes and muscle contraction. Overall, the spinal cord transmits and modulates nerve signals originated in the cortex and brainstem to muscles and efferent sensory information to higher centers.

1.2.1 Spinal Cord Composition

Similar to the brain, the spinal cord is composed of grey and white matter. On one hand, the grey matter is divided into the ventral and dorsal horns which contain MNs and sensory neurons respectively as well as an intermediate zone containing interneurons. It is further subdivided into areas called laminae ranging from I to X (19). The majority of upper MNs project either directly on alpha MNs (α-MNs) in lamina IX or indirectly via interneurons in laminae V-VIII (20). CST influences are excitatory for MNs and their inhibition is mediated by inhibitory interneurons(19).

On the other hand, the white matter consists of different, distinct although overlapping, descending and ascending axon bundles. Descending systems are thought to be organized in a somatotopic fashion such that tracts implicated in balance and posture are clustered more medially while the ones involved in more distal movements terminate laterally (2,19,21).

1.2.2 Lower Motor Neurons

As defined before, neurons transmitting signals from the cortex and brainstem centers are called upper MNs whereas MNs that innervate skeletal muscle fibers are called lower MNs. They are classified into three categories. Firstly, α-MNs innervate extrafusal muscle fibers and are responsible for muscular contraction. Second, γ-MNs innervate intrafusal fibers within muscle spindles, sensors informing about muscle length, and modify their sensitivity to muscle stretching and its speed (22). Finally, β-MNs innervate both types of fibers (19,22).

A α-MN together with all the muscle fibers it innervates is called a motor unit (23). As a general rule, the majority of muscle fibers are innervated by only one α-MN. In contrast, α-MNs often innervate multiple fibers (19). All α-MNs that innervate a single muscle are called a MN pool (22). In the spinal cord, MN pools clusters are located according to the muscles they innervate, medially

to the ventral horn for the axial and proximal musculature and laterally for the distal musculature (2).

1.2.3 Sensorimotor Reflexes

For any given movement, we classify muscles along two categories: agonists and antagonists. The agonist is the muscle that generates movement with its contraction, causing a shortening of myofibrils. On the other hand, the antagonist is a muscle that is being stretched by the agonist's contraction.

In addition to the cortical control of muscles, the spinal cord itself is responsible for several sensorimotor reflexes aiming to maintain muscle tonus and force. They can involve both pre- and postsynaptic monosynaptic and polysynaptic connections. For instance, when a muscle is stretched, muscle spindles are activated. Sensitive fibres Ia and II afferents that are coiled around them relay sensory information to the α-MN. To do so, they either make direct, excitatory contact to the agonist muscle's α-MN or indirectly, via inhibitory interneurons synapsing on α-MNs of the antagonist muscle. As a result, a simultaneous contraction of the agonist muscle and relaxation of the antagonist emerges. This reciprocal innervation contributes to maintaining muscular tonus. Sensorimotor reflexes can also be transcortical, and we can use the response latencies to identify whether they are mediated spinally or supraspinally.

In the same way, Golgi tendon organs (for review see (24)), which are encapsulated afferent nerve endings located at the junction between a contractile fiber and a muscle tendon, are innervated by group Ib afferents. Their role is to convey information about muscle tension arising from muscle contraction. By making contact with inhibitory interneurons which in turn synapse onto α-MNs, they reduce their discharge frequency. This inhibitory circuit helps regulate muscle tension and thus maintain muscle force.

1.3 Muscle Contraction

Skeletal muscles are major components of volitional movement. Their role is to convert chemical energy relayed by neurotransmitters into mechanical contractions (19). They are composed of

muscle contractile fibers which are innervated by α-MNs. Their synapse is called the neuromuscular junction.

1.3.1 Mechanism of Contraction

When an action potential reaches the presynaptic terminal of an α-MN, it activates voltage-gated calcium channels, letting calcium ions enter the neuron. In turn, they bind onto sensor proteins found on synaptic vesicles contained in the axon terminal and trigger their fusion with the cell membrane. Those vesicles carry a neurotransmitter, acetylcholine, that can then be released inside the synaptic cleft to bind onto nicotinic acetylcholine receptors situated on the cell membrane of the muscle fiber, the sarcolemma. Depolarization ensues and leads to the generation of a nerve impulse that causes T tubules to release the calcium stored in their sarcoplasmic reticulum. As a result, calcium then diffuses into myofibrils. These units of muscle cells are organized into an alternance of thick and thin filaments, which are divided by Z-stripes into segments called sarcomeres (Fig. 3). When calcium binds onto troponin, a group of proteins that regulate muscle contraction, it exposes the actin-binding sites of the thin filaments which can then bind to the actin from the thick filaments. This process leads to a change in conformation of the actin-myosin configuration such that cross-bridges rotate and pull the thin past the thick filaments. Contraction of the muscle happens when the thick and thin filaments slide past each other, reducing the sarcomere's length (Fig. 3).

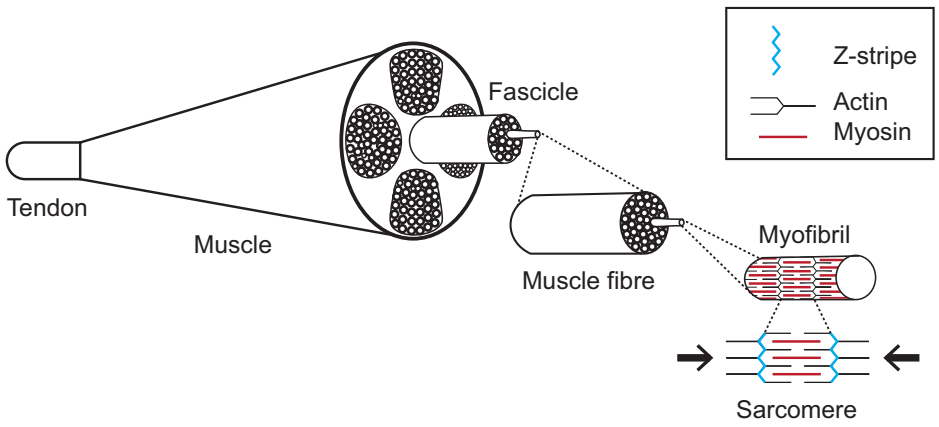

Figure 3. – Schematic Representation of the Muscle Microstructure.
Muscles are composed of bundles of fibers called fascicles in which muscle fibers are gathered. Muscle fibers contain myofibrils that can contract when sarcomeres length is reduced due to the sliding of thick and thin filaments.

1.3.2 Electromyography Recording

The electrical activity associated with muscle contraction, also called myoelectric signals, can be recorded via electromyography (EMG) by placing electrodes either on the skin or directly inside the muscles (25–27).

1.4 Choosing Between Different Frameworks of Motor Control

When it comes to the study of motor control, several theories have been developed over the years aiming to explain the cortical mechanisms involved in movement production. In particular, there are two dominant frameworks or theories of motor control, one biomechanical, based on computational and optimality principles (28,29) and one based on physiological principles.

1.4.1 Internal Model Theory

The internal model theory relies on the idea that neural mechanisms can mimic the input and output characteristics of the motor apparatus (30), allowing the preprogramming of volitional movements.

1.4.2 Equilibrium Point Hypothesis

In direct opposition to this theory is the Equilibrium Point Hypothesis, now advanced to Referent Control Theory of Action and Perception (31,32) developed by Feldman and colleagues in the sixties. It stipulates that instead of controlling movements by directly specifying biomechanical variables, the CS influences sets the spatial threshold position at which MNs of wrist muscles begin to be recruited (33–36). Depending on external conditions, changes in the spatial thresholds result in either a movement to another wrist position or an isometric force production (31).

Threshold positions can be considered as the origins, or referent points of the spatial frames of reference (FRs) in which MNs and reflexes are constrained to function. Intentional motor actions emerge, without preprogramming, from shifts in the referent points of spatial FRs, as suggested in the empirically established framework of indirect, referent control of motor actions (31,32). Experiments in this master's thesis are designed in this theoretical framework.

2. Importance of the Cutaneous Afferents in Motor Control

2.1 Somatosensory Systems

The somatosensory system plays an essential role by transmitting inputs, in particular about physical properties of objects the body interacts with in its environment. It integrates information about texture, hardness, weight, position and global shape of objects (37) as well as temperature and pain, though the latter two senses will not be discussed here.

2.1.1 Transduction

For a sensation to appear, a physical stimulus needs to be transduced. That means that the sensory stimulus needs to be turned into an electrical signal that will then be sent to the spinal cord and appropriate areas of the somatosensory cortex for integration.

Both touch and proprioception are mediated by mechanoreceptors. Cutaneous mechanoreceptors provide information about the physical properties of the surfaces and objects we encounter (38,39) such as their textures, shapes, friction, and weights (40).

There are two categories of cutaneous tactile receptors located either in the skin or in deep tissues: the first is fast adapting, responding to changes in stimulation (phasic, dynamic) and the second is slow adapting, responding to maintained stimulation (tonic). The fast adapting mechanoreceptors are the Meissner corpuscles (FA1) which detect pressure, and the Pacinian corpuscles (FA2) that detect deep pressure and vibrations. Finally, the two slow adapting mechanoreceptors are the Merkel cells (SA1) which detect static pressure but also texture, and the Ruffini endings (SA2) which inform about skin stretches and hand postures. Superficial receptors are present in higher density in the palms and fingers in contrast with the deeper receptors which are distributed more sparsely.

Johansson and Westling (39,41) have proposed that rapidly adapting receptors FA1 and FA2 as well as slowly adapting receptor SA1 were responsible for detecting slips, thus, to maintain grip forces during grasping tasks. They also suggested that slowly adapting receptors SA2 would play a role in friction sensing.

Proprioception, on the other hand, transmits information about body position and displacement of body segments via the muscle spindles and Golgi tendons.

2.1.2 Encoding and Transmission of Sensory Information

Cutaneous afferents travel through the dorsal column medial lemniscal system. The nervous system then recognizes the stimulus' modality (i.e. touch, pain, temperature), location, intensity and duration in the somatosensory cortex, where it is treated and integrated.

2.1.3 Integration

The primary somatosensory cortex (S1) is located posterior to the central sulcus. It is composed of four subdivisions and receives somatotopic inputs from the thalamus (ventro-posterior-lateral and ventro-posterior-medial). Areas 3a and 3b receive proprioceptive and cutaneous inputs respectively and further processing is realized in areas 1 and 2 (19). The secondary somatosensory cortex (S2) is situated in the parietal operculum (42) and receives connections from S1. Although its function is not completely understood, it is thought to accomplish sensorimotor integration and may transmit cutaneous signals to the motor cortex (43).

It is generally agreed that cutaneous mechanoreceptors send their information to the contralateral S1 (44). However, it has been shown that tactile information from one hand can reach S1 of both hemispheres (45). As no uncrossed tactile projections from distal limbs have been demonstrated, this transmission is likely to be transcallosal (45). On the other hand, S2 receives cutaneous inputs from S1 as well as from cutaneous receptors of both hands. It has been repeatedly observed that unilateral electrical nerve stimulation of a limb leads to the bilateral activation of S2, especially, but not exclusively, in proximal muscles (44,46,47). Therefore, it appears that sensory afferents have the means to be treated by the somatosensory cortexes not only contralaterally but also ipsilaterally.

2.2 From the Somatosensory Cortex to M1

2.2.1 Projections from the Somatosensory Cortex to M1

It has been generally accepted that there are projections from S1 (3a, 3b, 1, 2) and S2 to the motor and premotor cortexes (8,46). However, S1 fields participating at an early stage of processing, are

thought to send only modest inputs to M1 (8). Despite those projections, removal or cooling of the sensory cortex in monkeys appeared to have no impact on the evoked potentials recorded in the motor cortex after nerve stimulation (48). In other words, M1 may receive peripheral input independently of the somatosensory cortex, potentially from the thalamus (48). In addition, the large majority of inputs it receives seems to arise from area 5 in the superior parietal lobule (49–51) and to a lesser extent from area 7b. These regions have connections to both S1 and S2 and are thought to be involved in somatosensory and associative processing.

2.2.2 Involvement in Motor Control

All in all, the role of S1 and S2 in motor control remains unclear. There is only contentious evidence that sectioning the dorsal column leads to loss of somesthetic input and results in motor impairment, especially in grasping and holding tasks (52). Likewise, lesions in S1 have been reported to disturb motor activity in some studies whereas others observed only slight motor impairment (53,54). On the other hand, there is some evidence that electrical stimulation of S1 may induce movement, though those findings are still controversial (54).

2.2.3 Studying the Impact of Cutaneous Afferents on Cortical Excitability

Study of cutaneous afferent and their impact on cortical excitability has widely employed electrical nerve stimulation. However, results are controversial with evidence of both facilitatory (55,56) and inhibitory (57,58) effects. It has also been suggested that the electrical stimulation of peripheral afferent might excite some circuits and inhibit others (59).

Another method of investigation relies on “natural” stimulation such as skin brushing (60) and tactile exploration of surfaces (61). Again, results are debated, and researchers have observed both facilitation and inhibition (60). The existence of a topographical organization of facilitatory and inhibitory afferents has been suggested and results by Classen et al. (62) were in line with those findings, confirming that they may also facilitate one muscle while inhibiting others.

All things considered, it is still controversial whether peripheral inputs have an excitatory (39,60,63) or inhibitory (57,59,60) effect on corticomotor excitability. Additionally, cutaneous afferent also appears to be modulated by other criteria such as task (62), complexity (64) and attention (64,65).

2.3 Bimanual Holding Tasks

To ensure grasp stability, people have to apply grip forces perpendicular to the object's surface (38,66). They use information about friction (61) and the object's weight (39) to scale grasping forces adequately. Indeed, it is necessary to apply a force within a small safety margin above the minimal force required to prevent slipping, but not too much as it would lead to muscle fatigue and, in some cases, object damage (66).

2.3.1 Sensorimotor Interactions

Repetitive transcranial magnetic stimulation (TMS) applied to M1 can perturb the ratio of grip to load force (38,67), suggesting that the motor cortex plays an important role in the control of grasping (40). Lesion studies have also demonstrated that S1 and S2 may be involved in the adaptation of grip force to changes in object texture and load (19). In addition, anesthesia of the fingers, which inhibits cutaneous perception, has been shown to prevent people from adequately adjusting grasp forces within the safety margin (39). However, Westling and Johansson (66) showed that this was only the case for friction and not for weight, suggesting the existence of two different mechanisms of grip force control during grasping.

In summary, those experiments shed light on the importance of interactions between the somatosensory and motor cortexes in the production of adequate, functional motor actions. Although precise pathways involved in such interactions have not been established yet (8), research also suggests that somatosensory feedback may play an important role in the interhemispheric processing and integration of sensory input during cooperative hand tasks (68).

3. Ipsilateral Corticospinal Influences

Most studies have focused on the role of the contralateral hemisphere in the control of movement and its modulation by cutaneous influences. However, there is evidence that the ipsilateral hemisphere both receives ipsilateral sensory information and is involved in motor functions. We termed this cortical output from M1 to ipsilateral MNs ipsilateral corticospinal (iCS) influences. These influences can be facilitatory or/and inhibitory affecting components of motor

evoked potentials (iMEP), rebound (iRB), and silent period (iSP). iCS influences are likely involving both interhemispheric and descending projections to limb muscles (69).

3.1 Potential Pathways

Not to be confused with the CST, iCS influences can be carried by different pathways depending on the location of the target muscle. A first candidate is a direct monosynaptic pathway constituted by the uncrossed CST (vCST) that descends ipsilaterally from M1 to the spinal cord (10,70,71). A study by Wassermann et al. (72) showed that more proximal muscles such as the deltoids are likely to rely on such pathways. Secondly, the brainstem reticular formation receives numerous projections from both the ipsilateral and contralateral motor cortices (73). Thus, the reticulospinal tract and alternatively propriospinal neurons (74) could represent indirect pathways carrying iCS influences output. This is likely to be the case for iMEPs recorded in more distal muscles. Although some studies (10,70) argue that anatomical evidence in humans is missing, researches made on stroke and spinal cord injury patients (69,75,76) shed light on the capacity of the reticulospinal tract to take over in case of lesions. Finally, iCS influences output could be mediated transcallosally through the corpus callosum (CC) (10).

The question of which pathways mediate each component of iCS influences is still a matter of controversy and interpretation of iCS components remains hypothetical. Nonetheless, the latencies of each TMS component can be a good indicator of which pathways might be involved. For instance, the fact that iMEP arises after contralateral MEP (cMEP) implies that it is unlikely that iMEP involves transcallosal pathways (10). The dichotomy in cortical projections to MNs of proximal and distal muscles should also be considered when analyzing the role of ipsi- and contralateral CS effects in movement production.

3.2 Transcranial Magnetic Stimulation

3.2.1 Mechanisms and Uses

Brain stimulation techniques have been around for centuries. The first experiments were rather painful and often applied to the exposed motor cortex (77,78). Nowadays researchers use non-invasive and painless techniques such as transcranial electrical stimulation and, more often, TMS.

TMS is a tool that allows us to investigate the different neural circuits of the brain and their functions (79). It has been widely used in the literature to assess descending CS influences on MNs. TMS produces a motor-evoked potential (cMEP), a silent period (cSP) followed by a rebound (cRB) in contralateral muscles as well as transient excitatory (iMEP), rebound (iRB) and inhibitory (iSP) phases in ipsilateral muscles (Fig. 4; (80,81)).

TMS uses electrical currents in the coil to induce a magnetic pulse in the cortex. The changes in the magnetic field elicit an electrical current underneath the scalp which modifies neuronal excitability (82,83). Propagated to the spinal MNs, this activity leads to the contraction of a target muscle (84). Thus, TMS is an artificial way to contract specific muscles. This is possible due to the somatotopic organization of M1, such that one can draw a map between different brain stimulation spots and associated target muscles. In addition, by rotating the coil, one can change the orientation of current and stimulate different muscles and brain structures (82,83).

There are several types of coils with different characteristics such as the focus and depth of TMS. Compared to round coils, the figure-eight coils allow a more focal stimulation (85).

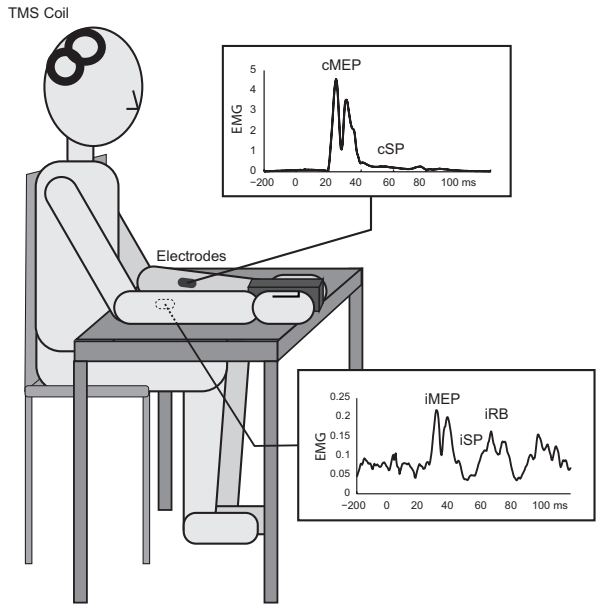

Figure 4. – EMG Response to TMS Over the Right M1 in Wrist Muscles.
TMS over the right M1 elicits both facilitation, the cMEP, the cRB (not shown), and inhibition, the cSP, in contralateral muscles. In ipsilateral muscles, the facilitatory phase (iMEP) is followed by an inhibition (iSP) and a secondary facilitatory phase (iRB).

3.2.2 Ipsilateral Motor Evoked Potentials

MEPs reflect both corticospinal MNs excitability at the time of TMS (77) as well as CST integrity (83). TMS is usually coupled with the execution of specific movements to evaluate their impact on corticospinal excitability. Since MEPs reflect both cortical and spinal MN excitability, it is better to equalize baseline muscle activity at different points of MEP testing to selectively evaluate changes in the cortical excitability during a motor task.

Two important characteristics of MEPs are their amplitude, which is a compound signal of its descending cortico-spinal volleys, and their latency which is the conduction time for the neural impulses triggered in M1 to reach the target muscle. TMS activates several neurons of M1 as well as their axons. The activation of multiple cortico-spinal volleys is responsible for the different components of the MEP. Earliest volley termed D-waves, and later I-waves result respectively from direct and indirect, transsynaptic activation of CST neurons (86,87).

In addition to the TMS coil's location on the scalp, which defines the target muscle where a response is observed, the coil orientation influences the MEP latency, threshold, and choice of activated cortical or subcortical structures (10,81).

In contralateral muscles, TMS produces cMEP by activating either directly or indirectly transynaptically fibers in the CST (72). The question of whether mechanisms mediating cMEP and iMEP are similar has been debated in the past, however, Chen et al. (81) showed that based on their directional preferences and latencies, this may not be the case. The optimal scalp positions for iMEP and cMEP are also different (72,74,88) but the difference is likely to be minimal as both iMEPs and cMEPS can be observed by stimulating the same spot.

The presence of iMEPs has been debated as some studies (10,89) were unable to reliably observe them in healthy adults. When it was the case, they were elicited mostly in proximal muscles (80,89) only in a small number of subjects (81,90) and required high TMS intensity as well as visible contraction of the target muscle (74). Chen et al. (70) concluded that the ipsilateral projections from M1 to upper limb muscles are weaker than contralateral projections, with a preference for proximal over distal muscles.

A particularity of iMEPs is that their amplitude can be modulated by several elements such as task, muscle contraction and head rotations (10,74,88,91). Tazoe and Perez (88) showed that depending on whether the head was turned medially or laterally, i.e., away or toward the muscle tested, iMEP size was decreased and increased, respectively. As corticoreticulopsinal and corticopropriospinal pathways are under a strong influence of sensory afferents, it has been proposed that this modulation of amplitude would be proof of activation of such tracts (10,74,88). In general, short-latency iMEPs are thought to be mediated by the vCST, corticoreticulospinal or the corticopropriospinal tracts depending on the muscle area stimulated in M1. The idea of a transcortical pathway has been put aside as latencies of iMEPs were maintained in patients with complete agenesis of the CC (74).

3.2.3 Ipsilateral Silent Period

The SP consists of a pause in the ongoing EMG activity after an MEP (87). It is considered to be a measure of interhemispheric inhibition (70,92,93).

After a single pulse suprathreshold TMS, a period of EMG inhibition following the MEP can be observed in EMG activity of contralateral muscles called the cSP (94). The early part of it results from post-spike hyperpolarization of spinal MNs. In contrast, the latter part appears to result from suppression of neuronal output by interneurons at the cortical level (87,94,95). Cracco et al. (96) observed that cortical stimulation excites inhibitory interneurons that project onto pyramidal cells, decreasing the firing of CST neurons. In the ipsilateral muscles, an iSP after an iMEP can also be obtained in both distal and proximal upper limb muscles (70). However, its threshold is lower than that of both cMEPs and iMEPs (72,81).

While trying to determine the origin of iSP, Wassermann et al. (80) found that it may not be mediated by spinal mechanisms since the H-Reflex's amplitude was not altered during iSPs. Furthermore, similar to iMEPs, iSPs are delayed in comparison with their contralateral counterparts, Wassermann et al. (80) argued that iSP may be mediated by indirect pathways such as the reticulospinal tract instead of CST. Nevertheless, iSP is generally thought to be mediated via transcallosal pathways (87,97) and to reflect the state of intracortical inhibitory systems (95,98). This conclusion is supported by studies of patients with agenesis of the CC or with lesions

suppressing any SP after TMS (87,92). Preschool children who have yet to develop a functionally competent CC also do not display iSP, reinforcing this hypothesis (99). CC connections between hand areas of M1s appear to be sparse but effective in transferring of iCS influences from one hemisphere to the other (97).

Similar to iMEPs, iSPs can be modulated by several stimuli elements such as activation of the contralateral hand. This reflects the possibility of task-specific modulation of inhibitory iCS influences from the M1 (92). The coil orientation can also affect its duration, in the same manner as it is the case for iMEPs (87).

3.2.4 Ipsilateral Rebound

In both contralateral and ipsilateral muscles, a SP is usually followed by a second wave of excitation called the rebound (RB) (100).

The iRB has not been widely investigated and both its origin and function remain unclear (101–103). Although there have been several proposals in the past, the majority of them are still debated. Nevertheless, a study on patients with multiple sclerosis by Mills et al. (101) suggested than iRBs may involve both central and peripheral components. He proposed multiple possible pathways involving slower conducting fibers from the CST and long-loop reflexes.

A second hypothesis is that iRBs could be produced in response to MEP's muscle twitch (100,103). However, Rábago et al. (102) argued that if it were the case, iRB latencies would be shorter, making iRBs happening during the iSP. Another critic comes from Holmgren et al. (103) who obtained an RB in the absence of any MEPs, although they made a reservation that a small MEP could be hidden in the background EMG activity. Alternatively, iRBs could be due to recovery from inhibition during iSP (72,102). Finally, it was proposed, although not confirmed, that iRBs could result from a startle reaction elicited by TMS sound (100,102).

3.2.5 Other TMS Paradigms

Different TMS paradigms are available and can be used to investigate intra- and interhemispheric physiological interactions. As indicated in the previous sections, single-pulse TMS can be used to

assess the motor cortex excitability which is likely involving cortico-spinal, intra-cortical and trans-cortical elements (104).

By using paired-pulse TMS applied to the same or both hemispheres, one can "condition" these responses to each TMS pulse (82) to get additional insights into the role of inter- and intrahemispheric circuits and interactions in motor productions. In paired-pulse paradigms, there are two stimuli: a baseline pulse called the test stimulus and a conditioning stimulus. The MEP resulting from a single pulse is then compared to a conditioned one. TMS intensity and interstimulus intervals (ISI) can be varied to observe different types of responses.

Finally, to study the interactions between intracortical circuits, a triple-pulse TMS paradigm with two conditioning stimuli and one test stimulus can be used (84). One can also use continuous, rhythmical TMS to change the state of different brain areas, which is often used in rehabilitation (105).

a. Interhemispheric Interactions

Interhemispheric interactions refer to the interaction between M1 neurons of both hemispheres and rely on the CC integrity. It is generally thought that transcallosal projections are excitatory. They then synapse onto either inhibitory or facilitatory local circuits in the target hemisphere M1 (87). However, this view is mainly based on neuroanatomical data from animals and direct evidence in human are still missing.

Ferbert et al. (97) was a pioneer in their study and demonstrated with paired-pulse TMS the existence of interhemispheric inhibition (IHI) and a poorly reproducible facilitation (IHF). IHI appears to be a very reliable phenomenon, appearing at two specific ISI latencies: short, 8-10 ms, and long, 40ms (81). IHI and SP both reflect interhemispheric inhibition although they are likely to be two different phenomena, at least for the short-latency IHI (81).

IHF was further investigated by Kujirai et al. (106) and Hanajima et al. (107) who debunked the claim that IHF is difficult to observe in Ferbert's experiments (97). They also highlighted the special conditions required for its appearance. By adjusting the interval between the conditioning

stimulus and the test stimulus, the authors were able to observe IHF modulation more or less consistently.

b. Intracortical Interactions

Intracortical interactions refer to the circuits in each M1 separately. In the same manner as interhemispheric, intracortical circuits can be probed using paired-pulse TMS. Several circuits have been identified as part of the intracortical interactions. First, there is the short interval intracortical inhibition and the intracortical facilitation which are thought to provide insights on the $GABA_A$ and NMDAR-dependent system in the motor cortex, respectively (108,109). Secondly, there is a long interval intracortical inhibition reflecting cortical inhibition mediated through the $GABA_B$ system (72), and finally, the short interval intracortical facilitation (84,109). Those different intracortical circuits usually interact with each other and their study can provide insights on the GABAergic and glutamatergic pathways' activity (109).

3.2.6 Caveats

One major caveat of studying MEP is that it reflects both spinal and cortical excitability which means that in theory, they cannot be measured separately (110). Incidentally, a visible increase in MEP size, for instance, could involve spinal mechanisms and skew the interpretations. Thus, some precautions such as equalization techniques need to be taken to dissociate them and ensure that any change properly reflects supraspinal changes.

Another issue comes from the nature of MEP. Its modulation could arise from other non-monosynaptic, e.g. from propriospinal circuits which means that it may not accurately reflect the excitability of the target M1 (110,111).

Finally, not all descending connections involved in movements are excited by TMS with the same strength (111). Indeed, TMS is thought to excite monosynaptic fast and possibly slow conducting fibers preferentially in comparison with polysynaptic slow conducting fibers (111). Thus, TMS may only probe the integrity of a subgroup of descending fibers.

3.3 Roles of iCS Influences in Uni- and Bimanual Movements

3.3.1 Unimanual Movements

In unimanual movements, iCS influences are mainly known to play an inhibitory role and participate in the lateralization of movements. In humans, there is a natural tendency to contract the homologous muscle in a symmetrical manner (112). It is even thought that movements of distal limbs are generated bilaterally at the beginning and only later become unilateral when transcallosal inhibition prevails (113). Mirror movements (MMs) are known to require less cortical activation than asymmetrical bimanual and unilateral movements (92,112). As a result, strictly unilateral movements require interhemispheric interactions, IHI, to inhibit the motor output from the homologous M1 contralateral to the non-active hand. Using single-pulse TMS over the ipsilateral M1 during an action with the contralateral hand, the IHI can be measured by the iSP in the non-active, ipsilateral hand (112).

MMs are frequently seen in children who have yet to develop a functional CC and patient with CC agenesis. For this reason, it is believed that the iCS influences coming into play in movement lateralization are mediated through transcallosal pathways.

By using repetitive TMS to disrupt the ipsilateral M1, Chen et al. (70) assumed the potential participation of iCS influences in fine and more complex movements as well as in their planning and coordination. In addition, studies using fMRI also showed activation of iM1 during unimanual tasks (113). In fact, they observed that iMEPs were facilitated when the contralateral hand was at rest but inhibited when the contralateral hand was active.

3.3.2 Bimanual Movements

Bimanual movements refer to a vast variety of actions. However, we can dissociate them depending on if the two effectors are performing different but complementary actions in a common goal (e.g. opening a bottle) or if their motor output is similar but produced in a specific temporal order (e.g. during typing) (114).

The functional role of iCS influences in bimanual movements is less understood than in unimanual movements. In particular, there is a lack of studies investigating the role of iCS influences in

object-oriented and goal-directed bimanual tasks (114). Goal-directed tasks are defined as bimanual tasks in which there is a functional object-oriented goal (114), such as holding tasks in which coordination and symmetrical forces of the two hands are required to carry an object (115). More common are continuous rhythmical, cyclical and oscillatory bimanual tasks (114).

Studies in monkeys have suggested that there are M1 neurons tuned to either bilateral or unimanual arm movements (17,116,117). Likewise, Dietz et al. (18) have observed with fMRI a stronger bilateral activation of S2 during cooperative hand movements in comparison with non-cooperative bimanual tasks. They also noted the presence of a bilateral reflex EMG response to unilateral electrical nerve stimulation (18). This suggests that the ipsilateral hemisphere would likely be involved in the coordination of cooperation hand movements in a task-specific manner (47). Moreover, different M1 neural circuits are likely involved during cooperative and non-cooperative movements (68).

In addition, Cardoso de Oliveira et al. (118) showed a correlation between interhemispheric interactions and the degree of bimanual coupling. They found that symmetric bimanual movements were accompanied by stronger interhemispheric interactions than asymmetric bimanual movements. It suggests that interhemispheric interactions participate in the production of symmetric bimanual movements and are thus involved in limb coordination. This way, interhemispheric coupling may explain the difficulties we face when producing asymmetric movements. This is further supported by studies from split-brain patients whose callosal connections are destroyed and who are able to produce asymmetric bimanual tasks better than healthy subjects (118,119). During bimanual tasks, they also noticed an increase in intrahemispheric interactions, suggesting that both hemispheres participate in bimanual control (118).

Thus, based on findings from inter- and intrahemispheric interactions, one can conclude that both hemispheres are involved in bimanual movements (118) and that M1 of the dominant hemisphere is more important in bimanual coordination (16).

3.4 Clinical Relevance

Despite some evidence that iCS influences on MNs may be important for recovery of motor functions after brain or spinal cord lesions (70,120), their role in movement production in normal and pathological populations has not been fully understood.

On one hand, several authors have raised the possibility that ipsilateral motor pathways might provide a way for the cortical output from the undamaged M1 to reach contralesional limb muscles (70). On the other hand, some authors argue that iCS influences may not actually be responsible for recovery (10,70) and could even prevent rehabilitation in some cases (69).

There are several different ways in which iCS pathways could be useful in recovery. It could, for instance, represent a substrate for functional restoration after lesion. Indeed, in the case where the CST originating from the ipsilesional hemisphere is extensively disrupted, iCS could offer the only pathway for descending commands to reach the paretic limb muscles (69). TMS studies could also provide insights about iCS pathways integrity by the presence of iMEPs (70,83). However, this hypothesis remains controversial as some authors have suggested that instead of being biomarkers for recovery, they would instead be indicators of poor motor recovery (10). Several studies have reported that iMEPs obtained in stroke patients were usually rare, small and had longer latencies than in healthy subjects (70,121). It is important to note that iMEPs are already thought to be difficult to elicit in healthy subjects, often requiring a slight voluntary contraction of the target muscle. Patients with severe upper limb deficits may not be able to achieve such contraction, thus increasing the difficulty to trigger iMEPs. Another factor to consider is the TMS intensity used during trials because ipsilateral responses usually require a higher TMS intensity than contralateral ones (121). Strong TMS intensities are generally not used in studies involving post-stroke patients since high-intensity stimulation can spread and activate the contralateral hemisphere (70,121). For this reason, it is difficult to accurately assess the role of iCS pathways in recovery from stroke.

In summary, the way iCS pathways participate in the recovery of motor function after stroke is still unclear. Nevertheless, by investigating how they are involved in voluntary motor behaviors in healthy subjects, we may better understand whether or not they might be useful in

rehabilitation. For example, this could help optimize the intensity and pattern of iTMS during a set of motor tasks, such as using cooperative movements needed during daily living activities as a training paradigm (47,88).

4. Problematic and Goals

Although it is mostly agreed upon that iCS influences are involved in both uni- and bimanual movements, how exactly they participate remains poorly understood. In addition, it is still unclear whether or not they are affected by cutaneous afferent and in which manner.

The motor cortex involvement in threshold position control during wrist movement in humans has been investigated in the past. It has been demonstrated in a previous study using TMS, that cCS were modulated such that cMEPs produced in wrist flexors were larger in flexion than in extension position, even though the tonic EMG activity at these positions was equalized (33). It was concluded that cCS facilitation is able to set and reset the spatial threshold position at which MNs of contralateral wrist muscles begin to be recruited (33–36), thus solving the posture-movement problem described by Von Holst and Mittelstaedt (122). In this paper, Von Holst and Mittelstaedt (121) discussed why self-initiated voluntary movements of a body segment from a stable posture to another are not met with resistance from postural reflexes. The ability to reset the threshold limb position provides a solution to this problem by allowing the nervous system to relay postural reflexes to a new position, converting them from movement-resisting mechanisms to movement-producing instead.

These results raise the question of whether or not the iCS system is also involved in such control. We thus aimed to extend this line of research by focusing on the role of iCS influences in both uni- and bimanual tasks. As iCS influences participation in unimanual and bimanual tasks differs, we investigated whether or not iMEPs elicited by iTMS in wrist flexors are different at different wrist positions. We hypothesized that iCS influences would be more strongly modulated in bimanual tasks than in the unimanual task. In testing this hypothesis, we also considered that bimanual movements often involve manipulation of an object held between the hands, which requires the generation of a bimanual holding force. Therefore, we also addressed the question

of whether or not direct contact of the hands with each other or via an object affects iCS influences in bimanual motor tasks.

Furthermore, cutaneous afferents appear to play a major role in cCS modulation, especially during tasks of holding an object where it participates to grip force scaling and maintaining. Hence, we also aimed to investigate if iCS are modulated in bimanual tasks in which subjects hold different blocks whose surfaces differ in terms of texture and associated friction. We hypothesized that the friction level between the hand and the block's surface would be a key element in iCS modulation (123).

Methods

To test our hypotheses, two separate experiments were made. Methods for both experiments will be described in more detail subsequently.

In the first experiment, we compared TMS responses during flexion and extension wrist position in a unimanual and two bimanual tasks. Our hypothesis was that iCS influences would be more strongly modulated in bimanual tasks than in unimanual. This work has been the object of an oral presentation at Progress in Motor Control XII in July 2019, and the associated paper was co-written by Lei Zhang* (Institut für Neuroinformatik, Ruhr-Universität Bochum, Germany), **Laura Duval*** (Institut de réadaptation Gingras-Lindsay-de-Montréal (IRGLM); Department of Neuroscience, Université de Montréal, Montreal, Canada), Fariba Hasanbarani (IRGLM; Department of Occupational and Physical Therapy, McGill University, Montreal, Canada), Yuqi Zhu (Faculty of Medicine, Université de Montréal, Montreal, Canada), Xiang Zhang (Faculty of Medicine, Université de Montréal, Montreal, Canada), Dorothy Barthelemy (IRGLM; Ecole de Réadaptation, Université de Montréal, Montreal, Canada), Numa Dancause (Department of Neuroscience, Université de Montréal, Montreal, Canada) and Anatol G. Feldman (IRGLM; Department of Neuroscience, Université de Montréal, Montreal, Canada).

In our second experiment, we compared iMEPs changes in response to variations of block surface texture and friction level in five bimanual holding tasks. We hypothesized that the amount of friction between the hands and the block would play an important role in iCS modulation. This work was carried-out in collaboration with Lei Zhang, Anne-Sophie Lauzé (Department of Neuroscience, Université de Montréal), Yuqi Zhu, Dorothy Barthelemy, Numa Dancause and Anatol G. Feldman.

Protocols used in those two studies were slightly different since a new EMG equipment was implemented in the laboratory.

1. Participation of iCS Pathways in Bimanual Wrist Movements in Humans.

1.1 Participants

Right-handed healthy participants (n=23, 13 males and 10 females, 26.0 ± 5.5 years old) participated in this study. They had no history of orthopedic or neurological disorders and did not take psychoactive or other drugs that could affect cortical excitability. All participants signed an informed consent form approved by the Center for Interdisciplinary Research in Rehabilitation (CRIR) Ethics Committee in accordance with the 1964 Declaration of Helsinki.

1.2 Experimental Procedures

Participants sat in a chair in front of a table (0.7 m height). Both forearms were placed on and attached to the table with Velcro straps in semi-supinated positions (elbow angle about 145°, shoulder horizontal abduction about 45°) (see Fig. 4).

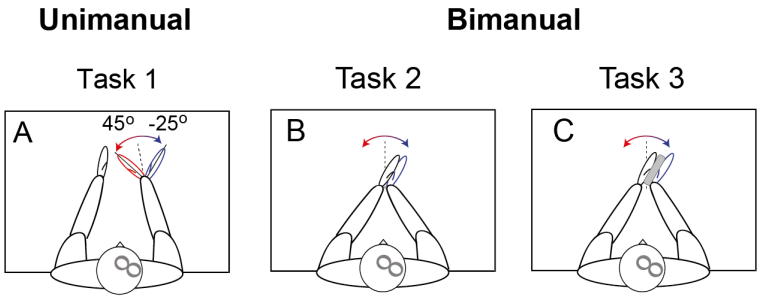

Figure 5. – Subjects Positions in Uni- and Bimanual Tasks.
A: Unimanual task; B, C: Bimanual tasks with hands in direct contact (B) or indirect contact through a block (C).

In the unimanual task (Task 1), the right hand was placed in a hand splint that could be freely rotated about a vertical axis fastened to the table. The wrist flexion-extension axis was aligned with the axis of rotation of the splint (Fig. 1A). Participants (n=16) actively established a right 45° wrist flexion or 25° extension from the neutral position (0°). Each position was indicated by a radial line on the table. Once reached in a self-paced way, each wrist position was maintained. In this task, subjects were instructed to relax the left arm with the wrist in the neutral position and to not move this arm during changes and maintenance of the right wrist angle.

In the bimanual task (Task 2), participant's (n=11) hands were held together within a single splint. The palms were in direct contact with each other and the hand dorsal surfaces just touched the splint walls (Fig. 1B). Participants actively established a position of 45° wrist flexion or 25° extension with the right wrist, while preserving contact with the left palm. In other words, in this task, the wrists were rotated together such that right wrist flexion was combined with left wrist extension and vice versa. After the end of the motion, both hands kept each wrist position stationary.

In another bimanual task (Task 3), participants (n=10) established the same wrist positions as in Task 2, while holding a light smooth wooden block (4 x 6 x 20 cm) between the two hands without lifting it (Fig. 1C). The proximal side of the block was oriented vertically, along the flexion-extension wrist axes such that the block was rotated together with the hands. The three tasks were performed in a random order across participants.

For each task, we tested whether or not there were position-related changes in ipsilateral cortical descending influences on MNs of wrist flexors (flexor carpi radialis, FCR) using TMS over M1 delivered after the end of wrist motion at each stationary position. There are limitations in using TMS and MEPs for the evaluation of descending influences. MEPs elicited by TMS depend not only on the excitability of the motor cortex but also on the excitability of MNs (33,36,124). To overcome this confounding factor, we measured responses to TMS at different wrist positions, when the tonic EMG activities at these positions were equalized (e.g. (33)). This was done by asking participants to press at each stationary wrist position in the flexion direction with the right hand against the wall of the splint (Task 1), against the left hand in Task 2) or on the wooden block in Task 3). This allowed the subject to maintain the rectified tonic EMG level of the right FCR within a specified window displayed in terms of maximal voluntary contraction (MVC), measured separately by asking participants to maximally press with the right hand 3 times against a motionless object in the flexion direction. The mean of the 3 MVC efforts was determined and participants had to maintain the EMG level within the window (30% MVC ±2SD) in the tested right wrist positions (flexion and extension).

As mentioned in the Introduction, descending influences from ipsilateral M1 are transmitted to MNs by multiple pathways. By recording responses to iTMS we could not evaluate individual contributions of each pathway and thus, by recording MEPs, we measured an integral effect of all descending influences from iM1.

To control for afferent influences from neck muscles on FCR excitability (74,88), head position and gaze were maintained during each trial by instructing participants to look at a computer screen directly in front of them.

1.3 TMS

At each wrist position, 20 TMS pulses were delivered. Single-pulse TMS (5-10s between pulses) was delivered via a cone-shaped figure-eight coil (110° between two cones, 70 mm outer diameter) and connected to a Magstim 200 system (UK). Although flat and cone-shaped figure-eight coils are very similar in terms of TMS focality (85), we used a cone-shaped coil as it conformed better to the shape of the head. The coil was positioned over the wrist area of the subject's right M1 (the middle point of the coil was about 2 cm anterior and 6 cm lateral to the vertex). TMS induced a posterior-anterior directed current. The optimal site for stimulation was located by moving the coil from the above location in small discrete steps on the surface of the head until the EMG responses to TMS, i.e. MEPs, in the left FCR remained stable for five consecutive trials while participants maintained a neutral wrist position with minimal EMG activity. During this procedure, MEPs were monitored on an oscilloscope. The TMS intensity was then decreased to determine the resting motor threshold (33) when MEPs just began to exceed the background EMG activity in at least 3 of 5 consecutive trials. TMS intensity was then increased to 1.5 × above threshold. For all participants, TMS intensity ranged from 50 to 68% of the maximal Magstim output. For each subject, the TMS intensity was kept the same during the whole experiment. Unlike other studies using maximal Magstim output (72,74,88), we decided not to use higher TMS intensities to limit the volume of iM1 excited by TMS.

Participants wore a swimming cap on which the optimal coil position was marked. In addition, six markers were placed on the cap around the coil perimeter as a visual reference to maintain the coil position throughout the experiments.

1.4 Data Recording

Bipolar surface EMG activity of right and left FCR was recorded. Prior to electrode application, the skin was cleaned with alcohol. Pairs of Ag–AgCl pre-gelled electrodes (1 cm diameter, interelectrode distance 2–3 cm) were placed above the muscle bellies. The reference electrode was placed over the epicondyle of the elbow joint. EMG signals were amplified (×2000) using a Noraxon telemetric system (USA).

A customized program (LabView, National Instruments, USA) was used to record EMG signals (sampling rate 5 kHz,) and control TMS timing. Signal software (Version 4.11, Cambridge Electronic Design, UK) was used to display the EMG signal online (root-mean-square values, time constant 100 ms).

1.5 Data Analysis

Raw EMG signals were filtered offline by a zero-phase 4^{th} order Butterworth band-pass filter (10–500 Hz). The ipsilateral EMG response has several components (74,81,88,125). After the short-latency iMEP, there was a silent period (iSP), then another facilitation (iRB). These components of TMS response were observed in 25-40, 40-60, and 60-80 ms windows, respectively. We often observed secondary iSP and iRB responses to iTMS which are not analyzed in the present study.

Fig. 6 shows typical rectified EMG responses elicited by TMS (cMEP and cSP in A, iMEP, iSP and iRB in B) over the right M1 when the subject maintained 45° right wrist flexion in Task 1. In the present study, we focused on the short-latency iMEP, the first iSP and the first rebound iRB (Fig. 6B). The EMG baseline was defined as the mean rectified average EMG level for 200 ms before TMS onset (time 0 in Fig. 6). For group comparisons, individual EMG levels were normalized with respect to the baseline in each position. Responses to TMS (cMEP, iMEP, iSP and iRB) were characterized by the onset time, duration, peak-to-peak amplitude, and area.

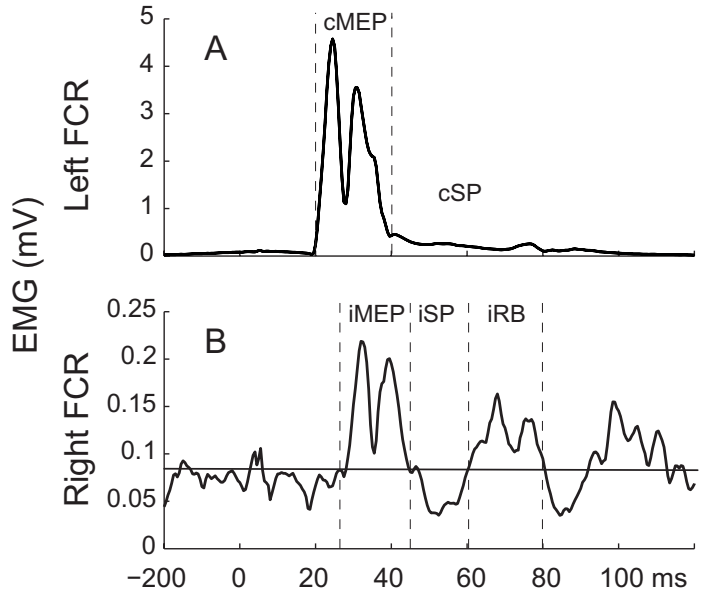

Figure 6. – Example of TMS Responses in Left and Right FCR.

A: cMEP and cSP (rectified, mean of 20 trials) elicited by TMS at time 0 of the right wrist area of the motor cortex and recorded from the left FCR; B: Components of response to iTMS recorded from the right FCR (rectified, mean of 20 trials). iMEP: short-latency component; iSP: primary silent period; iRB: first rebound (subsequent components of responses to iTMS were not analyzed). Dashed vertical lines show time windows for each analyzed component of the iTMS response. iTMS Data in A and B were obtained when the subject maintained 45° right wrist flexion in Task 1.

An iMEP was considered to be present if the post-stimulus EMG exceeded the baseline by 1 SD for 5 ms (81). The iMEP duration was defined as the time between the point when the EMG began to exceed the baseline by 1SD to the point when the EMG returned to its baseline level. The iMEP amplitude was defined as the maximal deflection of rectified iMEP from the baseline. The iMEP area was calculated as the area between the rectified iMEP and the EMG baseline. The corresponding characteristics of other potentials evoked by TMS and their components (cMEP, iMEP, iSP and iRB) were determined in similar ways and compared between the wrist flexion and extension positions, in all tasks, unless otherwise indicated.

1.6 Statistical Analysis

Data normality was evaluated by Shapiro-Wilk statistics. Paired t-tests were used to compare group data when normally distributed. Otherwise, the Wilcoxon rank-sum test was used. These tests were used to determine the effect of wrist position (flexion and extension) on the onset,

duration, amplitude, and area of responses to TMS. For significant results, the effect size was always reported as Cohen's d (126). To assess the similarity of background EMG levels of the right FCR in the two wrist positions, we also reported effect size to compare two means of data sets, even though the statistical result was not significant, and we considered background EMG levels to be similar if $d < 0.2$ with $p > 0.05$. Pearson correlation analysis was used to evaluate correlations between iMEP and iRB areas. Significance levels were set at $p < 0.05$ for all tests. Group data are presented as the mean ± standard error in the text and figures. Matlab software (The MathWorks, Natick, MA) was used for all offline data analysis.

2. Effect of Texture and Weight on iCS Pathways in Bimanual Wrist Movements in Humans.

2.1 Subjects

Right-handed healthy subjects (n=21, 7 males and 14 females, 23.0 ± 5 years old) participated in this study. They had no history of orthopedic or neurological disorders and did not take psychoactive or other drugs that could affect cortical excitability. All subjects signed an informed consent form approved by the CRIR in accordance with the 1964 Declaration of Helsinki.

2.2 Experimental Procedures

Subjects sat in a chair in front of a table whose height was adjusted to ensure elbow and shoulder angles continuity between subjects. The table used was narrow enough so that wrists and hands extended beyond its side. To provide support when required, a board could be securely fixed on the table. Both forearms were placed either directly on the table (unsupported condition) or on the board (supported condition) in semi-supinated positions (elbow angle about 145°, shoulder horizontal abduction about 45°) such that the flexion-extension axis of wrists rotation was vertical. A block (4 x 6 x 20 cm) was placed between the hands. Two versions of the block were used during this experiment. One had a smooth sanded surface (smooth block) and the second had Velcro taped on its sides to simulate roughness and provide friction (coarse block). In one task, a 988.65g weight was added to the smooth block to enhance load forces.

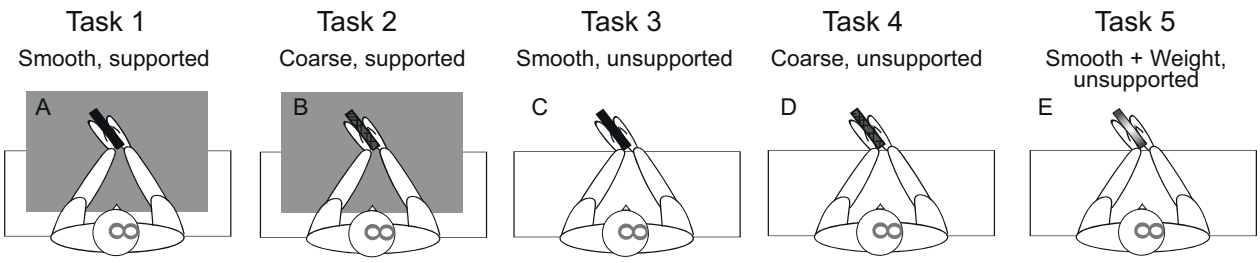

Figure 7. – Subjects Position in Bimanual Holding Tasks.
A: Smooth block in supported condition; B: Coarse block in supported condition; C: Smooth block in unsupported condition; D: Coarse block in unsupported condition; E: Smooth block with added weight in unsupported condition. All tasks were executed in flexion position.

Experiments consisted of five holding tasks, either supported or unsupported. In all tasks subjects actively established a right 45° wrist flexion position while holding a block (Fig. 7). Tasks 1 and 2 were realized in a supported condition with either a smooth or coarse block, respectively (Fig. 7 A, B). Tasks 3, 4 and 5 were accomplished in an unsupported condition with a smooth, coarse and weighted block (Fig. 7 C, D, E). Tasks were performed in a semi-random order across subjects.

We tested whether or not there were condition-related changes in iCS influences on MNs of FCR with TMS over the right M1. Since MEPs elicited by TMS depend on both motor cortex and spinal MNs excitability (33,36,124), we equalized tonic EMG activity of the right FCR in each condition. To do so, we asked subjects to maintain a muscle activity corresponding to 20% ± 2SD of their MVC in all tasks. To help subjects to reach and maintain an EMG level within this range, EMG activity was displayed on a computer screen. For each task, 20 TMS pulses and 5 shams were delivered. Before every new task, subjects were given 2 to 4 practice trials to reach an accurate level of contraction.

To control for neck influences (74,88), head position and gaze were maintained during each trial by advising subjects to look directly at the screen displaying EMG activity in front of them.

2.3 TMS

Single-pulse TMS (5-10s between pulses) was delivered via a cone-shaped figure-eight coil (110° between two cones, 70 mm outer diameter) connected to a Magstim 200 system (UK). The coil was positioned over the wrist area of the subject's right motor cortex (the middle point of the coil

was about 2 cm anterior and 6 cm lateral to the vertex). TMS induced a posterior-anterior directed current. The optimal site for stimulation was located by moving the coil from the above location in small discrete steps on the surface of the head until the cMEPs, in left FCR remained stable for five consecutive trials. During this search, MEPs were monitored on Signal (Cambridge Electronic Design box, UK). The TMS intensity was then decreased to determine the resting motor threshold when, visually, MEPs just began to exceed the background EMG activity in at least 3 of 5 consecutive trials. TMS intensity was then increased to 1.5× above threshold. Intensity ranged from 45 to 57% of maximal Magstim output. For each subject, the TMS intensity was kept the same during the whole experiment. TMS was triggered via the software Signal.

To maintain the coil position throughout the experiment, subjects wore a swimming cap on which the outline of the coil at the optimal site was marked with a removable marker pen.

2.4 Data Recording

EMG activity of the right and left FCR was recorded with Trigno™ Mini Sensors Delsys electrodes placed on the belly of the muscle. Prior to electrode application, the skin was cleaned with alcohol. Rectified EMG signals (root-mean-square values, time constant 100ms) of both flexors were displayed on a screen via the Cambridge Electronic Design box (CED Ltd, Cambridge, UK). EMG signals were recorded with Signal (sampling rates 2000Hz).

2.5 Data Analysis

Matlab software (The MathWorks, Natick, MA) was used for all offline data analysis. Raw EMG signals were filtered offline by a with a band-pass filter (45–500 Hz). Although the ipsilateral EMG response to TMS is composed of a short-latency iMEP which is then followed by one or several iSP and long-latency iRB (see also (74,81,88,125)), the analysis was focused on iMEPs.

EMG baseline was defined as the mean rectified EMG level averaged over 50 ms before the TMS onset. For group comparisons, individual EMG levels were normalized with respect to their baseline. Responses to TMS (cMEP and iMEP) were characterized by onset time, duration, amplitude, and area displayed in Table 2.

An iMEP was considered to be present if the post-stimulus EMG exceeded the baseline by 1SD (81) for 5 ms (Fig.8). The iMEP duration was defined as the time between the point when the EMG began to exceed the baseline by 1SD to the point when the EMG returned to its baseline level. The iMEP amplitude was defined as the maximal deflection of rectified iMEP from the baseline. The iMEP area was defined as the area between the rectified iMEP and the EMG baseline. It was calculated differently from the previous paper using the trapeze method.

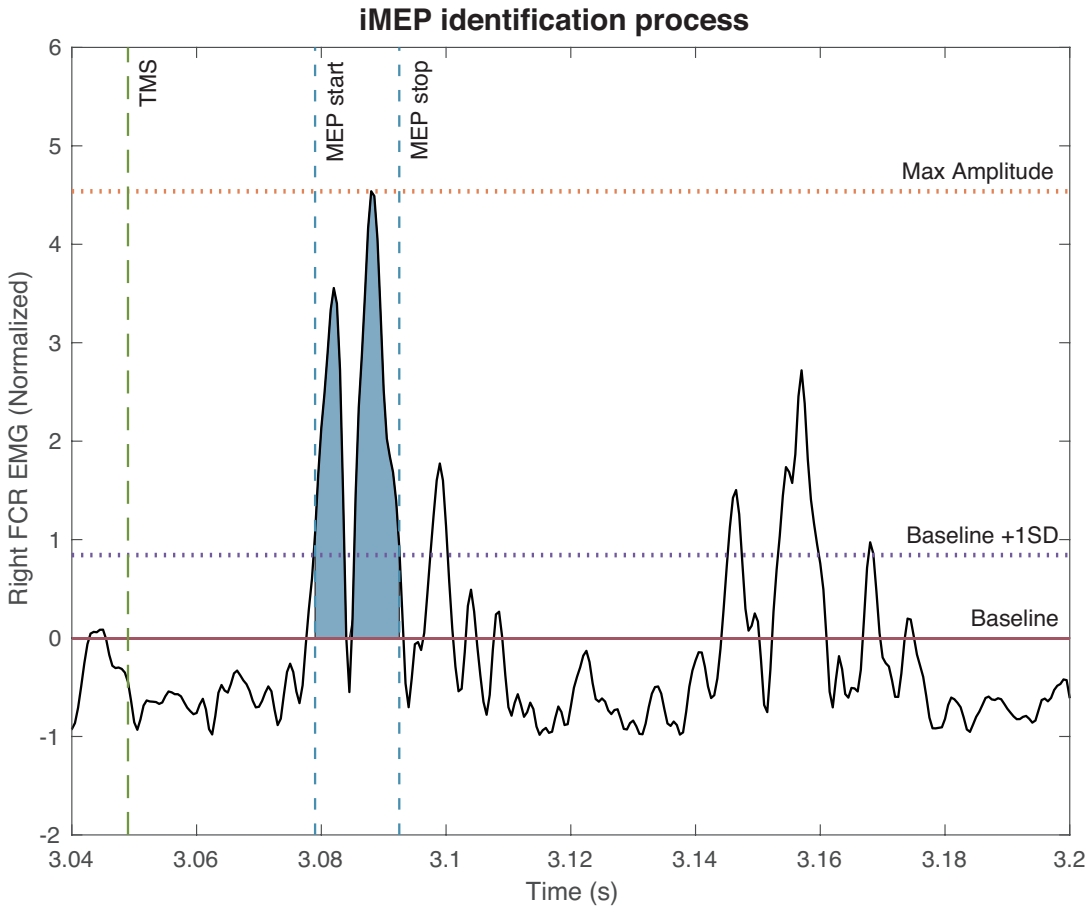

Figure 8. – Example of Selected iMEP.

In order to identify and iMEP, the baseline (red solid line) was defined as the average EMG 50ms before TMS onset at 3.049s (green dashed line) and the detection threshold was set at 1SD above the baseline (purple dotted line). An iMEP was considered valid when its EMG exceeded the detection threshold for more than 5ms. iMEP area is displayed as the blue area between MEP start and stop (blue dashed lines). Max amplitude is defined as the maximum iMEP peak amplitude (orange dotted line).

2.6 Statistical Analysis

Statistics were calculated using IBM SPSS Statistics 25 (New York, U.S). A Two-factor repeated-measures ANOVA was performed to determine the effect of texture (smooth, coarse) and support (supported, unsupported) on iMEP amplitude, area, onset, and duration. The effect of weight was assessed by doing paired t-tests between Tasks 1 and 5 as well as Tasks 3 and 5. For significant results, the effect size was always reported as Cohen's d (126). The significance level was set at $p < 0.05$. Group data are presented as the mean ± standard error in the text and figures.

Results

1. Participation of iCS Pathways in Bimanual Wrist Movements in Humans.

1.1 Characteristics of cMEP, iMEP, iSP and iRB

Responses to TMS in the left, contralateral FCR (cMEP) and the right, ipsilateral FCR (iMEP, iSP, and iRB) were identified in both unimanual and bimanual tasks in all participants despite the use of a lower TMS intensity compared to other studies (see Methods). Latencies of iMEPs onset were longer (24.3 ± 0.6 ms) than cMEPs (19.4 ± 0.3 ms; $p < 0.001$). The amplitude of iMEPs (0.16 ± 0.01 mV, range 0.13 ~ 0.17 mV) was much smaller than cMEPs (2.50 ± 0.21 mV, range 1.26 ~ 4.98 mV, $p < 0.001$). iSPs onset occurred 38.9 ± 0.8 ms after TMS and lasted 20.5 ± 0.9 ms. iRBs started 60.0 ± 0.8 ms after TMS and lasted 21.2 ± 0.9 ms. Characteristics of components of EMG responses to TMS for all conditions (3 tasks × 2 arm positions) are shown in Table 1.

1.2 iCS Influences in Unimanual Task 1

To evaluate iCS influences on MNs of the right FCR in the unimanual task, iMEP, iSP, and iRB amplitudes and areas were compared between the flexion and extension positions of the right wrist (Fig. 9A for a single subject and 9B for the group of 16 participants). For this task, no position-related changes in iMEP amplitudes ($p= 0.215$) or areas ($p= 0.326$) were found. The characteristics of iSPs and iRBs also remained unchanged (iSP amplitude: $p= 0.312$; iSP area: $p= 0.220$; iRB amplitude: $p= 0.091$; iRB area: $p= 0.731$, Fig. 2C). The background EMG level of the right FCR was similar across positions ($p= 0.934$, effect size $d= 0.029$).

In this task, the left wrist was in the neutral position and changes in the EMG activity of the left FCR during right wrist flexion and extension were insignificant ($p= 0.934$, Fig. 9D). The amplitude and area of cMEPs in the left FCR were also preserved when the right wrist position changed (amplitude: $p= 0.564$; area: $p= 0.973$, Table 1).

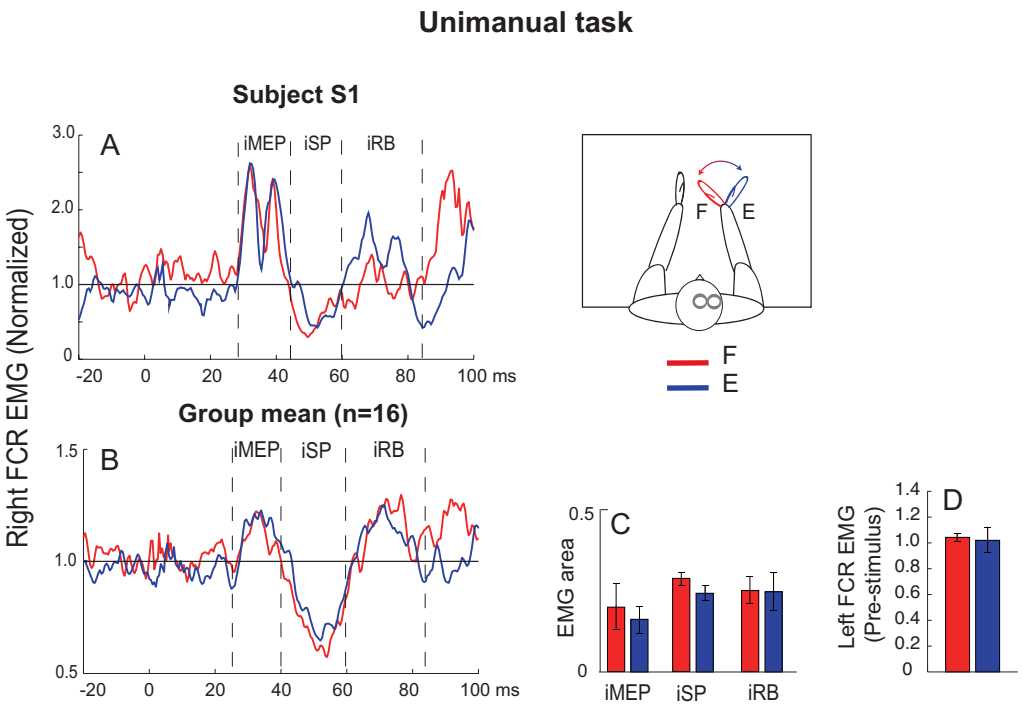

Figure 9. – Effect of Wrist Position in Unimanual Task 1.

Absence of position-related changes in iMEP, iSP and iRB in the unimanual Task 1. Unlike Fig. 6 A and B, all responses were normalized by the mean of background EMG signals 200 ms prior to TMS. A, B: EMG (rectified, mean of 20 trials) elicited by TMS at time 0 for one representative subject (A) and the group (B). C: ratio of EMG areas between flexion and extension positions for each component of the TMS response. D: pre-stimulus EMG of the left FCR during the different positions of the right wrist.

1.3 iCS Influences in Bimanual Tasks 2 and 3

In bimanual tasks, ipsilateral cortical descending outputs depended on the way the two hands interacted with each other.

In Task 2, in which the hands were in contact and the two hands moved together, only the late component of the response to TMS, the iRB, in the right FCR was affected by changes in the wrist position (Fig. 10A for a single subject and 10B for the group of 11 participants). The amplitude and area of iRBs of the right FCR were significantly larger (amplitude: p= 0.029, effect size d= 0.70; area: p= 0.016, effect size d= 0.82, Fig. 10C) when the right wrist was extended compared to when it was flexed. However, the iRB onset and duration were not affected by changes in wrist position (onset: p= 0.336; duration: p= 0.673). All measurable characteristics of the other components of responses to TMS (iMEP and iSP) were also unaffected by changes in wrist position (p > 0.320 in

all cases, Fig. 10C). Background EMG levels of the right FCR remained similar across positions (p= 0.967, effect size d= 0.028).

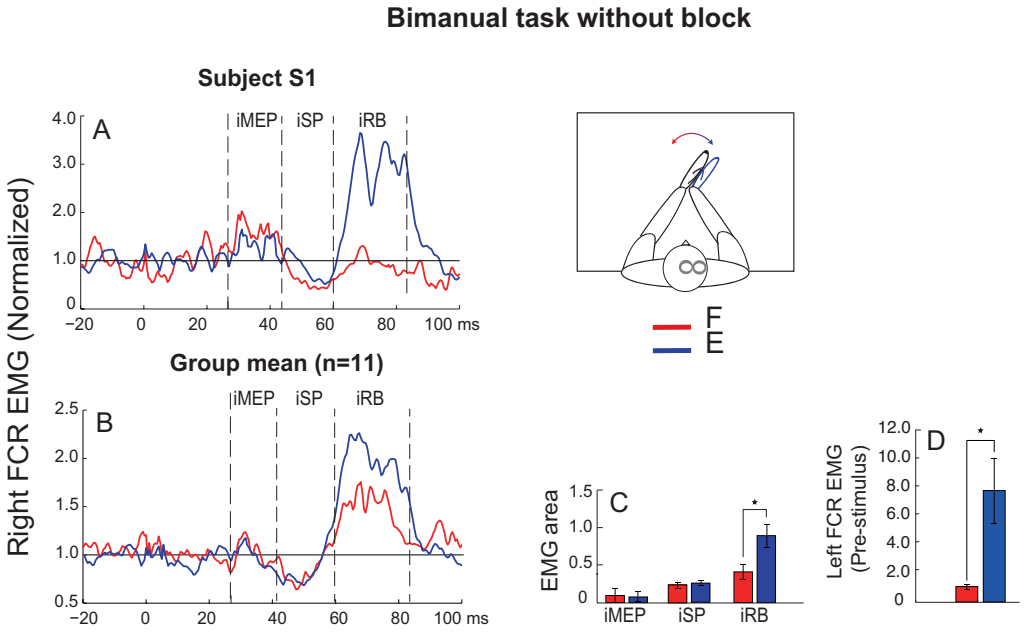

Figure 10. – Effect of Wrist Position in Bimanual Task 2.
Position-related changes in ipsilateral responses to TMS in bimanual Tasks 2 (A-C, p=0.029, and p=0.016 for amplitude and area of the iRB). D: pre-stimulus EMG of the left FCR was significantly different between the flexion and extension position of the right wrist (p= 0.035, effect size d= 1.04).

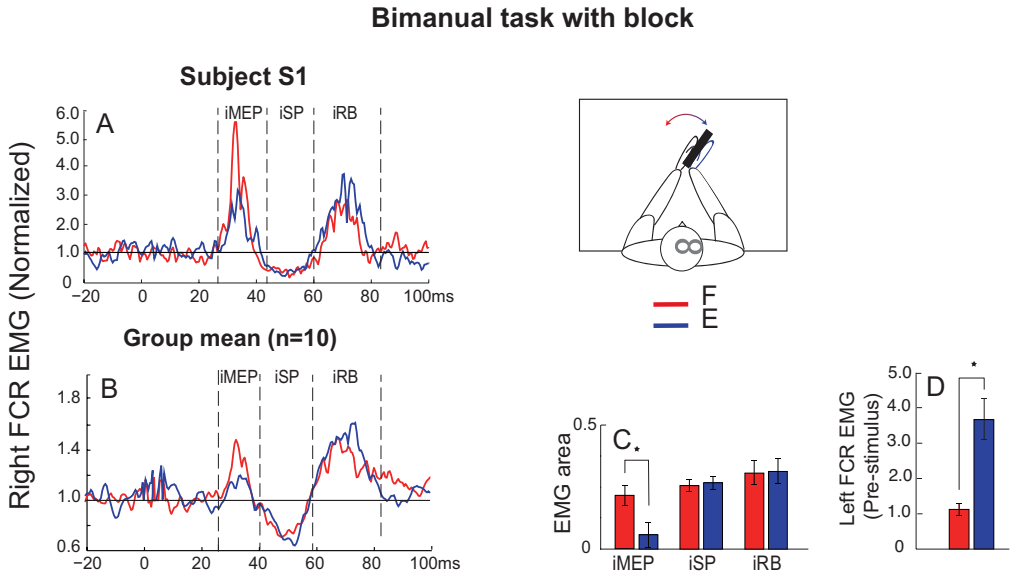

Figure 11. – Effect of Wrist Position in Bimanual Task 3.
Position-related changes in ipsilateral responses to TMS in bimanual Tasks 3(A-C, p=0.010 and p=0.012 for amplitude and area of the iMEP). D: pre-stimulus EMG of the

left FCR was significantly different between the flexion and extension position of the right wrist (p= 0.002, effect size d= 1.88).

In Task 3 with the wooden block between the hands, both iMEP amplitude and area were larger when the right wrist was flexed compared to when it was extended (Fig. 11A for a single subject and 11B for the group of 10 participants; for amplitude p= 0.010, effect size d= 0.63; for area p= 0.012, effect size d= 0.99), while the iMEP latency and duration, as well as other characteristics of iSP and iRB in the right (ipsilateral) FCR were not affected by changes in wrist position ($p > 0.366$; Table 1). Background EMG level of the right FCR remained similar across positions (p= 0.910, effect size d= 0.095). For all tasks, no correlations were found between iMEP and iRB EMG areas ($-0.5 < r < 0.25$, $p > 0.14$).

In both bimanual tasks, the magnitude of the tonic EMG activity of the left FCR, in contrast to the right FCR, changed with the wrist position, being significantly greater when the right wrist was extended and the left wrist was flexed for Task 2 (p= 0.035, effect size d= 1.04, Fig. 10D) and Task 3 (p= 0.002, effect size d= 1.88, Fig. 11D). After normalization of the background EMG levels, neither the magnitude (Task 2: p= 0.235; Task 3: p= 0.117) nor the area (Task 2: p= 0.128; Task 3: p= 0.100) of cMEPs differed between the wrist positions.

2. Effect of Texture and Weight on iCS Pathways in Bimanual Wrist Movements in Humans.

2.1 Characteristics of cMEP and iMEP

Although TMS intensities used in this experiment were lower in comparison with other studies (see Methods), responses to TMS in both the left, contralateral FCR (cMEP) and in the right, ipsilateral FCR (iMEP) were reliably obtained in all tasks and in all participants. Overall, iMEPs onset latencies were longer (Task 1: p< 0.000; Task 2: p< 0.000; Task 3: p< 0.000; Task 4: p p< 0.000; Task 5: p< 0.000) than those of cMEPs and their relative amplitude (Task 1: p= 0.001; Task 2: p= 0.001; Task 3: p= 0.004; Task 4: p= 0.001; Task 5: p< 0.000) and areas (Task 1: p= 0.001; Task 2: p< 0.000; Task 3: p= 0.002; Task 4: p= 0.001;Task 5: p< 0.000) were smaller. Characteristics of EMG responses to TMS for all conditions are shown in Table 2.

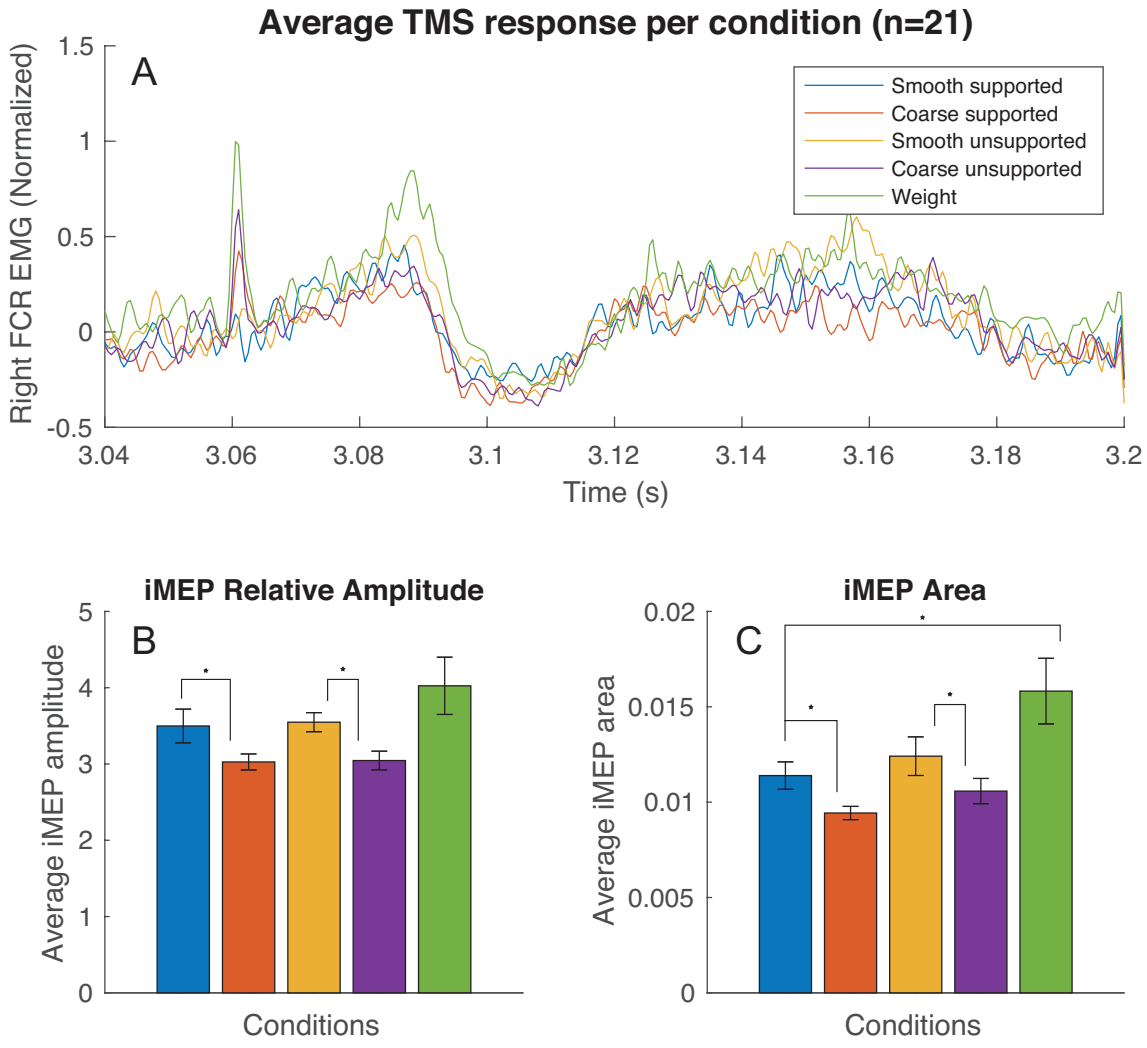

Figure 12. – Overall Results From Tasks 1, 2, 3, 4 and 5.
A: EMG (rectified, mean of 20 trials, n=21) elicited by TMS at time 3.049 for each condition; B: Ratio of iMEPs relative amplitude between each condition; C: Ratio of iMEPs area between each condition. Asterisks show significant effects.

2.2 Effect of Texture on iCS Influences

To assess the effect of texture on iCS influences, iMEPs were compared in two bimanual holding tasks where the block's surface was either smooth or coarse, first in a supported setting (Fig. 13; Tasks 1 and 2), then unsupported (Fig. 14; Tasks 3 and 4). Regardless of the support, the smooth block was associated with significantly larger iMEPs in both amplitude and area (amplitude: $F(1,20)= 14.419$, $p= 0.001$, $\eta p^2= 0.419$, Fig. 13B, 14B and 15A; area: $F(1,20)= 4.999$, $p= 0.037$, $\eta p^2= 0.2$, Fig. 13C, 14C and 15B) in comparison with the coarse block.

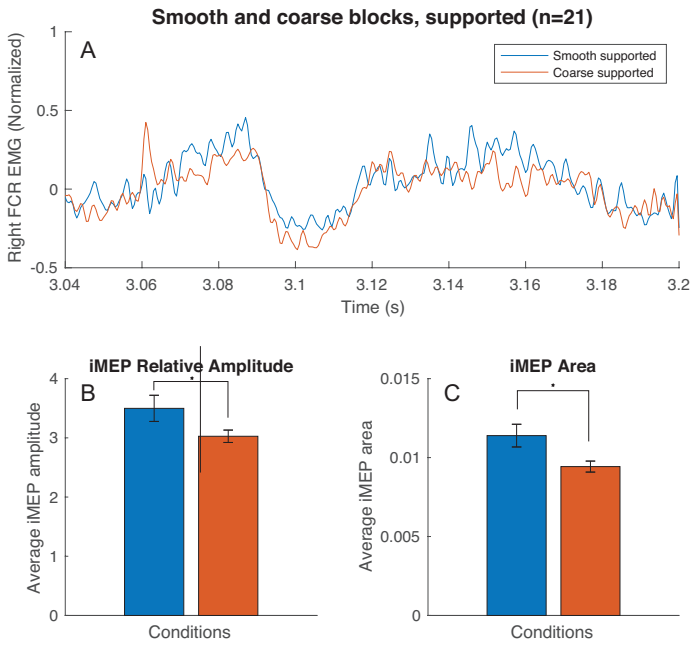

Figure 13. – Effect of Texture in Supported Conditions.
Texture-related changes in ipsilateral responses to TMS between Tasks 1 and 2 (B: p= 0.001, ηp^2= 0.419; C: p= 0.037, ηp^2= 0.2).

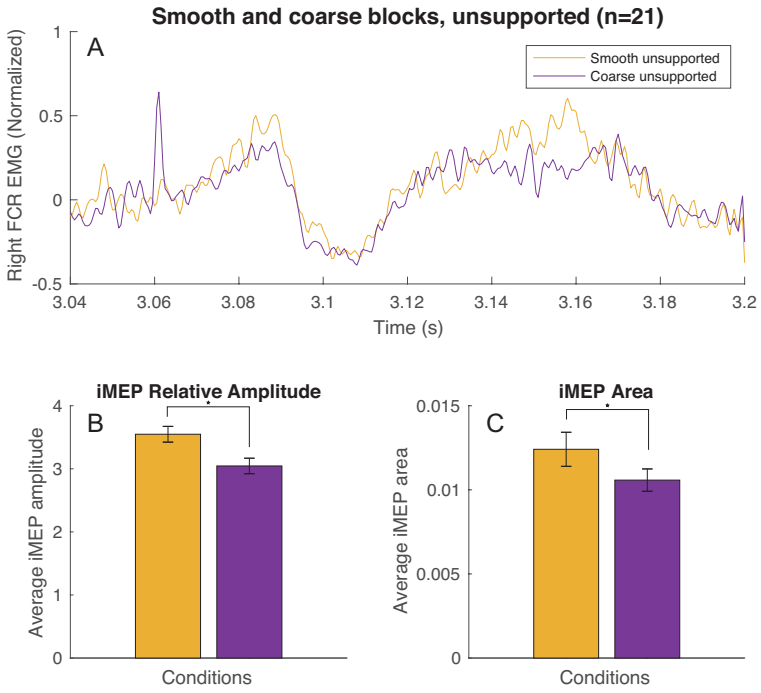

Figure 14. – Effects of Texture and Friction in Unsupported Conditions.
Texture-related changes in ipsilateral responses to TMS between Tasks 3 and 4 (B: p= 0.001, ηp^2= 0.419; C: p= 0.037, ηp^2= 0.2).

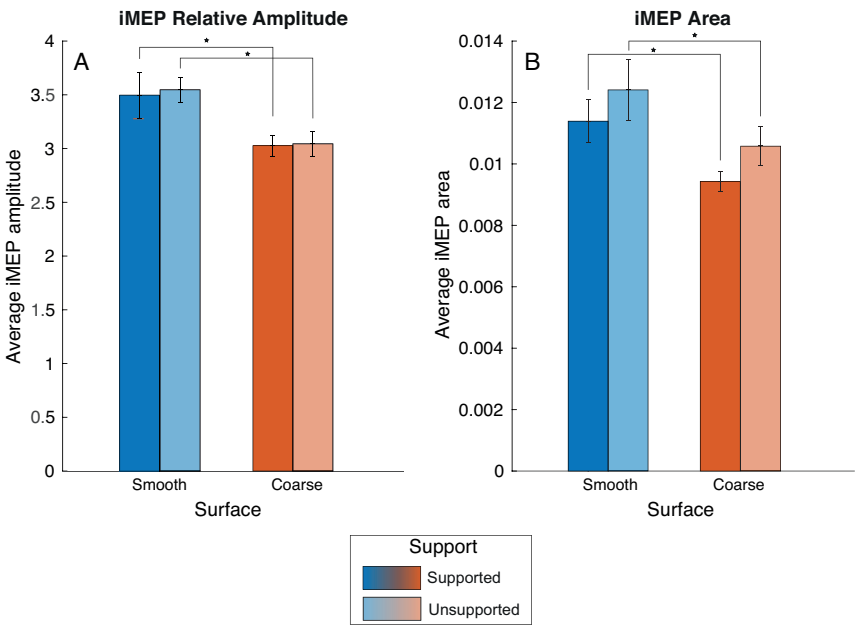

Figure 15. – Effects of Texture in Supported and Unsupported Conditions.
Texture-related changes in ipsilateral responses to TMS between the smooth and coarse surfaces with the block supported (Tasks 1 and 2; A: $p= 0.001$, $\eta p^2= 0.419$; B: $p= 0.037$, $\eta p^2= 0.2$) and unsupported (Tasks 3 and 4; A: $p= 0.001$, $\eta p^2= 0.419$; B: $p= 0.037$, $\eta p^2= 0.2$).

2.3 Effect of Support on iCS Influences

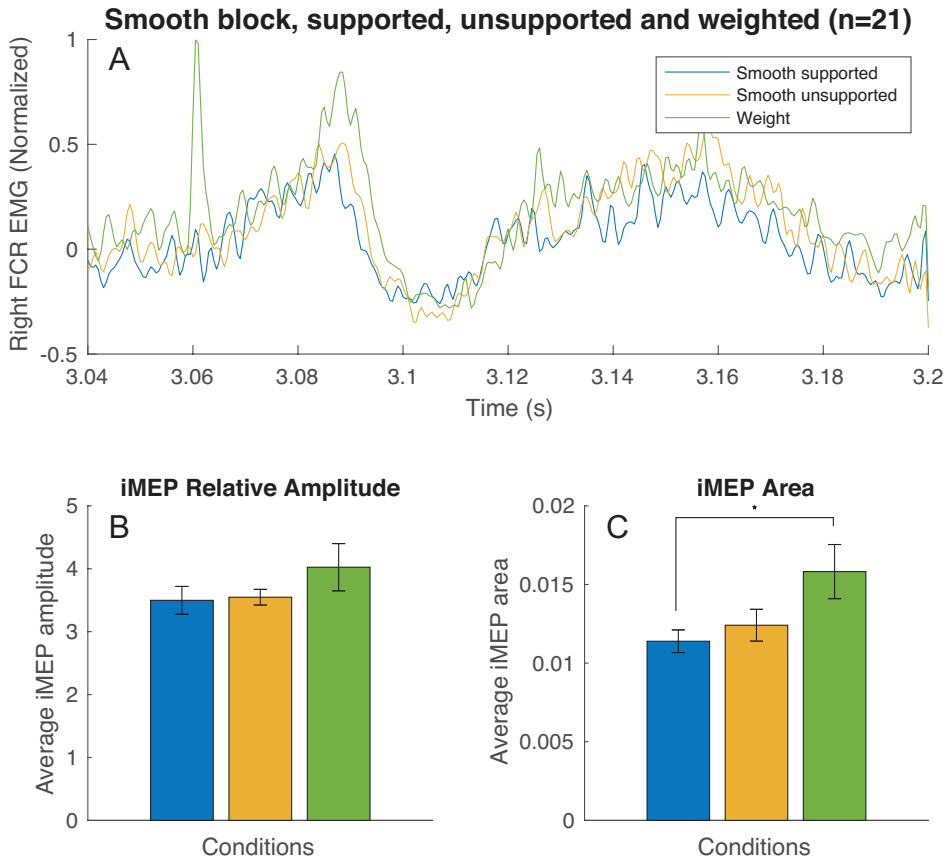

Figure 16. – Effects of Support and Weight on the Smooth Block.
Support- and weight-related changes in ipsilateral responses to TMS between Tasks 1, 3, and 5 (C, p=0.022 for area of the iMEP).

In order to investigate the role of support in iCS modulation, iMEPs were compared in two bimanual holding tasks with and without support, first with the smooth block (Fig. 15; Tasks 1, 3 and 5), then with the coarse block (See Fig. 17 in annexes; Tasks 2 and 4). No significant effect of support was observed in iMEPs amplitude and area in both the coarse and smooth blocks tasks ($F(1,20)= 0.063$, $p= 0.804$; $F(1,20)= 2.969$, $p= 0.1$). There was no effect of weight on iMEP amplitude (Fig. 15B; $p= 0.222$ between Tasks 1 and 5; $p= 0.193$ between Tasks 3 and 5). In contrast, iMEPs area in Task 5 was significantly larger than those of Task 1 (Fig. 15C; $p= 0.022$, effect size $d= -0.732$). There was no effect of weight on iMEPs area between Task 3 and Task 5 (Fig. 15C; $p= 0.077$).

Discussion

1. Basic Findings

Several elements have been identified as capable of modulating cCS influences. Among other things, Raptis et al. (33) have observed a position-dependent modulation of cMEPs obtained in FCRs. Similarly, multiple researchers have studied the impact of cutaneous afferent on cCS influences (59–61). We here aimed to extend those findings to iCS modulation in the right FCR.

Tested by TMS in a unimanual task in which only the position of the right wrist changed, no modulation of iCS influences on MNs was observed. In contrast, iCS influences were modulated in the bimanual tasks in which subjects changed the angular positions of both wrists together. However, the pattern of position-related iCS modulation depended on how the two hands interacted. Particularly, short-latency iMEPs were higher in wrist flexion than extension when the two hands contacted with each other indirectly, via a block. When the two hands were in direct contact, modulation of iMEPs was absent and, instead, the long-latency response, the iRB was higher when the right wrist was in extension. Results are consistent with the hypothesis that iCS influences are more strongly modulated during bimanual than unimanual changes in wrist position. The finding that various components of iCS influences on MNs could change differently, depending on conditions in the bimanual tasks, might indicate that these components involve different central and reflex pathways.

During bimanual holding tasks, the effects of texture and weight support were tested by TMS with different block's surface. The major finding was that regardless of the weight support, the smooth block was associated with increased cortical excitability in comparison to the coarse block. However, iMEP amplitude was not further increased by removing the support and adding weight to the block. In contrast, iMEP area was increased when weight was added to the unsupported smooth block. These results were surprising since we expected the support to play an important role during grasping. Indeed, in unsupported conditions, different textures provide different levels of friction, and task demands are increased to prevent the object from falling. Thus, results

suggest that texture may modulate iCS influences, although more experiments are required to confirm the effect of friction level.

2. iCS Modulation in Unimanual Tasks

Previous studies of unimanual wrist movements showed that cCS influences are modulated such that flexor TMS responses are larger in wrist flexion than in extension, even if the tonic EMG activity is equalized in both positions (31,33). Results suggested that cCS are involved in threshold position resetting (33) which implies shifting the spatial frame of reference in which muscles are predetermined to work.

In our study, the right FCR muscle length decreased with right wrist flexion. If the activation thresholds are measured in terms of the lengths at which muscles are activated, then, according to Raptis et al. (33), in order to flex the right wrist alone, the system should diminish the activation threshold lengths for MNs of flexor wrist muscles and increase the activation thresholds for MNs of wrist extensor muscles (reciprocal pattern of central influences on MNs of agonist and antagonist muscles).

Our results do not preclude that iCS influences have a similar role in the setting of the threshold position, but only in the context of bimanual wrist movements. Indeed, our observations only show the absence of position-related modulation of iCS influences in the unimanual task but do not exclude a functional role, for example of the background, tonic iCS influences in unimanual tasks. This possibility can be suggested based on the observation that supra-threshold TMS of the same brain spot can elicit mechanical (jerk contraction, (33)) and EMG responses to TMS in both ipsilateral and contralateral wrist muscles.

3. iCS Modulation in Bimanual Tasks

3.1 Task-Dependent Modulation of iCS Influences

3.1.1 Bimanual Task with Block

In Task 3, the presence of the object between the hands may have produced tactile stimulation eliciting a tendency to grasp the block. The application of bilateral hand pressure on the object's

sides can also be explained by the notion of indirect, referent, control. Some aspects of referent control in Task 3 are like those used in the production of grip forces to hold an object between the index and the thumb of one hand (127–130). It is assumed that to hold the object between the two hands, the descending CS specified referent positions of left (R_L) and right (R_R) hands at which respective wrist muscles began to be activated (Fig. 16A, red curves). The distance between the two referent hand positions is called the "referent aperture" (R). The actual hand aperture (Q) is constrained by the size of the object held between the hands. Given the referent hand positions, the palms of both hands virtually penetrate the object (Fig. 16A). Deviated by the object from their referent, activation thresholds, muscles generate activity and forces that press on the object in proportion to the gap between the actual (Q) and referent (R) hand aperture. The stretch reflex, with the possible contribution of cutaneous reflexes, could be responsible for these pressing forces. This can be visualized by asking an assistant to forcibly pull the object away from the hands. In response to the removal of the object, the hands would automatically move to their referent positions (Fig. 16B). This is an example of an unloading reaction in which the stretch reflex, with the possible contribution of cutaneous feedback, also plays a major role (e.g., (131)).

In order to flex the right wrist, while simultaneously extending the left wrist, the system should shift the referent positions of both hands in the flexion direction (Fig. 16C, arched arrow), thus facilitating MNs of the right wrist flexors. Our findings show that the iCS system may participate in such facilitation and thus in the referent control of wrist positions in Task 3 (Fig. 16A). We believe it would be helpful to verify this model in future experiments.

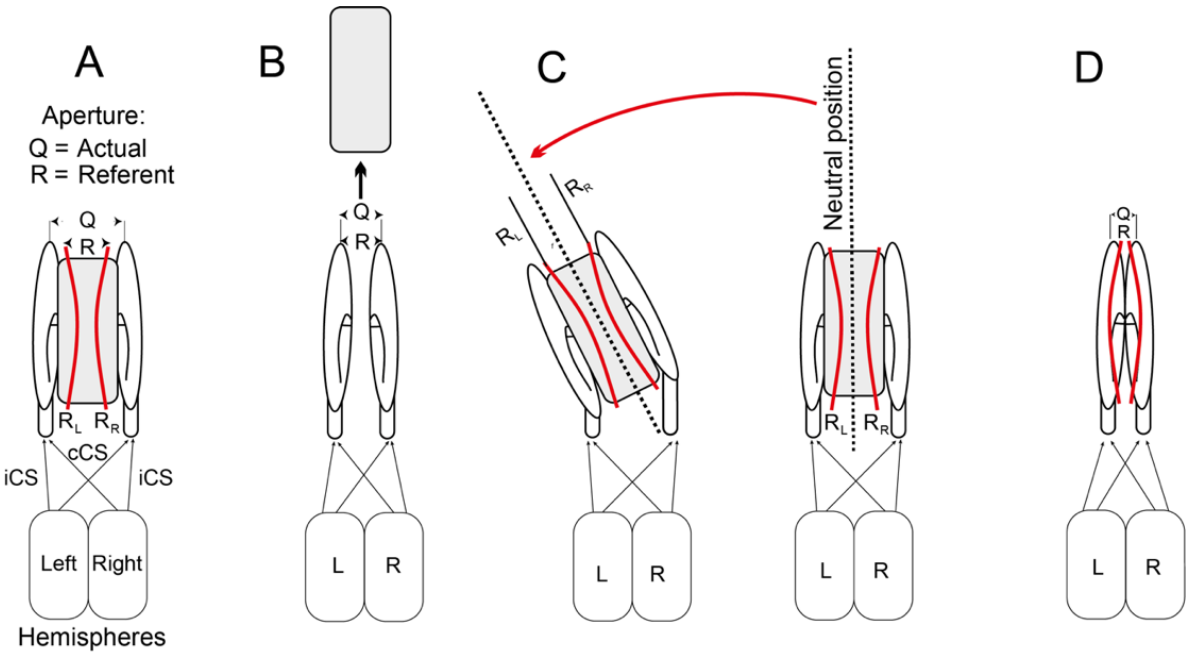

Figure 17. – Referent Control of Wrist Positions in the Bimanual Tasks.

A: By influencing wrist muscles MNs, descending CS systems set referent wrist positions, R_R and R_L of the right and left wrist, respectively. The distance between the two threshold wrist positions defines a virtual distance ("aperture") between the hands. In the presence of the block, the actual aperture (Q) is constrained by the size of the block whereas, in the referent positions, the hands virtually penetrate the block (R). The bottom part of the figure shows the two hemispheres and pathways (cCS and iCS) influencing MNs. B: The referent hand positions are reached when the block is forcefully pulled away by an assistant from the hands (vertical arrow). C: In order to flex the right wrist, while simultaneously extending the left wrist, the system could shift the referent positions of both hands in the flexion direction from the neutral position (arched arrow). D: In Task 2 in which the hands touched each other, the referent position of right hand virtually penetrated the left hand and vice versa.

3.1.2 Bimanual Task without Block

In the absence of the object in Task 2, the hands pressed against each other. In this case, the referent position of the right hand virtually penetrated the left hand and vice versa (Fig. 16D). Again, the gaps between the actual and referent hand positions would be responsible for the mutual pressure of the hands. As in Task 3, shifts in the referent positions of both hands in the respective directions were responsible for changes in the wrist positions. It is possible that, compared to Task 3, pressure forces in Task 2 were smaller and variations in the background EMG levels could mask the possible participation of the iCS system.

In Task 2, the gap between the referent and actual hand R was minimal (Fig. 16D). As a consequence, the force of the interaction between the two hands and the role of the stretch reflex would be lower in Task 2 than in Task 3. While wrist flexor iMEP modulation was not observed when the two hands were touching each other in Task 2 (Fig. 10A and B), the long latency facilitatory component, iRB, was modulated, being larger in the wrist extension position.

As described in the introduction, although the iRB component of the TMS response has been observed previously, it has rarely been discussed. We characterized iRB responses in terms of latency (about 60 ms), duration, amplitude, and area (see Results). Our results confirm that the iRB response was also modulated in a task-specific position-related way.

In addition, we observed an absence of correlation between the iMEP and the iRB (see Results) which may indicate that these components are controlled independently. Note that a higher iRB component was observed in the flexor muscle when the wrist was extended. The facilitation of flexor iRB could be a sign of preparation for the movement reversal from extension to flexion. Another possibility would be a reaction of the right FCR to the left hand jerk movement elicited by TMS. Indeed, at this position, right wrist was extended whereas the left wrist was flexed, resulting in larger cMEPs which could have pushed the right hand. The latency between the cMEP and the iRB would suggest a mediation through the stretch-reflex (132). Additional experiments are necessary to verify this hypothesis on the origin of this and other components of the response to iTMS.

3.2 Possible Neural Pathways Underlying Modulation of iCS Influences

3.2.1 Facilitatory iCS, iMEPs

In our study, the latency of iMEPs was too short to include interhemispheric inhibitory effects (88), suggesting that the iMEP was not processed through transcallosal (interhemispheric) pathways. This is also supported by the finding that large iMEPs were obtained in patients with complete agenesis of the CC (74). It is important to note that the pathways mediating TMS responses in healthy subjects and those with neurological lesions might be different (81). It seems also unlikely that iMEPs are transmitted via corticomotoneuronal or fast-conducting uncrossed

corticomotoneuronal (i.e. monosynaptic) pathways since otherwise one would expect a delay equal or close to zero between the iMEP and cMEP (74), which was not the case in our study (Fig. 6A and B, see also (88)). Wassermann et al. (72) reported a reduced delay between iMEPs and cMEPs in deltoid muscles and concluded that uncrossed fibers in the CST could mediate the ipsilateral short-latency response in more proximal limb muscles. Several studies (74,88) suggest an ipsilateral oligosynaptic pathway, such as corticoreticulospinal or corticopropriospinal projections as the route for the iMEP. Such pathways may also be responsible for the modulation of facilitatory short-latency iCS influences during bimanual tasks in our study.

3.2.2 Inhibitory iCS, iSPs

The iSP neural pathways are thought to be at least in part mediated by fibers passing through the CC, suggested in studies showing absent or delayed iSPs in patients with agenesis or surgical lesions of the CC (133), as well as in preschool children who have yet to develop a functionally competent CC (99).

The modulation of the inhibitory component of the EMG response was absent in all tasks in our study. Our bimanual tasks required flexion of one wrist and extension of the other (out-of-phase, or heteronymous), which is produced less stably and consistently compared to simultaneous patterns (in-phase, or homonymous) in which both wrists flex or extend together (134,135). Perez et al. (136) showed that in bimanual isometric tasks, iSP with out-of-phase movements was smaller than those with in-phase and with unimanual actions. This suggests that iCS inhibitory influences may be less effective during out-of-phase tasks, as was the case in our bimanual tasks.

4. iCS Modulation by Cutaneous Afferents

Cutaneous afferents may provide information about task constraints (137), in particular, they may be important in grasp scaling and maintaining during holding tasks (39,138).

In our experiment, by changing the surface texture and the weight support, we focused on the role of friction between the hand and object during a bimanual holding task. Other studies have investigated mainly precision grip between fingers in unimanual tasks. Although researchers have usually reported cutaneous effects on EMG activity of hand muscles, there is evidence that

cutaneous feedback from the pads of fingertips can also influence the activity of muscles of the whole arm (57,137). Our results showed that changes in block surface texture led to changes in iCS facilitation of wrist muscles MNs.

4.1 Effects of Texture

When investigating the effect of texture on motor cortex excitability, tactile exploration tasks and active sensing have been prevalent study paradigms in the past. Indeed, there is evidence that cCS influences are more strongly modulated by cutaneous afferents during dynamic than static conditions (91,139,140). Coarse, rough, textures especially tend to be associated with higher cutaneous receptors and cortical activity during dynamic touch compared to smoother surfaces (40,65,141). In contrast to the unsupported conditions in which both fast and slow adapting cutaneous mechanoreceptors should be active (41), the stationary supported holding task is thought to rely mainly on slow adapting receptors (142,143). According to a series of papers by Phillips and Johnson (144), those receptors are able to better sense uneven surfaces if their gratings are separated by a distance exceeding 2mm. As a result, the Velcro tape used in our study to produce a coarse surface might not have been perceived properly since Velcro hooks were not separate enough.

Moreover, Picard et al. (40) suggested the existence in monkeys of two populations of texture-sensitive cells in M1, one sensitive to coarse and the other to smooth textures. The ability of M1 neurons to encode sensory information about peripheral tactile stimulus was later confirmed by Jiang et al. (145). Thus, it possible that the stationary nature of the task and the characteristics of the rough surface used in our experiment prevented the hyper-activation of cutaneous receptors when holding the supported coarse block, resulting in reduced cortical excitability.

As enunciated in Master and Tremblay's (65) paper, behavioral context plays a crucial role in action-perception coupling. Accordingly, more recent evidence shows that tactile inputs which are not behaviorally relevant to M1 may be selectively gated (145). Although those findings were based on testing cCS facilitation, we can hypothesize that the coarse block was either unrecognize as such or simply dimmed functionally irrelevant because of the static nature of the task.

4.2 Effects of Friction

While holding an object, pressure or grasping forces are necessary to prevent the object from sliding off the hands. Each object, depending on its features (texture, friction, weight), requires a certain degree of hand coordination. It is also known that during holding tasks, the two hands are controlled as a single unit such that perturbation of motion of one arm elicits bimanual reflex reactions (129,146). In addition, Shibuya and Okhi (63) showed that cutaneous inputs generated by a load perturbation in a finger loading task elicited an increase in both cCS and iCS influences on MNs, thus supporting the idea that both hemispheres cooperate during holding, especially in bimanual tasks.

Friction plays a major role in grip force adjusting during grasping tasks as shown by experiment using different object surface features, coatings, and digit anesthesia (39,123). Overall, slippery objects are associated with lower friction level. To prevent slips, they require enhanced grip forces (39,123) which are associated with higher cMEP facilitation that can last until a stable condition is established (147). Our experiment is in line with such results as the smooth block led to significantly larger iMEPs in unsupported conditions, confirming that friction modulates iCS influences. Thereby, it appears that iCS influence may play a role in grip scaling during bimanual holding tasks. Surprisingly, within the same textures, no effect of support was reported despite the increased task demands associated with the non-supporting of the block's weight.

In addition to friction, weight plays a great role in influencing grip forces (66). When weight is added to a grasping task, subjects have to adapt the balance between their grip and load forces (38). In our experiment, we compared two conditions with low friction and low friction plus increased load forces for the smooth and weighted block, respectively. Surprisingly, no significant difference was observed between the smooth block unsupported and weighted. Even though these results differ from the general view, Salimi et al. (148) observed that slippery surfaces were associated with a higher increase in grip forces than increasing the weight. In contrast, iMEPs area associated with the weighted block were significantly larger than those of the supported smooth block, suggesting that weight may modulate iCS influences, although supplementary experiments with different weights are needed to confirm it.

5. Clinical Relevance

As previously mentioned, a growing number of studies suggest that iCS influences play a role in motor function recovery after lesions (70,88,120).

Based on our results, we have observed that iCS influences are modulated in a position-dependent fashion and by cutaneous afferents during bimanual holding tasks. Similarly, other groups have investigated iCS modulation by neck rotations (74,88), contralateral arm contraction (88), task complexity (64) and attention (64,65). Although this is fundamental research applied only to healthy subjects, those results provide more insights into both facilitatory and inhibitory iCS functions and how ipsilateral pathways excitability can be modulated. In a clinical setting, such knowledge could come useful when designing rehabilitation paradigms to optimize the trainings depending on patients' needs.

For instance, there is evidence that iCS pathways may play a role in cross education (149), a process in which unilateral strength training produces an increase in strength in the contralateral limb. A systematic literature review by Ehrensberger (150) has highlighted the potential of cross education to rehabilitation training in post-stroke patients, especially for people with hemiparesis. Hence, facilitating ipsilateral pathways to the untrained muscles by using strategies such as cutaneous afferents stimulation or neck rotations could potentially improve motor functions.

In a broader perspective, there is evidence that iCS activity may increase with task complexity, in particular when the contralateral hemisphere is not yet trained for such task (151,152). It suggests a potential supportive role of iCS influences during movement learning and early training which could be investigated in sport and music training.

6. Limitations

There are several methodological limitations to both of these studies that we can address.

6.1 Group Composition

In our study about position-dependent iCS modulation, one potential issue comes from the group composition. Indeed, as the protocol was refined, some tasks were abandoned and new tasks, more relevant to our hypothesis, were implemented. Although all subjects participated in the unimanual task, only 11 and 10 subjects participated in the bimanual with and without block tasks, respectively. Hence, given the small sample size, caution must be taken when drawing conclusions. In addition, as the groups were not the same across conditions, we were not able to compare them using an ANOVA. Instead, T-Tests were used which can increase the probability of Type 1 errors (153).

6.2 Probing of iSP

One limitation of our study on probing iSPs is the use of suprathreshold TMS such that iSP could be masked by the preceding iMEP, thus complicating the interpretation of results. As a result, we cannot be certain that there were no task-dependent changes in iSPs in our experiments

6.3 EMG Noise

Despite their treatment, EMG signals were often noisy, probably in part because of the difficulty to maintain the EMG in the equalization window. Though the detection threshold used here, 1SD above the baseline, has been used by other groups (81), raising it such as in Tazoe and Perez (88), 2SD above baseline could offer more precision and avoid false-positive iMEPs. Increasing the number of trials would also be a possible strategy.

6.4 Comparison with cMEPs

In the second paper about cutaneous afferents, an analysis of the cMEPs would have been a good addition to compare cCS and iCS modulation. However, as EMG activity from the left wrist was not equalized during the experiment, it is difficult to draw conclusions from the cMEPs obtained.

6.5 Impact of Attention

Other elements could influence iMEP size. For instance, cCS influences appear to be modulated by attention in a task-dependent way with more demanding tasks such as tactile recognition,

leading to increased facilitation (64,65). Provided that iCS are modulated in the same manner, we could argue that in our experiments, the task of equalization could be seen as attention-demanding especially in unsupported conditions with the weight in which keeping a maintained muscle activation in a given window during the whole block of trials becomes challenging.

7. Futures Directions

7.1 Hemispherical Asymmetry

There is a known asymmetry between the left and right hemispheres. In right-handed subjects, the left M1 appears to have greater ipsilateral involvement and fMRI studies have shown more ipsilateral M1 activation during left-hand activity (70). Furthermore, although results are still under debate, studies in stroke patients have revealed more ipsilateral impairment when the left hemisphere is lesioned (154). Conducting similar experiments to the ones performed here but with the TMS over the dominant, left hemisphere would bring a better understanding of iCS modulation.

7.2 Cutaneous Afferent During Unimanual and Dynamic Tasks

The results from our experiments are restricted to bimanual holding tasks. To get a better idea of how cutaneous afferents modulate iCS, we need to investigate them in more tasks, including unimanual. In addition, dynamic tasks tend to modulate cCS more than static ones (91,139,140). Further studies should investigate iCS modulation in such conditions as well.

7.3 Effect of Weight on iCS

Weight plays a critical role in grip scaling during holding tasks which is associated with cortical excitability modulation (66). Thus, we expected to see a significant difference between the smooth block unsupported and weighted. It is possible that the weight we used was not sufficient to trigger a change in iCS facilitation. Future work should settle this by testing different weights in comparison with a control unsupported block. Furthermore, to compare conditions with different friction levels and grip force requirements, it would be relevant to include a weighted coarse block as well.

7.4 Other Components of the TMS Response

As previously explained, our methodology does not allow us to compare iSPs. In future studies, a subthreshold TMS could be applied to evaluate the possible modulation of iCS inhibitory influences (88). Investigating the iRB and its modulation by cutaneous afferent may also give us a better understanding of its mechanisms.

7.5 Premotor and Supplementary Areas

Both the PMC and the SMA appear to participate in coordination and bimanual movements control (155). Thereby, future studies could also address the question of whether CS influences originated from those areas of the motor cortex are involved in the tasks analyzed in the present study as well as their modulation.

Conclusion

We aimed to investigate iCS influences on wrist MNs and their modulation in uni- and bimanual tasks. Results are consistent with the hypothesis that iCS influences originated from M1 on MNs are modulated depending on the wrist position in bimanual but not in unimanual tasks. Furthermore, facilitatory influences from cutaneous afferents modulate iCS influences on MNs and thus may participate in scaling and maintaining of grip forces.

It is suggested that the left and right cortices cooperate in bimanual tasks involving grasping of an object between the hands, with the possible participation of mono- and polysynaptic (cortico-reticulospinal, cortico-propriospinal and transcallosal) projections to MNs, as well as spinal and trans-cortical stretch reflexes.

Our results may be essential for the understanding of the role of interhemispheric interaction in healthy and neurological patients. While discussing the results, we illustrate how the analysis of the participation of the iCS systems in bimanual tasks might be advanced by considering such behavioral tasks in the context of indirect, referent control of motor actions, resulting from central shifts in the threshold wrist position at which muscles begin to be activated.

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Tables

Characteristics of TMS responses		Unimanual Task 1 (n=16)		Bimanual Task 2 (n=11)		Bimanual Task 3 (n=10)	
		F	E	F	E	F	E
cMEP	Onset	19.99±0.57	20.17±0.60	18.79±0.45	18.66±0.52	18.74±0.51	18.92±0.29
	Duration	22.22±1.47	21.97±1.40	26.89±1.84	25.96±1.76	28.77±1.24	25.92 ±1.43
	Amplitude	83.11±22.62	80.41±22.21	33.05±8.24	24.88±6.50	68.72±24.16	53.97±11.48
	Area	33.93±9.80	34.00±9.66	15.93±4.29	12.59±2.48	27.48±12.49	23.42±5.42
iMEP	Onset	21.36±1.26	22.97±1.21	25.58±0.99	24.71±0.88	24.54±1.05	25.24±0.84
	Duration	14.98±0.63	15.64±0.79	12.15±1.23	12.77±1.25	15.41±2.10	14.66±1.50
	Amplitude	0.61±0.12	0.44±0.09	0.41±0.10	0.31±0.10	0.81±0.33 *	0.37±0.15 *
	Area	0.20±0.08	0.13±0.06	0.09±0.06	0.06±0.05	0.24±0.07 *	0.09±0.08 *
iSP	Onset	36.61±1.62	38.87±1.66	36.60±1.08	37.00±1.73	38.84±1.66	39.62±1.72
	Duration	25.85±1.43	21.21±1.22	21.06±1.27	18.85±1.36	15.41±2.10	14.66±1.50
	Amplitude	0.57±0.03	0.54±0.03	0.49±0.03	0.49±0.02	0.57±0.04	0.54±0.05
	Area	0.29±0.02	0.25±0.03	0.24±0.02	0.24±0.02	0.29±0.04	0.30±0.04
iRB	Onset	62.97±1.24	63.27±1.78	55.95±1.27	57.12±0.86	59.92±1.74	58.63±1.60
	Duration	21.63±1.34	20.19±0.98	26.78±2.57	25.87±1.94	15.41±2.10	14.66±1.50
	Amplitude	0.72±0.08	0.61±0.08	0.95±0.13 *	1.39±0.25 *	0.87±0.12	0.96±0.14
	Area	0.25±0.05	0.24±0.06	0.36±0.08 *	0.75±0.14 *	0.32±0.07	0.36±0.08

Tableau 1. – Characteristics of Components of TMS Responses in Experiment 1.
Characteristics of components of TMS responses (cMEP, iMEP, iSP and iRB) in Tasks 1-3 in flexion (F) and extension (E) wrist positions, shown as means with standard errors. Onset and duration are in ms. All EMG components were normalized to the mean EMG level before TMS. Asterisks show significant effects.

MEP characteristics		Smooth supported (n=21)	Coarse supported (n=21)	Smooth unsupported (n=21)	Coarse unsupported (n=21)	Weight (n=21)
cMEP	Onset (ms)	23.1 ± 0.55	23.1 ± 0.32	23.2 ± 0.32	23.4 ± 0.4	23.1 ± 0.32
	Duration (ms)	20.07 ± 1.1	21.0 ± 0.72	20.0 ± 0.9	19.9 ± 0.77	20.7 ± 0.71
	Relative Amplitude	23.21 ± 5.16	24.48 ± 5.29	16.06 ± 3.82	15.36 ± 3.12	12.51 ± 1.74
	Area	0.1557 ± 0.0381	0.1571 ± 0.0311	0.1 ± 0.0248	0.1024 ± 0.024	0.0846 ± 0.0136
iMEP	Onset (ms)	27.3 ± 0.71	27.1 ± 0.44	27.1 ± 0.42	27.3 ± 0.59	26.8 ± 0.5
	Duration (ms)	11.4 ± 0.57	10.9 ± 0.63	12.1 ± 0.64	11.8 ± 0.72	13.6 ± 0.74
	Relative Amplitude	3.5 ± 0.22 *	3.03 ± 0.10	3.55 ± 0.13 *	3.05 ± 0.12	4.02 ± 0.38
	Area	0.0114 ± 0.00072 *	0.0094 ± 0.00035	0.0124 ± 0.001 *	0.0106 ± 0.00066	0.0158 ± 0.0017 *

Tableau 2. – Characteristics of Components of TMS Responses in Experiment 2.

Characteristics of components of TMS responses (cMEP, iMEP) in Tasks 1-5 in flexion (F) wrist position, shown as means with standard errors. Onset and duration are in ms. All EMG components were normalized to the mean EMG level before TMS. Asterisks show significant effects.

Supplementary figure

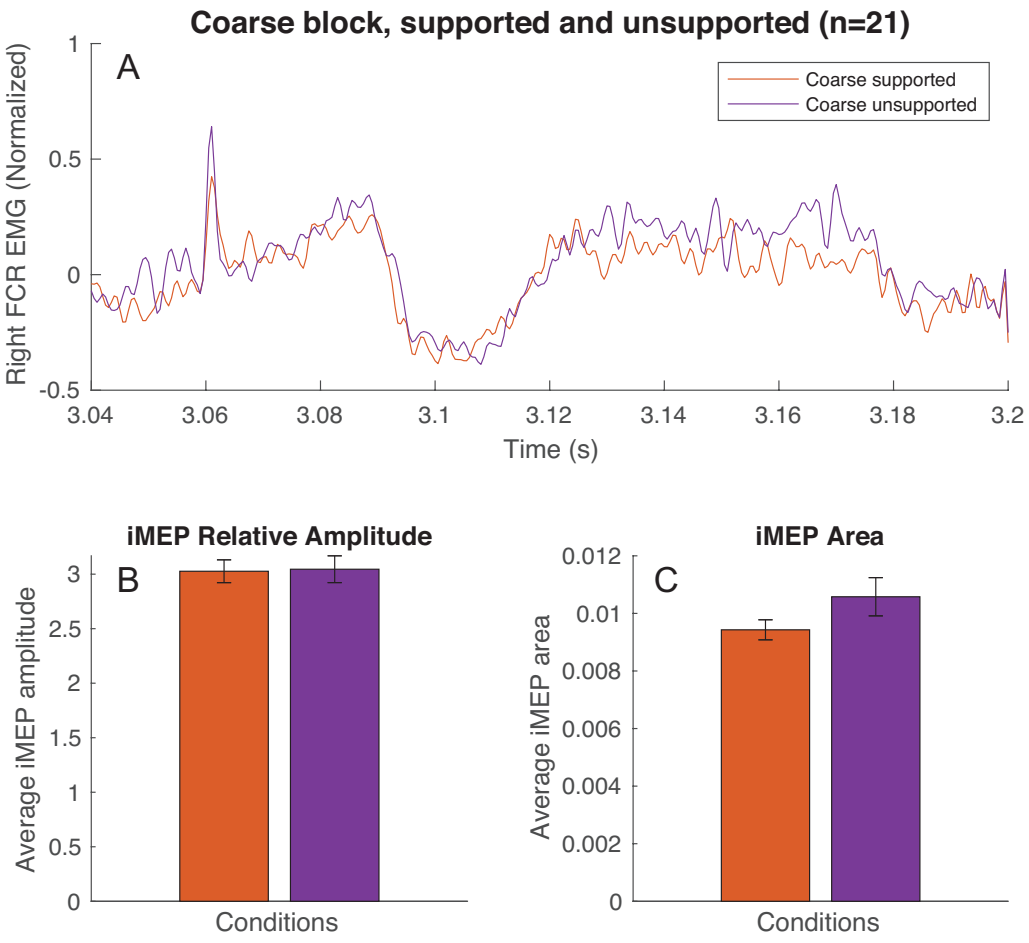

Figure 18. – Effect of Support on Coarse Block.
Absence of support-related changes in ipsilateral responses to TMS between Tasks 2 and 4.